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# Prognostic and predictive markers of systemic sclerosis-interstitial lung disease in a clinical trial and long-term observational cohort

**Running head:** Systemic sclerosis lung disease biomarkers

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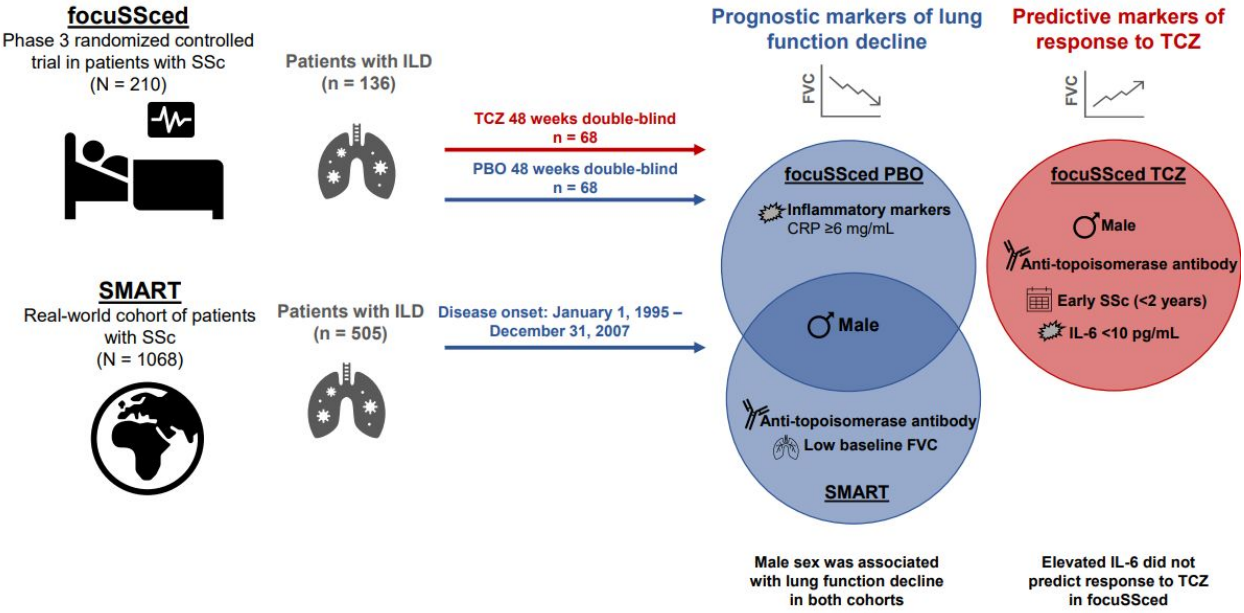
**Keywords:** Autoantigens and autoantibodies; biological therapies; biomarkers; cytokines and inflammatory mediators; interstitial lung disease; scleroderma and related disorders; systemic sclerosis

## Key messages

- Clinical trial and real-world systemic sclerosis-interstitial lung disease cohorts shared prognostic lung function change markers
- Male sex was associated with lung function decline in both cohorts
- Elevated interleukin-6 level did not predict response to tocilizumab in clinical trial patients

## Graphical Abstract




CRP, C-reactive protein; FVC, forced vital capacity; IL-6, interleukin-6; ILD, interstitial lung disease; PBO, placebo; SSc, systemic sclerosis TCZ, tocilizumab.

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## Abstract

**Objectives:** Explore prognostic and predictive markers of systemic sclerosis-associated interstitial lung disease (SSc-ILD) outcomes in a phase 3 trial (focuSSced) and prognostic markers in a real-world cohort (SMART).

**Methods:** The focuSSced SSc-ILD subgroup included 68 of 106 placebo-treated and 68 of 104 tocilizumab-treated patients. The SMART cohort included 505 patients with SSc-ILD. Linear mixed-effect models were used to identify factors associated with change in forced vital capacity (FVC). Kaplan-Meier estimation and Cox regression were used for time-to-event analyses.

**Results:** In placebo-treated focuSSced patients, sex was a significant prognostic factor for FVC decline; males had increased risk for absolute decline ≥10% in percent-predicted FVC (ppFVC) and 0.22% faster weekly FVC decline than females ($P = 0.0001$). FVC was 9.8% lower in patients with C-reactive protein >6 mg/mL versus those with C-reactive protein ≤6 mg/mL ($P = 0.0059$). Tocilizumab reduced the risk for ≥10% decline in ppFVC in patients who were male, had earlier disease (<2 years duration), had interleukin-6 levels <10 pg/mL, or had anti-topoisomerase antibodies (ATA). In the SMART cohort, prognostic factors for ppFVC <70% were male sex, ATA, and low baseline FVC. Males had 3.3% lower FVC 1 year after disease onset ($P < 0.001$) and 0.6% faster yearly decline ($P = 0.03$) than females.

**Conclusion:** Prognostic markers in SSc-ILD were similar between focuSSced and SMART. Male sex and inflammatory markers were associated with lower FVC but interleukin-6 ≥10 pg/mL was not predictive of response to tocilizumab.

**Trial Registration:** ClinicalTrials.gov: NCT02453256

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## Introduction

Systemic sclerosis (SSc) is a clinically heterogeneous multisystemic disease with internal organ complications including interstitial lung disease (ILD) [1].

Interstitial lung abnormalities are evident in high-resolution computed tomography (HRCT) of the chest in up to 80% of patients [2] and 30–40% develop clinically significant ILD [3], which is the leading cause of death in SSc [4].

