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Tocilizumab Prevents Progression of Early Systemic Sclerosis–Associated Interstitial Lung Disease

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Objective. Tocilizumab (TCZ) has demonstrated lung function preservation in 2 randomized controlled trials in early systemic sclerosis (SSc). This effect has yet to be characterized in terms of radiographically evident quantitative lung involvement. We undertook this study to assess the impact of TCZ on lung function preservation in a post hoc analysis, stratifying treatment arms according to the degree of lung involvement.

Methods. The focuSSced trial was a phase III randomized placebo-controlled trial of TCZ in patients with SSc and progressive skin disease. Participants underwent baseline and serial spirometry along with high-resolution chest computed tomography at baseline and at week 48. Quantitative interstitial lung disease (QILD) and fibrosis scores were assessed by computer software. We classified QILD into the following categories of lung involvement: mild (>5–10%), moderate (>10–20%), and severe (>20%).

Results. Of 210 participants recruited for the trial, 136 patients (65%) had ILD. The majority of these patients (77%) had moderate-to-severe involvement (defined as >10% lung involvement). The TCZ arm demonstrated preservation of forced vital capacity percent predicted (FVC%) over 48 weeks (least squares mean change in FVC% = −0.1) compared to placebo (−6.3%). For mild, moderate, and severe QILD, the mean ± SD change in FVC% in the TCZ arm at 48 weeks were −4.1 ± 2.5% (n = 11), 0.7 ± 1.9% (n =19), and 2.1 ± 1.6% (n = 26), respectively, and in the placebo group were −10.0 ± 2.6% (n = 11), −5.7 ± 1.6% (n = 26), and −6.7 ± 2.0% (n = 16), respectively. Similar treatment-related preservation findings were seen independent of fibrosis severity.

Conclusion. TCZ in early SSc–associated ILD with progressive skin disease stabilized FVC% over 48 weeks, independent of the extent of radiographically evident QILD.

INTRODUCTION

The majority of systemic sclerosis (SSc) patients will develop interstitial lung disease (ILD) (1,2). The disease process of SSc-associated ILD (SSc-ILD) usually proceeds through different phases. The initial phase is associated with findings from high-resolution computed tomography (HRCT) of the chest that predominantly show ground-glass opacity with minimal fibrotic changes (considered by some to be immunoinflammatory), followed by more dense fibrotic changes with a nonspecific interstitial pneumonia pattern on HRCT scans; however, some patients may present with findings of usual interstitial pneumonitis (3). Those

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at risk of progressive disease have an archetype: early, diffuse cutaneous systemic sclerosis (dcSSc), with elevated acute-phase reactants such as C-reactive protein (CRP) level and topoisomerase I (topo I) antibody positivity (4–7). Patients with these high-risk features, especially those with disease in the initial phase of development, represent an important target for early intervention, as ILD is largely irreversible in SSc (4,8).

Tocilizumab (TCZ) is an anti–interleukin-6 (anti–IL-6) agent (IgG1 humanized anti–IL-6 receptor monoclonal antibody), approved for use in rheumatoid arthritis, giant cell arteritis, juvenile idiopathic arthritis, Castleman's disease, and other immune-mediated diseases. Two well-designed randomized controlled trials of TCZ in early dcSSc demonstrated a significant lung preservation effect in the treatment arm compared to placebo (9,10). This effect has yet to be characterized in terms of radiographically evident quantitative lung involvement.

In this post hoc analysis, we comprehensively characterized the ILD participants in the focuSSced trial (10), assessed the relationship between degree of total lung involvement and fibrosis (using well-established quantitative HRCT measurements) and lung physiology, and evaluated the treatment effect of TCZ compared to placebo on forced vital capacity percent predicted (FVC%) and quantitative HRCT. Investigating the treatment effects in terms of radiographic changes in this cohort at high risk for progression of ILD provides important insight into disease pathophysiology and potential mechanisms of therapeutic benefit.

PATIENTS AND METHODS

Study design. This phase III trial (ClinicalTrials.gov identifier: NCT02453256) was a multicenter, randomized, double-blind placebo-controlled trial with 1:1 randomization to active treatment (1 subcutaneous injection of 162 mg TCZ per week) or placebo for 48 weeks (10). Background immunosuppressive therapy was not allowed in the trial, but escape therapy was allowed for prespecified skin and lung function progression and SSc-related complications.

Participants. All patients met the 2013 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria (11), with disease onset <60 months from the onset of their first non–Raynaud's phenomenon sign or symptom, and had a modified Rodnan skin thickness score (MRSS) (12) between 10 and 35. All patients had early progressive skin disease with diffuse cutaneous distribution, because the main goal of the trial was to evaluate beneficial impact of TCZ on MRSS score. Participants also had elevated acute-phase reactants (≥1 of the following: CRP level >6 mg/liter, erythrocyte sedimentation rate >28 mm/hour, or platelet count >330 × 10^9/liter), and active disease was defined as having >1 of the following at screening: disease duration ≤18 months, MRSS increase of ≥3, involvement of 1 new body area and MRSS increase of ≥2, or involvement of 2 new body areas (each within the previous 6 months), or ≥1 tendon friction rub. The presence of lung disease was not required for enrollment. The study was approved by the institutional review boards of all participating sites, written informed consent was obtained from all participants, and the study was conducted in compliance with the Declaration of Helsinki.

