Tocilizumab Prevents Progression of Early Systemic Sclerosis Associated Interstitial Lung Disease

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Abstract

Objective: Tocilizumab has demonstrated lung function preservation in two randomized controlled trials in early systemic sclerosis (SSc). This effect has yet to be characterized in terms of quantitative radiographic lung involvement. To clarify tocilizumab's impact on lung function preservation, stratified by the degree of radiographic lung involvement in this post-hoc exploration.

Methods: The focuSSced trial was a phase 3, randomized placebo-controlled trial of tocilizumab in patients with SSc and progressive skin disease. Participants had baseline and serial spirometry along with high resolution chest CT at baseline and week 48. Quantitative interstitial lung disease and fibrosis were derived using computer software. We divided quantitative interstitial lung disease in mild (5-10%), moderate (>10-20%), or severe (>20%) categories.

Results*:* Of 210 participants recruited in the trial, 136 [65%] had interstitial lung disease. The majority of these participants had moderate-to-severe involvement defined by >10% lung involvement (77%). The tocilizumab arm demonstrated preserved forced vital capacity over 48 weeks (least squared mean change in% predicted=-0.1) compared to placebo (-6.3). For mild, moderate, and severe QILD, the mean decline in the %pFVC in the tocilizumab arm at 48 weeks were -4.1, 0.7, and 2.1, and in the placebo group were -10.0, -5.7, and -6.7 respectively. Similar treatment-related preservation findings were seen independent of fibrosis severity.

Conclusion: Tocilizumab in early SSc- associated interstitial lung disease with progressive skin disease stabilized forced vital capacity over 48 weeks, independent of the extent of quantitative radiographic interstitial lung disease or fibrosis.

Word Count: 241

Keywords: Clinical Trial, Tocilizumab, Systemic Sclerosis, Quantitative Interstitial Lung Disease, Quantitative Lung Fibrosis

Introduction

Systemic sclerosis (SSc) is a debilitating autoimmune disease hallmarked by immune activation, vasculopathy, and fibrosis of the skin and internal organs(1, 2). The majority of SSc patients will develop interstitial lung disease (SSc-ILD), a complex process of inflammation and potentially fatal lung fibrosis. The SSc-ILD disease process usually proceeds through different phases—the initial phase is associated with high resolution chest computed tomography (HRCT) findings of predominantly ground glass opacity with minimal fibrotic changes (that has been considered by some to be immune-inflammatory) followed by more dense fibrotic changes with a non-specific interstitial pneumonia pattern on HRCT, although some patients may present with finding of usual interstitial pneumonitis(3). Those at risk for progressive disease have an archetype: early, diffuse cutaneous systemic sclerosis (dcSSc), with elevated acute phase reactants like c-reactive protein (CRP) and topoisomerase-1 antibody positivity (4–7). The severity of SSc-ILD may be staged based on the extent of radiographic disease, with visual estimates of <20% of the whole lung involved designated as limited disease and >20% as extensive disease. For intermediate cases where visual discernment is not possible, a threshold of 70% FVC (forced vital capacity) predicted helps to adjudicate(8). This radiographic designation is predictive of morbidity and mortality(9). Thus in patients with these high-risk features, there exists a great need to intervene early as ILD is largely irreversible in SSc (4, 10).

Patients with early SSc have elevated levels of serum IL-6, a cytokine produced by fibroblasts, lymphocytes and macrophages(11). Serum IL-6 levels correlate with the extent of skin fibrosis(12). Patients with lung fibrosis express high concentrations of IL-6. Serum IL-6 levels predict early disease progression and mortality in SSc-ILD, especially those with mild restrictive

lung disease, but did not predict progression or mortality in more those with extensive disease(13). Advances in understanding the molecular mechanism of SSc have led to rational repurposing of existing immunosuppressive and anti-fibrotic agents(14). Tocilizumab (TCZ) is an anti-IL 6 agent (IgG1 humanized anti-IL-6 receptor monoclonal antibody), approved for the use of rheumatoid arthritis, giant cell arteritis, juvenile idiopathic arthritis, Castleman's disease, and other immune-mediated diseases. Although considered a potent anti-inflammatory agent, TCZ was also shown to have a potent anti-fibrotic effect on the dermal fibroblasts in the FaSScinate study(15). FaSScinate (16) was a phase 2 trial of TCZ in participants with early dcSSc (less than 5 years from first non-Raynaud's symptom). While the trial failed to meet its primary endpoint of a decrease in the modified Rodnan skin score over 48 weeks, an exploratory analysis showed preservation of FVC compared to the placebo group; fewer patients in the treatment arm had a decline in the percent predicted FVC (%pFVC): 10% in the TCZ group compared to 23% in the placebo group had $\geq$10% absolute decrease in the %pFVC.