Heterogeneity in SSc-ILD means prognostic markers would be valuable to indicate disease outcome for clinical practice or trial design. Prognostication in SSc-ILD based on clinical and laboratory characteristics aims to identify patients most at risk for developing severe ILD and those more likely to have mild disease or a slowly progressive course [5]. Prognostic factors identified for SSc-ILD progression and mortality include diffuse cutaneous SSc (dcSSc) phenotype, anti-Scl-70 (anti-topoisomerase 1) positivity, elevated acute-phase reactants, and ethnicity [5-7]. However, studies were limited by cross sectional design, selective patient recruitment in clinical trials, small patient numbers, and limited duration of follow-up.

Identifying subgroups likely to benefit from therapy, or enriching cohorts, may be crucial for maximizing treatment benefit [8, 9]. Mycophenolate is often used as first-line treatment for SSc-ILD,[10] based on results from the Scleroderma Lung Study II, where it showed a modest improvement or stabilization in lung function comparable to cyclophosphamide with less toxicity [11]. The emergence of nintedanib and tocilizumab as the first approved treatments for SSc-ILD [10] suggests that predictive markers of treatment response could be determined. It is unclear whether results from highly selective clinical trial populations could be generalized to real-world SSc-ILD patients receiving concomitant immunosuppressive therapy.

FocuSSced was a randomized, double blind, placebo-controlled phase 3 trial of the interleukin-6 (IL-6) receptor inhibitor, tocilizumab, in patients with early dcSSc. Although the study was not designed to recruit for patients with SSc-ILD, it enrolled an early dcSSc population with high levels of inflammatory markers; consequently, 66% of patients had ILD on baseline HRCT visual read [12]. The primary endpoint of change from baseline in modified Rodnan skin score (mRSS) at week 48 for tocilizumab versus placebo was not met. However, secondary forced vital capacity (FVC) results showed stabilization of lung function in patients who received tocilizumab and exploratory and post hoc HRCT results supported an antifibrotic effect of tocilizumab in radiologically evident lung fibrosis [12].

The present study used data from the subgroup of patients in focuSSced who had SSc-ILD to investigate prognostic markers of lung function decline in the placebo arm of this short-term, 48-week, highly selective clinical trial SSc-ILD population. Prognostic factors of clinical outcomes were also investigated during long-term follow-up of a large, well-characterized real-world cohort of patients with SSc-ILD receiving standard management. The analysis aimed to investigate whether there is any congruency between prognostic factors in short-term and long-term decline in lung function in SSc-ILD. Predictive markers of treatment response to tocilizumab in focuSSced were investigated to elucidate characteristics that may identify patients who benefit from early immunomodulatory therapy and could be used to enrich interventional SSc trials for patients at the highest risk of progressive ILD.

## Methods

*FocuSSced cohort*

FocuSSced (NCT02453256) enrolled adults with dcSSc, classified according to 2013 American College of Rheumatology/European League Against Rheumatism criteria, of 60 months' duration or less (from first non-Raynaud phenomenon manifestation) and mRSS 10–35 units at screening [12]. The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice and approval was obtained from the investigators' independent ethics committees. All patients provided written informed consent to participate in the study. Individuals with pulmonary disease who had percent-predicted FVC (ppFVC) ≤55%, or diffusing capacity for carbon monoxide ≤45% of that predicted, were excluded. Randomization was centralized and stratified by serum IL-6 levels at screening (<10, ≥10 pg/mL). The primary endpoint of the trial was the difference between the tocilizumab and placebo treatment arms in change from baseline to week 48 in mRSS. FVC was a secondary endpoint assessed at baseline and weeks 8, 16, 24, 36, and 48. Baseline HRCT read by an experienced thoracic radiologist was conducted to identify patients with ILD.

*Prediction of prognostic factors in focuSSced*

To investigate prognostic factors that might predict clinical outcomes, time to events of ≥10% decline in ppFVC[13] and ppFVC reaching ≤70% was analyzed up to week 48 by treatment group (placebo, tocilizumab) and additionally stratified by baseline factors including IL-6 levels (<10, ≥10 pg/mL), IL-6 receptor levels (IL-6R; high [≥ median of 38.2 ng/mL], low [<38.2 ng/mL]), age (≥65 years, <65 years), sex (male, female), duration of disease (≥2 years, <2 years), CRP levels (>6 mg/mL, ≤6 mg/mL), and platelet counts (≥330×$10^9$/L, <330×$10^9$/L). Cox regression and mixed-effect model were used for statistical analysis (Supplementary Data S1, available at *Rheumatology* online).

*Prognostic markers in real-world patients*

Potential risk factors for lung function decline in real-world SSc-ILD were investigated in a group of patients with HRCT-confirmed ILD and disease onset at least 10 years prior to data retrieval from the Royal Free Scleroderma Cohort (SMART), a prospective observational cohort of SSc patients who consented for research. FVC changes over the first 10 years from disease onset and the effects of age, sex, cutaneous subset, and autoantibodies were assessed using linear mixed-effect models. We explored potential prognostic factors for poor long-term outcome determined by thresholds of lung function decline indicative of severe disease with poorer survival (time to development of <70% and <50% ppFVC) starting from the first available FVC result within the first 5 years of disease, using Kaplan-Meier estimates and Cox regression.

*Autoantibodies*

We analyzed associations between SSc-specific antibodies and morbidity or mortality in the SMART cohort and focuSSced trial (anticentromere antibodies [ACAs], ATA, anti-RNAP, anti–U3 RNP, anti-PM/Scl). Patients positive for at least one antibody type were included in the SSc-specific antibody group. Patients positive for antinuclear antibodies (ANA+) and negative for anti–extractable nuclear antigen (ENA−) formed another group. Patients with any other defined antibodies (U1 RNP, Th/To, SL, Ku, Jo-1, Ro, La, XR, PL-7, heterogeneous nuclear RNP, and Sm antibodies) and ANA− patients were included the “other” group.