Outcome measures. Serial spirometry plus diffusing capacity for carbon monoxide corrected for hemoglobin (DL_{CO}) was conducted at weeks 8, 16, 24, 36, and 48, based on the American Thoracic Society/European Respiratory Society Consensus Statement recommendations (13). Patients performed 3–8 exhalations into a spirometer, and the highest value was recorded. Patients received HRCT scans at baseline and week 48, completed at maximal inspiration. Images were acquired from 30 multidetector CT scanner models from 4 manufacturers, using a standardized procedure and following strict quality control protocols. HRCT quantification was performed on all scans based on previous publications (14–16).

The quantitative ILD (QILD) score refers to the summation of ground-glass opacities, honeycombing, and fibrotic reticulation, while the quantitative lung fibrosis (QLF) score refers to quantitative fibrosis (fibrotic reticulation) alone. Both scores range from 0% to 100% involvement of the whole lung (17). All scans had QILD and QLF measurements; ILD was identified visually by a thoracic radiologist (JG) based on the presence of ground-glass opacification and/or fibrosis with a basal predominance. Participants who had minimal interstitial changes without defined ILD were characterized as having no ILD; these cases were screened for factors other than SSc-ILD and were excluded (factors included body habitus, atelectasis, bronchitis, aspiration, and bronchiectasis). QILD cutoff points were set as minimal (≤5%), mild (>5–10%), moderate (>10–20%), or severe (>20%), based on the following: 1) classification by a chest radiologist (JG), and 2) findings from Goh et al that demonstrate total lung involvement of >20% was associated with higher mortality in a longitudinal cohort (18). Cutoff points for QLF were organized in tertiles according to the range (0.1–18.5%) of involvement.

Statistical analysis. Continuous and categorical variables were summarized using the mean ± SD and percentages, respectively. We used *t*-tests to compare baseline FVC% according to baseline QILD and QLF cutoffs. Spearman's correlation coefficients were calculated for scatterplots of baseline FVC% according to numerical baseline QILD and QLF scores, separately. To assess how the baseline QILD or QLF score affects the change in FVC% over time, we fitted linear mixed-effect models, with change in FVC% as the outcome. Covariates included the following: 1) baseline FVC%, 2) treatment arm, 3) study time points, 4) baseline QILD/QLF group, 5) interaction of baseline FVC% and study time point, 6) interaction of treatment arm and study time point, 7) interaction of baseline QILD/QLF group and treatment arm, 8) interaction of baseline QILD/QLF group and study time

point, and 9) 3-way interaction of treatment arm, study time point, and baseline QILD/QLF group. We obtained least squares means (LSMs) from the models and plotted the LSM to show the FVC% change trend. Ninety-five percent confidence intervals (95% CIs) were calculated. No data were imputed. All analyses were done using SAS software (version 9.4).

RESULTS

Baseline characteristics of patients with ILD. The distribution of patients according to treatment arm and baseline radiographic assessments are shown in Supplementary Figure 1 (available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41668/abstract). Two hundred ten participants were randomized and received treatment (placebo arm [n = 106], TCZ arm [n = 104]). Of these patients, 136 were confirmed by a thoracic radiologist to have ILD based on HRCT imaging performed at baseline. Table 1 shows the baseline characteristics of the overall population (n = 210) compared to the subset of patients with ILD (n = 136), which was further divided by treatment arm. Three participants were confirmed as having ILD based on baseline visual assessment of HRCT scans, but the quantitative measurements (including QILD and QLF scores) were missing. Compared to those without ILD, the remaining 133 patients with ILD had numerically lower FVC% and DLco percent predicted (DLco%), a higher CRP level, and a greater proportion of anti–topo I antibody positivity. ILD patients had a mean ± SD FVC% of 79.6 ± 14.5% and a mean ± SD QILD of 18.7 ± 11.1%; most of the QILD score was made up of ground-glass opacities (mean ± SD 14.9 ± 8.3%), with a mean ± SD QLF of 3.0 ± 3.6%. There were no significant differences between the TCZ and placebo arms in the ILD groups at baseline (Table 1).

Moderate-to-severe whole-lung involvement with limited fibrosis in majority of ILD patients. Baseline QILD scores of 133 patients were stratified into 4 groups corresponding to minimal (≤5%), mild (>5–10%), moderate (>10–20%), and severe (>20%) lung involvement. The majority of patients with ILD (n = 102; 77%) had moderate or severe lung involvement, as defined by a QILD of >10% (range 10.2–52.6) (Table 2). Higher degrees of QILD scores were associated with increasing MRSS scores, percentages of anti–topo I antibody positivity, lower baseline FVC% and DLco%, and higher QLF scores. Table 2 also shows ILD patients stratified according to QLF tertiles (0.1–1.0%, 1.1–2.7%, or 2.8–18.5%), with approximately two-thirds of patients (n = 89; 67%) having <2.8% fibrosis. Similar to QILD, increasing QLF scores were associated with

Table 1. Baseline characteristics of the overall focuSSced population and those with ILD detected on HRCT scans*

	Total patients (n = 210)	ILD patients (n = 136)	TCZ group with ILD (n = 68)	Placebo group with ILD (n = 68)
Demographics				
Female, %	81.4	79.4	77.9	80.9
Age, years	48.2 ± 12.4	48.1 ± 12.9	47.6 ± 12.5	48.7 ± 13.3
SSc duration, months	22.6 ± 16.5	22.8 ± 16.8	23.0 ± 17.2	22.6 ± 16.6
Disease features†				
Total MRSS	20.3 ± 6.8	20.8 ± 7.0	20.7 ± 6.8	20.9 ± 7.2
CRP, mg/liter	7.9 ± 13.1	9.6 ± 15.4	11.2 ± 17.4	8.0 ± 13.1
ANA positive, no. (%)	183 (92.4)	124 (96.9)	65 (98.5)	59 (95.2)
Anti–topo I positive, no. (%)	103 (51.0)	90 (68.7)	46 (68.7)	44 (68.8)
Anti-RNAP positive, no. (%)	35 (17.3)	19 (14.5)	13 (19.4)	6 (9.4)
ACA positive, no. (%)	17 (8.4)	2 (1.5)	1 (1.5)	1 (1.6)
PFTs				
FVC, ml	2,996.7 ± 836.8	2,885.4 ± 835.8	2,826.8 ± 873.7	2,944.1 ± 798.3
FVC%	82.1 ± 14.8	79.6 ± 14.5	77.7 ± 13.9	81.5 ± 14.9
DLco%‡	75.6 ± 18.9	70.4 ± 16.9	68.7 ± 16.8	72.1 ± 17.0
QILD measurements, whole lung %§				
HRCT total QILD	15.9 ± 11.4	18.7 ± 11.1	20.5 ± 12.8	16.8 ± 8.8
Ground-glass opacity	13.0 ± 8.8	14.9 ± 8.3	16.2 ± 9.5	13.6 ± 6.7
QLF	2.3 ± 3.3	3.0 ± 3.6	3.5 ± 4.2	2.5 ± 3.0
Honeycombing	0.4 ± 1.2	0.4 ± 1.3	0.5 ± 1.5	0.3 ± 1.2

* Except where indicated otherwise, values are the mean ± SD. None of the differences between the tocilizumab (TCZ) and placebo groups were significant. SSc = systemic sclerosis; MRSS = modified Rodnan skin thickness score; CRP = C-reactive protein; PFTs = pulmonary function tests; FVC% = forced vital capacity percent predicted; DLco% = diffusing capacity for carbon monoxide corrected for hemoglobin percent predicted.
† Data were not available for all patients, as follows: for antinuclear antibody (ANA) positivity (total patients, n = 198; interstitial lung disease [ILD] patients, n = 128; TCZ arm, n = 66; placebo arm, n = 62); for anti–topoisomerase I (anti–topo I), anti–RNA polymerase (anti-RNAP), and anticentromere antibody (ACA) positivity (total patients, n = 202; ILD patients, n = 131; TCZ arm, n = 67; placebo arm, n = 64).
‡ Data were not available for all patients, as follows: total patients, n = 208; ILD patients, n = 135; TCZ arm, n = 68; placebo arm, n = 67.
§ Three patients were confirmed to have ILD based on baseline visual assessment of high-resolution computed tomography (HRCT), but data on quantitative measurements (including quantitative ILD [QILD] and quantitative lung fibrosis [QLF] scores) were missing. For these parameters, data were not available for all patients, as follows: total patients, n = 202; ILD patients, n = 133; TCZ arm, n = 67; placebo arm, n = 66.