*Predicting change in the SMART cohort*

Random-effect models were used to explore FVC changes over the first 10 years from disease onset and the effects of age, sex, cutaneous subset, and autoantibodies.

*Prognostic factors mixed-model analysis*

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To explore prognostic markers, we used a mixed-model approach that investigated subgroups in the SMART and focuSSced cohorts according to baseline characteristics including sex, age, disease subset, and ANA reactivity and in the focuSSced cohort according to levels of IL-6, platelets, IL-6R, and CRP.

## Results

### Patient characteristics

*FocuSSced*

Between November 20, 2015, and February 14, 2017, 212 individuals were recruited and randomly assigned to receive weekly placebo ($n$ = 107) or tocilizumab 162 mg ($n$ = 105) subcutaneously[12]. Overall, 93 patients in the placebo group (87%) and 95 in the tocilizumab group (90%) completed 48 weeks of assessment. The intention-to-treat and safety populations comprised 106 patients in the placebo group and 104 patients in the tocilizumab group. ILD was detected in 68 of 106 and 68 of 104 patients, respectively, on baseline HRCT visual read (**Table 1**).

The weekly change in ppFVC was −0.13% (95% CI −0.19, −0.08) in the placebo group and 0.02% (95% CI 0.03, 0.06) in the tocilizumab group, resulting in a weekly difference of 0.15% (95% CI 0.08, 0.21; $P < 0.0001$). The estimated mean change in ppFVC at week 48 was −6.32% (95% CI −8.49, −4.14) in the placebo group and 0.74% (95% CI −1.40, 2.88) in the tocilizumab group and the difference in ppFVC after 48 weeks of treatment was estimated to be 7.06% (95% CI 4.00, 10.12, $P$ <0.0001).

*SMART*

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The SMART cohort has been described [14]. The SMART cohort patients included in the current analysis had disease onset between January 1, 1995, and December 31, 2007, to ensure a minimum 10 years of available follow-up. From a single-center cohort of 1068 patients with SSc with at least 1 pulmonary function test (PFT) result available, we identified 505 (47.3%) with ILD confirmed on visual HRCT read (**Table 1**). FVC measurements on at least 3 occasions were available for 364 (72.1%) patients. The mean period between PFTs was 13 months (SD 11.2). The mean ppFVC 12 months after SSc onset was 80.1% (SD: 19.3). At a group level, there was a small but statistically significant absolute FVC decline of 0.32% per year (95% CI 0.09, 0.55; *P* = 0.007). There was no significant correlation between baseline FVC and subsequent FVC change (correlation coefficient −0.13, 95% CI −0.26, 0.01).

**Prognostic factors—time-to-event analyses**

*FocuSSced*

In focuSSced, 55 of 136 patients (40.4%) experienced an event of <70% ppFVC during the 48-week follow-up. Overall, 38 of 136 patients (27.9%) had experienced ppFVC <70% before or at study day 1 (16 placebo, 22 tocilizumab). For time-to-event analysis, this group was left censored at day 1 and 97 patients who had baseline FVC ≥ 70% and at least 1 follow-up FVC result available were included. Therefore, the sample size was small and none of the candidate predictors for reaching the <70% ppFVC threshold were statistically significant (**Supplementary Table S1,** available at *Rheumatology* online). In the placebo arm, only male sex was associated with ≥10% absolute decline in ppFVC (**Figure 1, Supplementary Figure S1,** available at *Rheumatology* online); males were 2.7 times more likely than females to experience ≥10% decline in ppFVC (95% CI 1.07, 6.82).

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*SMART*

In the SMART cohort, 410 of 505 patients had their first PFT within 5 years of disease onset. Of those, 203 (49.5%) experienced decline in ppFVC to <70% and 132 of 203 (65%) had reached this by their first assessment. Sixty-four of the 410 patients (15.6%) developed ppFVC <50% and 27 of 64 (42.2%) had reached this by their first assessment. The proportion of patients with ILD who developed ppFVC <70%, if they had FVC ≥70% at the first available test result, was 7.7% at 1 year, 13.6% at 2 years, 17.2% at 3 years, 18.7% at 4 years, and 19.8% at 5 years from the first FVC assessment. The proportion of patients with ILD who developed ppFVC <50%, if they had FVC ≥50% at the first available test result, was 2.1% at 1 year, 4.4% at 2 years, 5.8% at 3 years, 7.6% at 4 years, and 10.5% at 5 years from the first FVC assessment (**Figure 2**).

Factors that increased the risk for ppFVC <70% were male sex, ATA positivity, and lower baseline FVC. For males, the hazard ratio for decline to ppFVC <70% was 1.92 times higher than females (95% CI 1.16, 3.16; $P = 0.011$). ATA-positive patients were 1.68 times more likely than ATA-negative patients to reach ppFVC <70% (95% CI 1.05, 2.69; $P = 0.03$). Every 1% decrease in baseline FVC increased the risk of reaching the ppFVC <70% threshold by 19% (HR 1.19 [95% CI 1.12, 1.27; $P < 0.001$]). Only baseline FVC was significantly associated with increased risk of reaching ppFVC <50% (HR 1.10 [95% CI 1.06, 1.12; $P < 0.001$]).

**Prognostic Factors—Mixed-model analysis**

*FocuSSced placebo*

Mixed-model analysis showed significant association between FVC and sex and between FVC and CRP in the placebo arm. Males had 0.22% faster decline in FVC per week than females ($P =$

0.0001). Patients with CRP >6 mg/L had 9.8% lower FVC than those with CRP ≤6 mg/mL at any time point ($P = 0.006$). There was no significant association between FVC and IL-6, IL-6R, platelet levels, ATA positivity, age, or disease duration. (**Table 2**).

*FocuSSced tocilizumab*

In the tocilizumab arm, only IL-6 levels ≥10 pg/mL were associated with ≥10% decline in ppFVC . Patients with IL-6 levels ≥10 pg/mL were 4.9 times more likely to reach this threshold than those with IL-6 levels <10 pg/mL (95% CI 1.21, 19.60). However, in the tocilizumab arm, patients with IL-6 ≥10 pg/mL had a significantly lower baseline FVC (71.9%) than those with IL-6 <10 pg/mL (80.7%) ($P = 0.01$) (**Figure 3; Supplementary Table S2,** available at *Rheumatology* online).

*SMART*

Multivariable analysis demonstrated significant associations between FVC and age at disease onset, sex, cutaneous subset, and antibodies. For each increased year of age at SSc onset, mean FVC increased by 0.3% ($P < 0.001$). Males had 3.3% lower FVC 1 year after onset ($P < 0.001$) and 0.6% faster decline per year ($P = 0.034$) compared to females. Patients with dcSSc had 5.6% lower FVC than those with limited cutaneous SSc ($P = 0.003$). The average FVC 1 year after disease onset in ATA+ patients was lower than anti-RNA polymerase (ARA)+ patients by 14.6% ($P < 0.001$). Rates of FVC decline were similar between ARA+ and ATA+ patients (difference −0.1%; $P = 0.8$) whereas ACA+ patients had a small increase in FVC per year versus ATA+ (difference 0.7%; $P = 0.04$) (**Table 3**).

**Exploration of predictive markers of treatment response in focuSSced**

Change in FVC over time by treatment arm and ATA or treatment arm and CRP levels is shown in **Supplementary Figure S2.** available at *Rheumatology* online. Tocilizumab significantly reduced the risk of reaching ≥10% decline in ppFVC compared with placebo in patients who were male (HR 0.22; 95% CI 0.05, 0.93), had disease duration <2 years at baseline (HR 0.23; 95% CI 0.08, 0.70), were aged <65 years (HR 0.42; 95% CI 0.19, 0.93), had IL-6 levels <10 pg/mL (HR 0.22; 95% CI 0.06, 0.77), or were ATA+ (HR 0.27; 95% CI 0.10, 0.76). IL-6 levels ≥10 pg/mL were not predictive of response to tocilizumab (HR 0.64; 95% CI 0.23, 1.80) (**Supplementary Table S1**).

## Discussion

This study identified that male sex and inflammatory markers (CRP) were prognostic for short-term lung function decline in patients with dcSSc-ILD from the placebo arm of focuSSced, a prospective, randomized controlled trial with short-term follow-up. Detailed analysis of prognostic markers in focuSSced provided higher quality standardized data and more frequent assessment than a real-world cohort. Long-term follow up in the real-world SMART cohort of patients with SSc-ILD demonstrated that decline to ppFVC <70% was associated with male sex, low baseline FVC, and ATA positivity; furthermore, males and patients with dcSSc had lower FVC across the 10-year follow up. Overall, we directly compared a highly selective clinical trial cohort followed up over 48 weeks with a large, single-center, nonselective real-world cohort followed up over 10 years and found congruity among prognostic factors associated with lung function decline. Exploration of potential predictive markers of treatment response in focuSSced showed that prognostic and predictive markers may overlap, and male sex appears to have prognostic and predictive value in determining outcome.

The threshold of ppFVC <70% was a meaningful measure of lung function decline in the long-term real-world SMART cohort. However, ppFVC <70% was not a meaningful measure in the short-term focuSSced clinical trial cohort, a high-risk population that may have already reached the threshold because it was dependent on baseline FVC. Absolute decline in ppFVC ≥10% was a more valuable indicator of lung function decline in focuSSced. This is consistent with data suggesting that short-term changes in surrogate measures of SSc-ILD progression may have important effects on long-term outcomes and mortality [6, 15].

Compared to the SMART cohort, in which ppFVC declined by a mean of −0.3% per year, the decline in ppFVC over 48 weeks was higher (−6.3%) in the focuSSced placebo group. This is likely a result of patients with active dcSSc and evidence of recent disease progression being selected for enrollment in focuSSced and these patients being more likely to experience FVC decline. Only 18 patients in the focuSSced placebo group received immunosuppressive escape therapy, whereas in the SMART cohort, there was background immunosuppressive therapy, limited SSc and dcSSc subsets were included, and patients may not have been disease progressors, which might reduce the average yearly decline in FVC.

IL-6 is a potentially important mediator driving lung fibrosis progression in SSc. IL-6 levels are elevated in the skin and serum of patients with SSc[16-19], particularly those with SSc-ILD [20], and increased serum IL-6 predicts higher mortality, worse skin involvement, and increased pulmonary decline [17, 21]. In the placebo arm of focuSSced, elevated CRP but not serum IL-6 levels was predictive of FVC decline in these patients with dcSSc-ILD; this association was observed for the tocilizumab arm and for the whole cohort (data not shown). This suggests that acute phase markers rather than IL-6 levels may be used as a simple prognostic biomarker in clinical practice in this population to indicate increased risk for FVC decline in the immediate

years after diagnosis when the acute phase response may predict progression in treatment-naive patients. This finding contrasts with a previous observational study that included patients from the SMART cohort (in which background immunosuppressive therapy was allowed) as a second validation cohort, which showed that serum IL-6 >7.67 pg/mL was predictive of FVC decline within the first year after diagnosis and was predictive of death within the first 30 months in SSc-ILD patients[21]. This may be because patients with normal or low levels of IL-6 were not represented in the focuSSced trial cohort or could reflect the impact of background immunosuppression or other factors in real world observational cohorts.