Table 2. Baseline characteristics of ILD patients stratified by QILD and QLF involving the whole lung*

		QILD severity				QLF severity		
	Total ILD (n = 133)†	Minimal, ≤5% (n = 6)	Mild, >5–10% (n = 25)	Moderate, >10–20% (n = 54)	Severe, >20% (n = 48)	First tertile, 0.1–1.0% (n = 45)	Second tertile, 1.1–2.7% (n = 44)	Third tertile, 2.8–18.5% (n = 44)
Demographics								
Female, %	79.0	66.7	76.0	83.3	77.1	77.8	81.8	77.3
Age, years	48.0 ± 13.0	45.2 ± 16.6	45.5 ± 11.3	45.9 ± 13.3	52.1 ± 12.3	43.2 ± 12.7	48.5 ± 12.4	52.5 ± 12.3
SSc duration, months	22.9 ± 16.9	24.4 ± 13.5	22.3 ± 16.6	27.0 ± 17.2	18.5 ± 16.5	22.3 ± 13.5	26.5 ± 19.6	19.9 ± 16.9
Disease features†								
Total MRSS	20.8 ± 7.1	16.6 ± 7.3	18.8 ± 5.8	20.9 ± 7.6	22.3 ± 6.7	19.7 ± 6.9	20.9 ± 7.4	21.9 ± 6.8
CRP, mg/liter	9.8 ± 15.5	31.0 ± 39.6	5.4 ± 8.3	11.4 ± 16.8	7.5 ± 9.0	10.9 ± 18.7	11.5 ± 17.0	6.8 ± 9.1
ANA positive, no. (%)	121 (96.8)	6 (100)	24 (100)	48 (96.0)	43 (95.6)	42 (97.7)	40 (97.6)	39 (95.1)
Anti–topo I positive, no. (%)	88 (68.8)	4 (66.7)	15 (62.5)	33 (66.0)	36 (75.0)	28 (65.1)	26 (63.4)	34 (77.3)
Anti-RNAP positive, no. (%)	19 (14.8)	1 (16.7)	3 (12.5)	5 (10.0)	10 (20.8)	4 (9.3)	9 (22.0)	6 (13.6)
ACA positive, no. (%)	2 (1.6)	0	1 (4.2)	1 (2.0)	0	1 (2.3)	1 (2.4)	0
PFTs								
FVC, ml	2,881.4 ± 833.6	3,483.3 ± 1,079.0	3,268.8 ± 1,031.4	2,945.7 ± 672.4	2,532.1 ± 720.8	3,216.4 ± 908.1	2,817.5 ± 656.4	2,602.7 ± 810.8
FVC%	79.5 ± 14.5	88.4 ± 18.3	85.4 ± 13.1	81.1 ± 14.4	73.6 ± 12.9	84.8 ± 14.6	79.6 ± 13.9	74.0 ± 13.1
DL_{CO}%‡	70.4 ± 17.1	88.5 ± 19.7	85.3 ± 17.2	67.3 ± 12.9	63.6 ± 14.9	75.9 ± 17.4	70.9 ± 17.0	64.0 ± 14.9
QILD measurements, whole lung %§								
HRCT total QILD	18.7 ± 11.1	4.0 ± 0.9	7.8 ± 1.4	14.5 ± 2.8	30.8 ± 8.6	9.8 ± 4.2	16.4 ± 5.6	30.1 ± 10.3
Ground-glass opacity	14.9 ± 8.3	3.7 ± 0.8	6.9 ± 1.2	12.3 ± 2.7	23.5 ± 7.2	8.9 ± 3.9	14.0 ± 5.4	22.0 ± 8.8
QLF	3.0 ± 3.6	0.3 ± 0.1	0.8 ± 0.6	1.5 ± 1.0	6.1 ± 4.5	0.6 ± 0.3	1.7 ± 0.4	6.8 ± 4.3
Honeycombing	0.43 ± 1.3	0	0	0.3 ± 0.9	0.8 ± 2.0	0.1 ± 0.5	0.3 ± 0.9	0.9 ± 2.0

* Except where indicated otherwise, values are the mean ± SD. See Table 1 for definitions.
† Data were not available for all patients, as follows: for ANA positivity (total ILD patients, n = 125; mild QILD, n = 24; moderate QILD, n = 50; severe QILD, n = 45; first tertile QLF, n = 43; second tertile QLF, n = 41; third tertile QLF, n = 41); for anti–topo I, anti-RNAP, and ACA positivity (total ILD patients, n = 128; mild QILD, n = 24; moderate QILD, n = 50; severe QILD, n = 48; first tertile QLF, n = 43; second tertile QLF, n = 41).
‡ Data were not available for all patients, as follows: total ILD patients, n = 132; severe QILD, n = 47; third tertile QLF, n = 43.
§ Three patients were confirmed to have ILD based on baseline visual assessment of HRCT, but data on quantitative measurements (including QILD and QLF scores) were missing.