Our predictive analysis showed that the treatment effect of tocilizumab likely offsets lung function decline in the most high-risk patients (younger age, earlier disease duration, or ATA positivity). ATA was not predictive of FVC decline in the SENSCIS trial, which recruited patients at a more fibrotic phase of the disease [22]. This suggests that early lung function decline is driven in part by IL-6,[21] whereas later stages of ILD may be driven by other pathways such as fibrosis. In SSc-ILD, IL-6 production is believed to occur locally via interaction between pulmonary B cells and resident fibroblasts [23]. Elevated IL-6 ≥10 pg/mL was not a predictive marker of response to tocilizumab within the focuSSced population of patients with dcSSc-ILD. Although high IL-6 level likely indicates patients most at risk for severe disease, it has not been shown to predict response to tocilizumab[24-26], which suggests that the disease may have moved to an IL-6-independent phase and the opportunity to intervene might have been missed. This is an apparent paradox that requires further consideration. One hypothesis is that SSc is a multicompartmental disease. Patients recruited to focuSSced had active skin disease and all, including patients in the IL-6 ≤10 pg/mL group, had higher IL-6

levels than healthy controls [17, 19]. In patients with the highest IL-6 levels, there might be additional IL-6-independent mechanisms driving the disease process. This supports the rationale for IL-6 blockade as early as possible in the disease course when it might be mostly driven by IL-6 rather than pathways downstream of IL-6 signaling.

There are some limitations of our comparison between real-world and clinical trial data. SMART cohort patients could receive background immunosuppressive therapy. Cyclophosphamide and mycophenolate have modest efficacy, but treatment effect may not be sustained [11, 27], and we are unable to clearly establish any treatment effects on lung function progression in the SMART cohort due to the lack of a comparator. Another limitation is that there were less frequent data points and less standardization of assessments in SMART than focuSSced. Limitations of the focuSSced data include the fact that lung function endpoints were secondary or exploratory. Some analyses of the SSc-ILD subgroups had small patient numbers, particularly antibody subgroups, which were too small to allow for conclusions. Most patients were ATA positive in the focuSSced SSc-ILD subgroup as this is the most frequent ANA pattern in patients with early dcSSc and ILD; therefore, we cannot comment reliably on other antibody associations. In this analysis, CRP, age, platelets, and disease duration were considered as dichotomous variables for consistency with the focuSSced study design and prespecified statistical analysis plan, which may limit the power of the analysis.

Time-to-event analyses for FVC <50% could not be performed because only a small number of patients with SSc-ILD reached this threshold possibly, because it might not usually occur within the first few years of disease. There were also small patient numbers for analysis of the 70% FVC threshold and no statistically or clinically significant results were observed, likely because a substantial proportion had already reached this by their first assessment. The ≥10% decline in

ppFVC threshold appears to be a more valuable outcome to predict ILD progression in a short-term clinical trial setting.

Heterogeneity in SSc-ILD progression is an issue for clinical trial design[28], as it has a major influence on statistical power and makes interpreting group-level change in lung function difficult because of subgroups that differ in potential treatment benefit. This was evident in abatacept[29] and riociguat[30] clinical trials, in which group-level change in lung endpoints was disappointing but post hoc subgroup analyses appeared more encouraging. This could reflect lack of efficacy of the investigational drugs and/or the trials not being enriched for patients with progressive lung disease. Results from clinical trials, with strict inclusion criteria, may not be considered generalizable to a real-world cohort. However, congruity in predictors of lung function decline between the 10-year outcome analysis in SMART and the 48-week analysis in focuSSced suggests that models developed from real-world data can be applied to short-term outcomes relevant to clinical trials and clinical practice for early management of SSc-ILD. Prognostic biomarkers such as CRP can be readily measured in SSc-ILD patients at diagnosis and could be used to risk-stratify patients early to identify those who may experience SSc-ILD progression and ultimately benefit most from early immunomodulatory treatment with tocilizumab.

Our study demonstrates that although there are likely to be differences in characteristics between a real-life cohort of patients with SSc and patients in a clinical trial, there were shared predictors of progression over 48 weeks in the clinical trial and longer-term outcomes in the real-world cohort. Male sex was associated with lower FVC in both populations and raised inflammatory markers were associated with lower FVC in the focuSSced clinical trial population. We observed differences in the treatment effect of tocilizumab in the clinical trial population; however,

interleukin-6 ≥10 pg/mL was not predictive of response to tocilizumab. These results suggest that subgroups may be identified in which certain pathways or mediators are more relevant, which is important for future clinical trial design and application of results to real-world populations.

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**Data Availability Statement**

Qualified researchers may request access to individual patient level clinical trial data through the clinical study data request platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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## Tables and Figures

**Table 1** Demographics and clinical features of study cohorts.

| **focuSSced ILD Cohort (*N* = 136)** | | | |
|---|---|---|---|
| **Baseline characteristic** | **Placebo SC QW *n* = 68** | **Tocilizumab 162 mg SC QW *n* = 68** | **All Patients *N* = 136** |
| Female, n (%) | 55 (80.9) | 53 (77.9) | 108 (79.4) |
| Age (years) | | | |
| Mean (SD) | 48.7 (13.3) | 47.6 (12.5) | 48.1 (12.9) |
| Median (Min, Max) | 50.0 (20, 73) | 48.0 (19, 72) | 48.5 (19, 73) |
| Duration of SSc, months | | | |
| Median (IQR) | 17.0 (9.4–31.6) | 18.3 (8.6–36.0) | 17.6 (9.4–33.8) |
| Mean (SD) | 22.6 (16.6) | 23.0 (17.2) | 22.8 (16.8) |
| ppFVC | | | |
| Median (IQR) | 82.7 (71.3–92.3) | 78.1 (66.9–87.5) | 80.5 (68.7–90.9) |
| Mean (SD) | 81.5 (14.9) | 77.7 (13.9) | 79.6 (14.5) |
| IL-6 at screening, pg/mL | | | |
| <10, n (%) | 47 (69.1) | 45 (66.2) | 92 (67.6) |
| ≥10, n (%) | 21 (30.9) | 23 (33.8) | 44 (32.4) |
| CRP, mg/mL | | | |
| Median (IQR) | 4.1 (1.3–9.3) | 4.8 (1.5–12.4) | 4.3 (1.5–9.9) |
| Mean (SD) | 8.1 (13.0) | 11.2 (17.4) | 9.6 (15.4) |