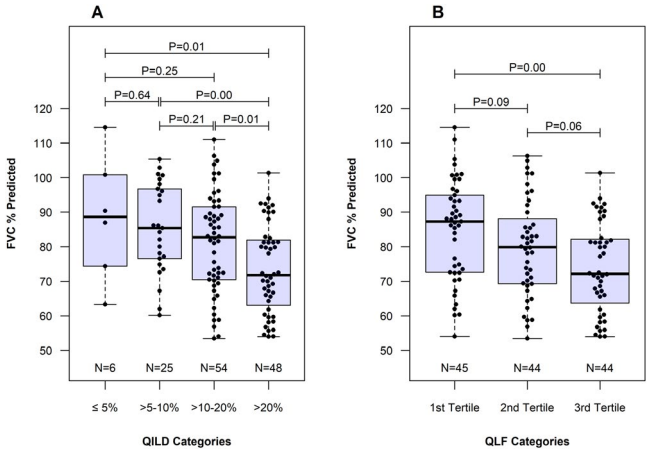

Figure 1. Relationship of forced vital capacity percent predicted (FVC%) with increasing severity of baseline quantitative interstitial lung disease (QILD) (**A**) and with increasing severity of baseline quantitative lung fibrosis (QLF) (**B**). Data are shown as box plots. Each box represents the upper and lower interquartile range. Lines inside the boxes represent the median. Whiskers represent the minimum and maximum values. Each symbol represents an individual subject.

higher percentages of anti–topo I antibody positivity and QILD, and lower baseline FVC% and DLco%.

Inverse correlation of QILD and QLF with FVC%. Figure 1 demonstrates an inverse relationship between baseline FVC% and degree of QILD; baseline FVC% significantly declined with each escalating QILD cutoff point. The mean baseline FVC% in patients with severe QILD was significantly lower (mean ± SD 73.6 ± 12.9%) compared to those with minimal QILD (mean ± SD 88.4 ± 18.3%; $P = 0.01$), mild QILD (mean ± SD 85.4 ± 13.1%; $P = 0.00$), and moderate QILD (mean ± SD 81.1 ± 14.4%; $P = 0.01$). There is an inverse correlation between baseline FVC% and QILD, with a correlation coefficient of –0.36 ($P = 0.00$). Figure 1 also demonstrates a similar inverse relationship between baseline FVC% and QLF, with the mean baseline FVC% significantly higher in the first tertile compared to the third tertile ($P = 0.00$). The correlation coefficient was also –0.36 ($P = 0.00$).

Stabilization by TCZ of FVC% over 48 weeks for mild-to-severe baseline QILD and all ranges of baseline QLF scores. The TCZ arm demonstrated preserved FVC% over 48 weeks: the LSM of FVC% change was –0.1% for TCZ and –6.3% for placebo (Figure 2). The difference between treatment groups was 6.2% ($P < 0.0001$). Figure 2 shows the mean trend over 48 weeks of FVC% change, accounting for the covariates listed in Methods; the results are separated by treatment arm and stratified according to the extent of QILD. As there were only 2 and 4 evaluable patients with ≤5% QILD in the placebo and TCZ groups, respectively, they were excluded from what is depicted in Figure 2. Specifically, those with >5% QILD in the TCZ group showed FVC% stabilization over 48 weeks; this preservation was not influenced by the escalating degree of QILD involvement. For mild, moderate, and severe QILD, the mean ± SD change in FVC% in the TCZ arm at 48 weeks were –4.1 ± 2.5% (n = 11), 0.7 ± 1.9% (n =19), and 2.1 ± 1.6% (n = 26), respectively, and in the placebo group were –10.0 ± 2.6% (n = 11), –5.7 ± 1.6% (n = 26), and –6.7 ± 2.0% (n = 16), respectively. A pairwise comparison at week 48 in the TCZ arm showed no significant differences between the mild, moderate, and severe QILD strata. Those with >5% QILD in the placebo arm showed worsening

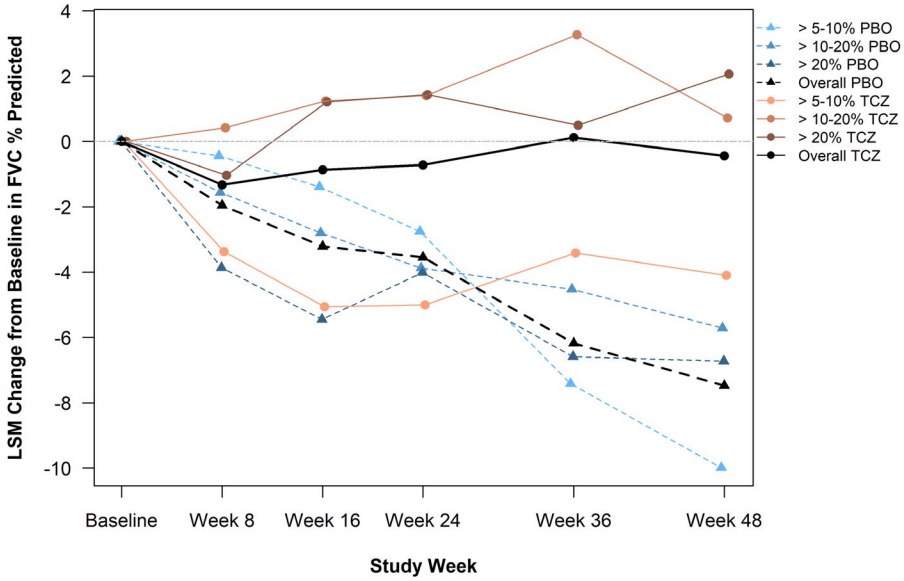

Figure 2. Mean trend over time of change in forced vital capacity percent predicted (FVC%) in the interstitial lung disease (ILD) patients, according to treatment group and quantitative ILD (QILD) score of the whole lung. The QILD severity category of ≤5% was removed from this model, as there were only 2 evaluable patients in the placebo (PBO) group and 4 evaluable patients in the tocilizumab (TCZ) treatment group with ≤5% QILD over 48 weeks. LSM = least squares mean.