| | | | |
|---|---|---|---|
| ESR, mm/h | *n* = 66 | *n* = 64 | *n* = 130 |
| Median (IQR) | 35.0 (25.0–45.0) | 36.0 (27.0–45.0) | 35.0 (27.0–45.0) |
| Mean (SD) | 36.2 (19.3) | 37.2 (17.7) | 36.7 (18.5) |
| Platelet count, $\times 10^9$/L | | | |
| Median (IQR) | 285.5 (228.5–355.0) | 315.0 (250.5–392.5) | 298.5 (240.5–378.0) |
| Mean (SD) | 297.0 (92.2) | 323.7 (95.1) | 310.4 (94.3) |
| Antinuclear antibody | 58 (95.1) | 64 (98.5) | 122 (96.8) |
| positive, n (%) | *n* = 61 | *n* = 65 | *n* = 126 |
| Anti–centromere | 1 (1.6) | 1 (1.5) | 2 (1.6) |
| antibody positive, n (%) | *n* = 63 | *n* = 66 | *n* = 129 |
| Anti–RNA polymerase 3 | 6 (9.5) | 13 (19.7) | 19 (14.7) |
| antibody positive, n (%) | *n* = 63 | *n* = 66 | *n* = 129 |
| Anti–topoisomerase 1 | 43 (68.3) | 45 (68.2) | 88 (68.2) |
| antibody positive, n (%) | *n* = 63 | *n* = 66 | *n* = 129 |
| **SMART ILD Cohort (*N* = 505)** | | | |
| Male, n (%) | | 109 (21.6) | |
| Age at SSc onset, mean (SD) | | 47.1 (13.3) | |
| dcSSc subset, n (%) | | 249 (49.3) | |
| Overlap syndromes, n (%) | | 99 (19.6) | |
| Autoantibodies, n (%) | | | |
| Anti-centromere | | 36 (7.1) | |
| Anti-topoisomerase 1 | | 204 (40.4) | |
| Anti-RNA polymerase | | 59 (11.7) | |

| | |
|---|---|
| Anti-U3RNP | 15 (3.0) |
| Anti-PmScl | 26 (5.1) |
| Other[a] | 98 (19.4) |
| ANA+/ENA− | 83 (16.4) |
| ANA− | 18 (3.6) |
| Organ complications | |
| Clinically significant pulmonary fibrosis | 474 (93.9) |
| Pulmonary hypertension | 99 (19.6) |
| Cardiac scleroderma[a] | 32 (6.3) |
| Renal crisis | 38 (7.5) |

[a]Defined as hemodynamically significant arrhythmias, pericardial effusion, or congestive heart failure (left ventricular ejection fraction below 50%) requiring specific treatment in the absence of other known cardiac causes.

CRP: C-reactive protein; dcSSc: diffuse cutaneous systemic sclerosis; ESR: erythrocyte sedimentation rate; ILD: interstitial lung disease; IL-6: interleukin-6; IQR: interquartile range; ppFVC: percent predicted forced vital capacity; QW: every week; SC: subcutaneously.

[a]Includes anti-Th/To, SL, Ku, Jo1, Ro, La, XR, nRNP, hnRNP, rRNP, PL4, PL7, PL12, Sm.

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**Table 2** focuSSced placebo arm prognostic factors—multivariable mixed-effect model for ppFVC.

| **Fixed effects parameters** | **β** | **95% CI** | ***P* value** |
|---|---|---|---|
| Male | 1.06 | −7.80, 9.92 | 0.8 |
| Male * week | −0.22 | −0.33, −0.11 | **0.0001** |
| IL-6 ≥ 10 pg/mL | −1.45 | −8.93, 6.02 | 0.7 |
| IL6 ≥ 10 pg/mL * week | −0.03 | −0.12, 0.07 | 0.6 |
| CRP ≥ 6 mg/mL | −9.77 | −16.67, −2.86 | **0.006** |
| CRP ≥ 6 mg/mL * week | −0.08 | −0.17, 0.02 | 0.1 |
| High IL-6 receptor level | 1.59 | −5.47, 8.66 | 0.7 |
| High IL-6 receptor level * week | 0.02 | −0.07, 0.11 | 0.7 |
| Platelets > 330 × $10^9$/L | 2.11 | −5.71, 9.94 | 0.6 |
| Platelets > 330 × $10^9$/L * week | −0.10 | −0.20, 0.003 | 0.06 |
| ATA positive | −7.22 | −14.92, 0.48 | 0.07 |
| ATA positive * week | −0.07 | −0.17, 0.03 | 0.2 |
| Age >65 years | 1.36 | −9.60, 12.31 | 0.8 |
| Age >65 years * week | 0.05 | −0.10, 0.19 | 0.5 |
| Disease duration >2 years | 7.11 | −0.11, 14.33 | 0.05 |
| Disease duration >2 years * week | 0.09 | −0.001, 0.18 | 0.05 |

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* = interaction term between the parameter and time in study (weeks); ATA: anti-topoisomerase 1 antibody; CRP: C-reactive protein; FVC: forced vital capacity; IL-6: interleukin-6; ppFVC: percent predicted forced vital capacity.

The model for each stratum factor was fitted with ppFVC as the outcome, with week, treatment group, interaction of week and treatment group, stratum factor, interaction of stratum factor and week as covariates. Interaction of stratum factor and week, and three-way interaction of stratum factor, week and treatment group, were additionally included while exploring the effect of interaction term of stratum factor and week. All models take into account the random subject effect of intercept and week. Bold text indicates statistical significance ($P$ <0.05).

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**Table 3** SMART prognostic factors—multivariable mixed-effect model for FVC.

| **Fixed effects parameters** | **β** | **95% CI** | ***P* value** |
|---|---|---|---|
| Time, years (centered at 1 year) | −0.41 | −0.78, −0.03 | **0.03** |
| Age at onset, years (centered at 45 years) | 0.32 | 0.19, 0.45 | **<0.001** |
| Male | −3.28 | −7.69, 1.13 | 0.1 |
| Male * Time (centered at 1 year) | −0.62 | −1.19, −0.05 | **0.03** |
| dcSSc subset | −5.57 | −9.24, −1.90 | **0.003** |
| Antibodies | | | |
| Anti-topoisomerase 1 antibody | REF | | |
| Anti-centromere antibody | 2.12 | −6.17, 10.41 | 0.6 |
| Anti-RNA polymerase | 14.60 | 8.78, 20.41 | **<0.001** |
| Anti-U3RNP antibody | 5.51 | −5.12, 16.14 | 0.3 |
| Anti-PMScl antibody | 1.20 | −7.25, 9.65 | 0.8 |
| ANA+ ENA− | −0.52 | −5.74, 4.69 | 0.8 |
| Other antibodies | −0.99 | −6.22, 4.24 | 0.7 |
| Antibodies*Time (centered at 1 year) | | | |
| Anti-topoisomerase 1 antibody | REF | | |
| Anti-centromere antibody | 1.10 | 0.05, 2.15 | **0.04** |
| Anti-RNA polymerase | −0.09 | −0.80, 0.63 | 0.8 |
| Anti-U3RNP antibody | 0.69 | −0.70, 2.09 | 0.3 |
| Anti-PMScl antibody | 0.88 | −0.28, 2.04 | 0.1 |
| ANA+ ENA− | −0.16 | −0.87, 0.56 | 0.7 |
| Other antibodies | 0.93 | 0.26, 1.59 | **0.007** |

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| | | | |
|---|---|---|---|
| Constant | 80.90 | 77.36, 84.45 | **<0.001** |

ANA: antinuclear antibodies; dcSSc: diffuse cutaneous systemic sclerosis; ENA: anti–extractable nuclear antigen; FVC: forced vital capacity.

Bold text indicates statistical significance ($P$ <0.05).

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**Figure Legends**

**Figure 1.** FocuSSced placebo arm prognostic factors

Data are shown as time to ≥10% ppFVC decline according to (A) disease duration, (B) sex, (C) anti-topoisomerase 1 antibodies, and (D) age in the focuSSced placebo arm only.

ppFVC: percent-predicted forced vital capacity.

**Figure 2.** SMART—time to development of threshold FVC levels.

FVC: forced vital capacity.

**Figure 3.** Performance of biomarkers as prognostic factors in the focuSSced tocilizumab arm.

Data are shown for patients in the focuSSced tocilizumab arm only: (A) IL-6, (B) IL-6R, (C) platelets, and (D) CRP.

CRP: C-reactive protein; FVC: forced vital capacity; IL-6: interleukin-6; IL-6R: interleukin-6 receptor; ppFVC: percent-predicted FVC.

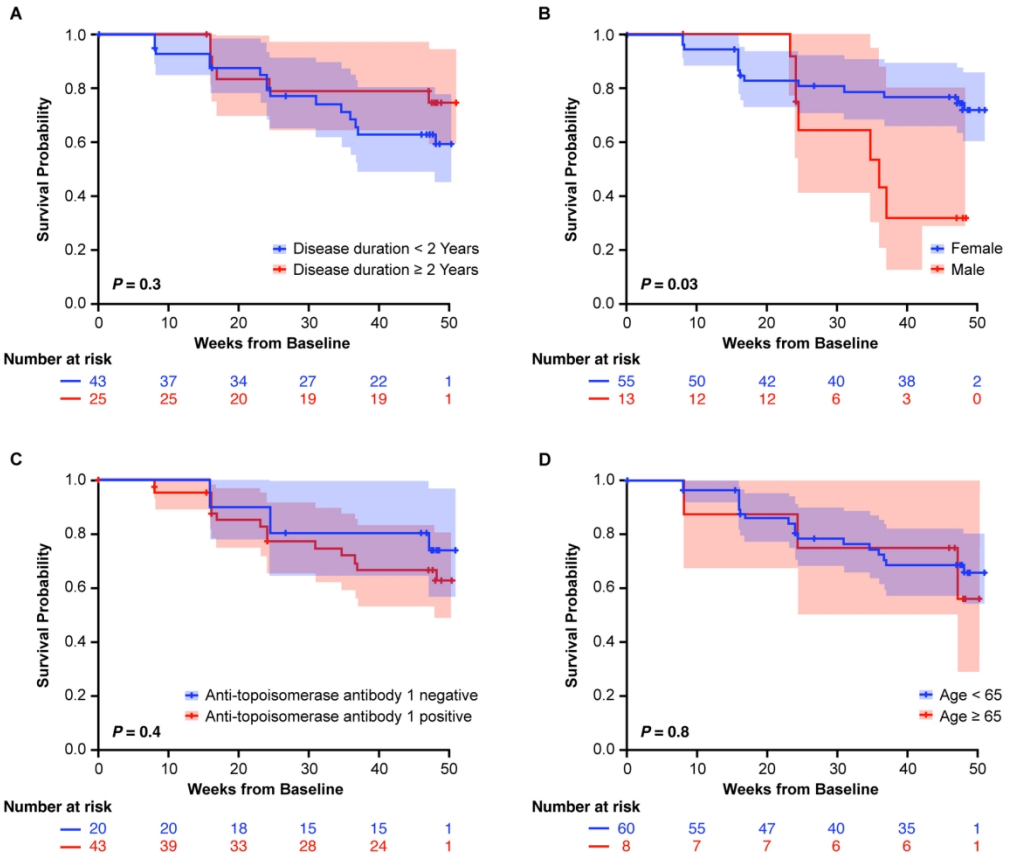


Fig 1

159x135mm (300 x 300 DPI)