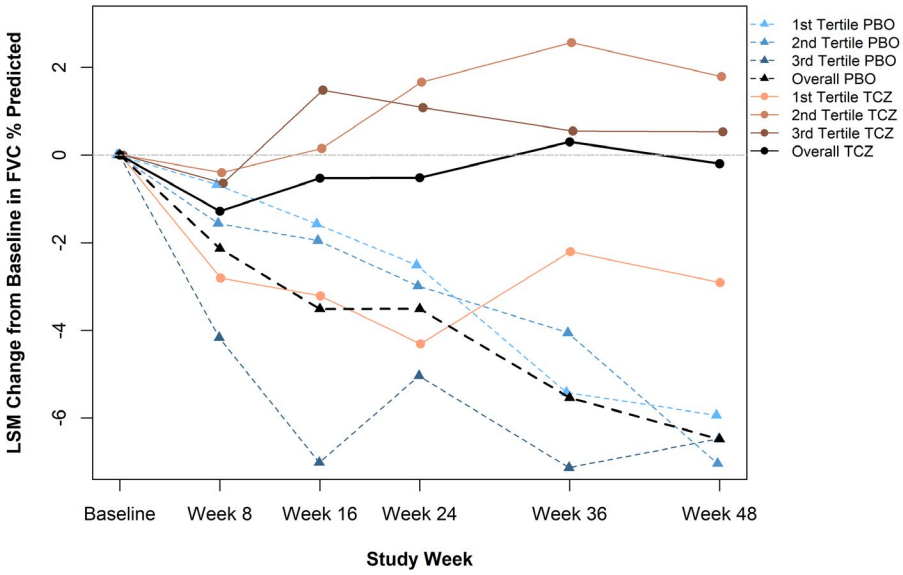

Figure 3. Mean trend over time of FVC% in the ILD patients, according to treatment group and quantitative lung fibrosis score of the whole lung. See Figure 2 for other definitions.

FVC% decline, also with no significant pairwise differences in the trajectory of decline based on QILD severity.

Figure 3 shows a similar preservation effect in the TCZ arm, which was not present in the placebo arm when stratified according to QLF severity. The mean trend over time of FVC% change, accounting for the covariates listed in Methods, did not differ based on the extent of QLF for either the TCZ or placebo arm.

Stabilization by TCZ of QILD and QLF over 48 weeks, for all ranges of baseline QILD and QLF scores. Table 3 shows QILD and QLF scores at baseline and at 48 weeks, separated by treatment arm and stratified according to baseline QILD and QLF cutoff points. As expected, higher baseline QILD and QLF scores reflected higher QILD and QLF scores at 48 weeks. At 48 weeks, the overall QILD scores for the TCZ arm showed significant improvement (mean −1.8% [95% CI −3.8, 0.09]; $P = 0.02$). This benefit appears to be largely driven by high degrees of QILD at baseline; patients with >20% QILD showed the largest improvement of any of the subsets (mean −4.9 [95% CI −8.5, −1.2]; $P = 0.01$). In terms of fibrosis, there was a significant increase in QLF scores at 48 weeks in the placebo arm (mean 0.7 [95% CI 0.3, 1.2]; $P = 0.00$) that was not seen in the TCZ arm (mean −0.5 [95% CI −1.3, 0.3]; $P = 0.12$). This decline in the placebo arm appears to be driven by worsening of QLF scores in the first and second tertiles.

DISCUSSION

In an earlier phase II trial, TCZ showed preservation of FVC% compared to the placebo group in a population of patients with early dcSSc; fewer patients in the TCZ arm showed a decline in FVC% (10% in the TCZ group versus 23% in the placebo group had ≥10% absolute decrease in FVC%) (9). Based on these preliminary findings, the focuSSced trial was designed showing that, in patients with early dcSSc, the effect of lung function preservation was replicated over 48 weeks (mean decline in the TCZ group −0.6% versus −4.0% in the placebo group; $P = 0.002$) (10). In the present study, we performed a post hoc analysis using individual patient data from the focuSSced trial and demonstrated that ~65% of patients with early dcSSc had HRCT-defined ILD, with 77% of participants having >10% total lung involvement (as assessed by QILD). The preservation of FVC in the TCZ arm did not vary according to baseline QILD or QLF score, emphasizing the importance of early intervention to retard progression for those with even mild lung involvement. In addition, the placebo arm showed worsening lung fibrosis on HRCT scans at 48 weeks, whereas the TCZ arm showed attenuation of development of progressive fibrosis.

Our population in the focuSSced trial included an at-risk group for progressive ILD: early dcSSc patients with progressive skin disease and elevated acute-phase reactants. This cohort may represent an immunoinflammatory phase, rather than advanced-stage fibrotic ILD studied in previous SSc-ILD trials. Four large prior studies (e.g., the Scleroderma Lung Study I [SLS I] [19] and SLS II [20], the FAST trial [21], and the SENSCIS trial [22]) included patients with both limited cutaneous SSc and dcSSc, with a median disease duration of ≤7 years, and included patients who were categorized as having clinical ILD based on respiratory symptoms (grade ≥2 exertional dyspnea according to baseline Mahler Dyspnea Index [23] in SLS I and SLS II) and fibrosis (≥10% of the lungs in the SENSCIS trial) (4,24,25). Participants in these trials had moderate-to-severe fibrotic disease: subjects in SLS II had a mean ± SD QLF score of 8.6 ± 6.9%, and subjects in the SENSCIS trial had a mean ± SD visual fibrosis score of 36.8 ± 21.8 in the treatment arm and of 35.2 ± 20.7

Table 3. Patient QILD and QLF scores at baseline and at week 48*

	Baseline, mean (95% CI) [n]		Week 48, mean (95% CI) [n]		Change from baseline, mean (95% CI) [n]	
	TCZ group	Placebo group	TCZ group	Placebo group	TCZ group	Placebo group
Whole-lung QILD						
Overall (n = 103)	21.1 (17.6, 24.5) [55]	16.0 (13.8, 18.1) [48]	19.2 (16.2, 22.3) [55]	17.4 (14.9, 19.9) [48]	−1.8 (−3.8, 0.09) [55]†	1.5 (−0.3, 3.3) [48]
≤5% (n = 4)	3.9 (1.5, 6.3) [3]	4.3 (NA) [1]	3.6 (−1.2, 8.4) [3]	5.9 (NA) [1]	−0.3 (−3.8, 3.2) [3]	1.6 (NA) [1]
>5–10% (n = 19)	7.2 (6.0, 8.4) [9]	8.0 (7.0, 9.0) [10]	7.8 (5.0, 10.6) [9]	11.6 (6.6, 16.7) [10]	0.6 (−1.6, 2.7) [9]	3.6 (−0.9, 8.1) [10]
>10–20% (n = 43)	15.1 (13.8, 16.4) [19]	14.4 (13.2, 15.6) [24]	15.7 (12.6, 18.7) [19]	16.8 (14.9, 19.9) [24]	0.6 (−2.3, 3.4) [19]	2.4 (0.06, 4.7) [24]
>20% (n = 37)	33.2 (29.5, 36.8) [24]	25.8 (22.6, 29.0) [13]	28.3 (24.5, 32.1) [24]	24.0 (18.2, 29.7) [13]	−4.9 (−8.5, −1.2) [24]‡	−1.9 (−6.0, 2.3) [13]
Whole-lung QLF						
Overall (n = 104)	3.7 (2.6, 4.9) [55]	2.3 (1.4, 3.2) [49]	3.3 (2.3, 4.2) [55]	3.0 (2.0, 4.1) [49]	−0.5 (−1.3, 0.3) [55]	0.7 (0.3, 1.2) [49]§
First tertile (n = 35)	0.6 (0.4, 0.7) [15]	0.6 (0.5, 0.8) [20]	0.7 (0.3, 1.0) [15]	1.1 (0.7, 1.5) [20]	0.09 (−0.2, 0.4) [15]	0.5 (0.06, 0.8) [20]§
Second tertile (n = 36)	1.7 (1.5, 1.9) [18]	1.7 (1.4, 1.9) [18]	1.7 (1.1, 2.3) [18]	3.1 (2.0, 4.1) [18]	0.01 (−0.7, 0.7) [18]	1.4 (0.5, 2.3) [18]§
Third tertile (n = 33)	7.6 (5.4, 9.7) [22]	6.3 (3.2, 9.3) [22]	6.3 (4.6, 8.0) [22]	6.4 (2.4, 10.4) [11]	−1.3 (−3.3, 0.7) [22]	0.1 (−1.3, 1.6) [11]