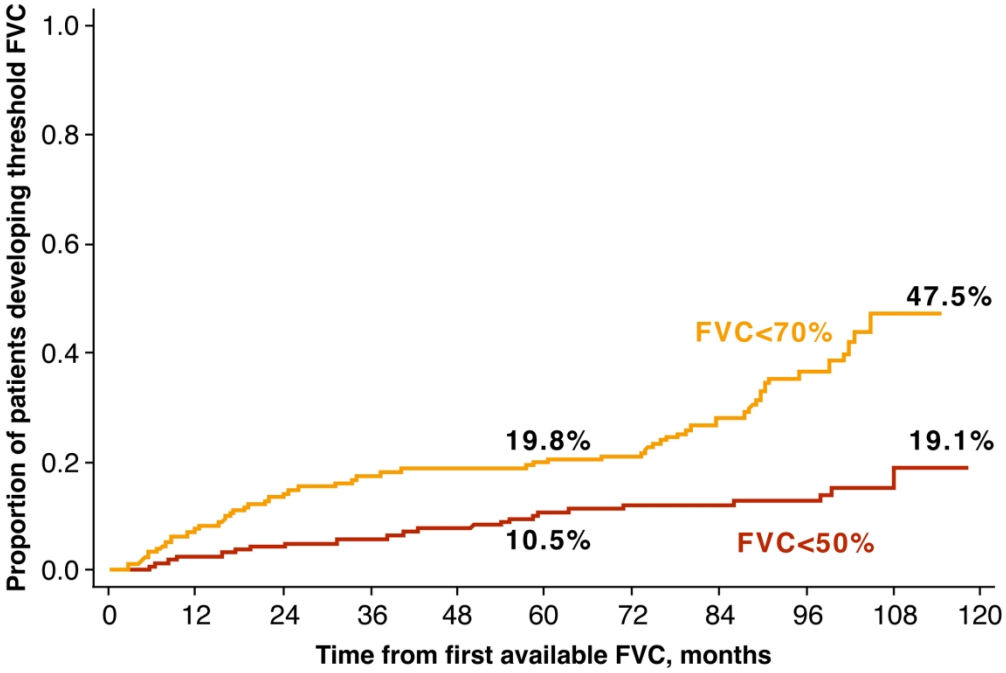


Fig 2

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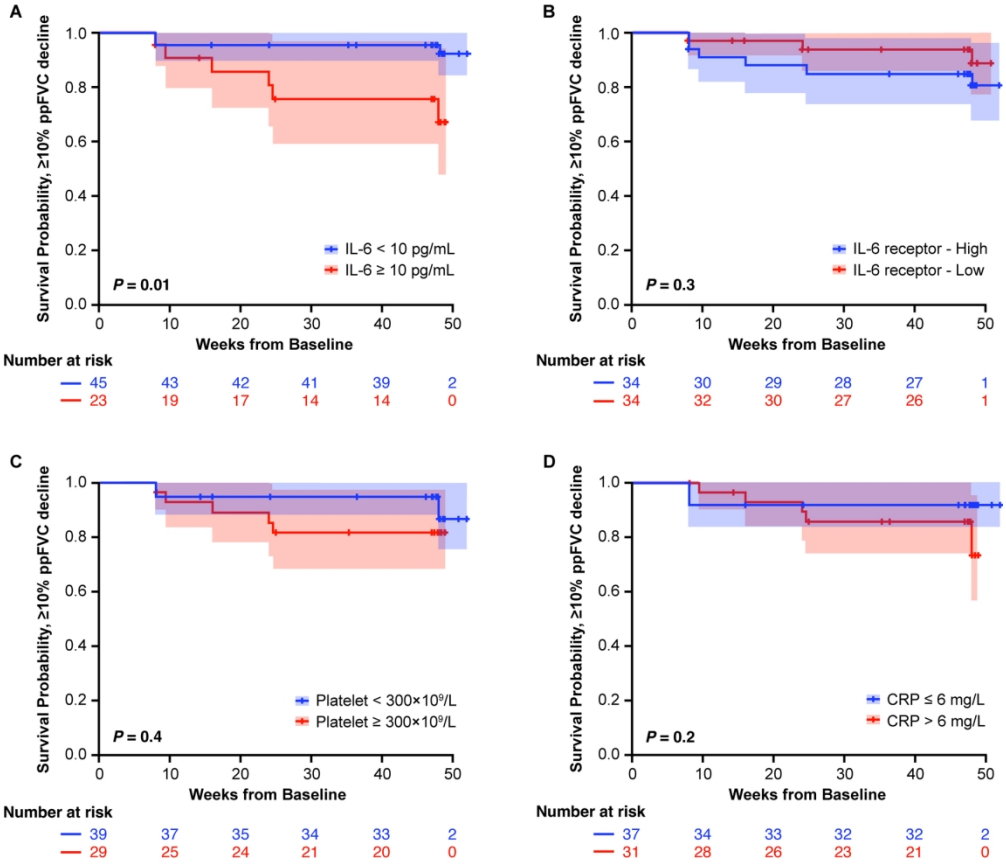


Fig 3

157x135mm (300 x 300 DPI)