* Negative score denotes improvement. QILD data are missing for 33 patients: 19 patients dropped out between weeks 0 and 48 (7 in the TCZ arm and 12 in the placebo arm), and 14 were active through week 48 but had missing data at week 48 (6 in the TCZ arm and 8 in the placebo arm). QLF data are missing for 32 patients: 19 dropped out between weeks 0 and 48 (7 in the TCZ arm and 12 in the placebo arm), and 13 were active through week 48 but had missing data at week 48 (6 in the TCZ arm and 7 in the placebo arm). NA = not applicable (i.e., the 95% confidence interval [95% CI] could not be calculated, as n = 1) (see Table 1 for other definitions).
† $P = 0.02$ versus baseline, by Wilcoxon's signed rank test.
‡ $P = 0.01$ versus baseline, by Wilcoxon's signed rank test.
§ $P = 0.00$ versus baseline, by Wilcoxon's signed rank test.

in the placebo arm (24,26). With the exception of the FAST trial (FVC% 80.1% and 81.0% in the treatment and placebo arms, respectively), participants in these studies demonstrated FVC% impairment: 68.1% in SLS I, 66.5% in SLS II, and 72% in SENSCIS (19,20,22).

Placebo-controlled trials and observational cohort studies inform our understanding of the natural progression of SSc-ILD; these data play an important role in illuminating the pathogenesis of SSc-ILD progression in our group with additional clinical ILD patients (26–30). The resulting mean ± SD rate of decline of FVC in the focuSSced placebo group was 228.2 ± 394.2 ml over 48 weeks, or an FVC% of ~6.5%, which was considerably higher than those previously reported. For instance, the FAST trial demonstrated a mean decline of 3.0% (21), which was similar to that of the SLS I trial (2.6%) (19), and the SENSCIS cohort showed a decline of 2.6%, or mean ± SD 93.3 ± 13.5 ml, over 52 weeks (22). As such, our current analysis may influence trial design by providing a template to target early ILD, in which the participants have no or minimal respiratory symptoms, and include more patients with progressive fibrotic ILD, where treatment impact may be easier to detect (31).

Considerable variability in screening for SSc-ILD with HRCT still exists (32). There is increasing consensus that all patients with SSc should receive screening with HRCT (33). Our data demonstrate the value of obtaining HRCT scans at the time of diagnosis: pulmonary function tests (PFTs) are not sensitive enough to accurately assess the presence of ILD, and delays in treatment initiation may lead to irreversible disease (25,34). Recently, the Fleischner Society published a consensus statement on interstitial lung abnormalities (35). They acknowledged that abnormalities identified during screening for ILD in high-risk groups (e.g., those with SSc) are not considered to be interstitial lung abnormalities because they are not incidental (35). Data analysis shows that QILD involvement of >5% (with a majority of patients having involvement in their lower body areas) was associated with a large decline in FVC% in the placebo group over 48 weeks, which was mirrored in those with >10% QILD in the placebo group, highlighting the need for universal screening with HRCT in early dcSSc.

A unified treatment algorithm does not yet exist for SSc-ILD. Recent published work has established evidence-based consensus statements on medical management of SSc-ILD; however, these do not address the varying subsets of SSc-ILD severity that impact clinical treatment decisions in practice (4,24,25). Our treatment algorithm classified patients as having either subclinical ILD (those with minimal ILD and preserved lung function) or clinical ILD (those with moderate-to-severe ILD and/or decline in PFTs). Based on the current data, we propose to treat those with subclinical ILD with at-risk features (4,24,25). As evidence accumulates for treatment effects in subsets of SSc-ILD, practice guidelines may favor targeted immunomodulatory therapies in early disease versus antifibrotic therapy in later disease.

Strengths of our analysis include well-characterized data from a clinical trial and utilization of a well-established quantitative lung disease program to provide finer granularity for understanding the lung preservation effect of TCZ. This study serves as an example of the use of quantitative HRCT measurements in understanding SSc-ILD pathophysiology and its response to treatment (14,36).

This analysis is not without limitations. First, the analysis is post hoc and should be considered as hypothesis-generating. Second, while the reduction in FVC reflects fewer functional alveolar units (37), it is an indirect measurement of the flow-resistive properties of the lung (38), and other factors in early SSc may confound the results (e.g., hide-bound chest thickness can cause thoracic restriction, poor patient effort, an inability to form a tight seal around the mouthpiece). This was addressed by standardizing spirometry in the clinical trial. Finally, the minimal (≤5%) QILD group had too few patients to establish any meaningful assumptions. Nevertheless, as the field of quantitative radiomics advances its ability to reliably identify interstitial disease changes this small, even this low percentage of lung involvement may prove to have clinical implications.

In conclusion, early dcSSc is associated with high prevalence of ILD, with 77% having moderate-to-severe ILD. TCZ was effective in preserving the lung function, irrespective of the degree of QILD and QLF at baseline. This likely represents targeting of the immunoinflammatory, early fibrotic phase of the disease (39) and may be a window of therapeutic opportunity to preserve lung function in early dcSSc. We also highlight the natural history of early ILD that may serve as a template for other fibrotic diseases.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Khanna had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ADDITIONAL DISCLOSURES

Author Lin is an employee of Genentech.

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