FocuSSced(17) was a phase 3 trial in a similar population, replicating the effect of lung function preservation over time in a key secondary analysis: the baseline %pFVC was 83.9% (15.0) in the placebo group, 80.3% (14.4) in the treatment arm; the mean change at 48 weeks in the TCZ group was -0.6% (-3.2 to 2.0) and -4.0% (-5.3 to 1.7) in placebo, p=0.002. FocuSSced trial participants with ILD represent a contrast when compared to previous trials(18–20) focusing on those with symptomatic clinical ILD, significant baseline impairment in pulmonary physiology, increased CRP and extensive fibrosis on HRCT: these patients are early in their disease, homogenous in their diffuse skin involvement classification, with preserved lung function. In this post-hoc analysis, we comprehensively characterized the ILD participants in the FocuSSced

trial, assessed the relationship between degree of total lung involvement and fibrosis (using well-established quantitative HRCT measurements) and lung physiology, and evaluated TCZ's treatment effect compared to placebo on FVC and quantitative HRCT.

Patients and Methods

Study Design

This phase III trial (ClinicalTrials.gov, NCT02453256) was a multicenter, randomized, double-blind placebo-controlled trial with 1:1 randomization to active treatment (TCZ 162 mg subcutaneous injection/week) vs placebo for 48 weeks(17).

Participants

All participants met 2013 American College of Rheumatology/European League Against Rheumatism classification criteria, with disease onset <60 months from the onset of their first non-Raynaud's Phenomenon symptom, and had a modified Rodnan Skin Score (mRSS) between 10-35 units; all had early progressive skin disease with diffuse cutaneous distribution as the main goal of the trial was to see a beneficial impact of TCZ on the mRSS. Participants also had elevated acute-phase reactants (≥1 of the following: CRP >6mg/L, ESR >28mm/h, or platelet count >330 $x10^9$/L) and active disease defined as >1 of the following at screening: disease duration ≤18 months, mRSS increase ≥3 units, or involvement of one new body area and mRSS increase ≥2 units, or involvement of two new body areas (each within the previous 6 months), and ≥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 Helsinki Declaration.

Outcome Measures

Serial spirometry plus diffusing capacity for carbon monoxide corrected for hemoglobin (DLco) was conducted at weeks 8, 16, 24, 36, and 48, based on the American Thoracic Society/European Respiratory Society (ATS/ERS) Consensus Statement recommendations. Participants performed three to eight exhalations into a spirometer with the highest value recorded. Participants received a baseline and week 48 HRCT, completed at maximal inspiration. Images were acquired from 30 different multidetector CT scanner models from four manufacturers using a standardized procedure following strict quality control protocols. HRCT quantification was performed on all scans based on previous publications (21–23).

Quantitative ILD (QILD) refers to the summation of ground glass opacities, honeycombing, and fibrotic reticulation, while quantitative lung fibrosis (QLF) refers to the quantitative fibrosis (fibrotic reticulation) alone. Both scores range from 0-100% of the whole lung(24). All scans had QILD and QLF measurements; ILD was identified visually by a thoracic radiologist (J. G.) as 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 no ILD. All cases that showed presence of QILD were screened for factors other than SSc-ILD and excluded (these included body habitus, atelectasis, bronchitis, aspiration, bronchiectasis). QILD cutoff points were set as minimal ($\leq$5%), mild (5-10%), moderate (>10-20%), or severe (>20%) based on 1) a chest radiologist's (J.G.) classification and 2) publication by Goh et al., where total lung involvement of >20% was associated with higher mortality in a longitudinal cohort(8). Cutoff points for QLF were set into tertiles given the range (0.1-18.5%) of involvement.

Statistics

Continuous and categorical variables were summarized using means and standard deviations (SD), and percentages, respectively. T test was used to compare baseline %pFVC by baseline QILD and QLF cutoffs. Spearman correlation coefficients were calculated for scatter plots of baseline %pFVC by numerical baseline QILD and QLF, separately. To assess how the baseline QILD or QLF affects the change of %pFVC over time, we fitted linear mixed effect models, with change of %pFVC as the outcome. Covariates included: 1) baseline %pFVC, 2) treatment arm, 3) study time points, 4) baseline QILD/QLF group, 5) interaction of baseline %pFVC 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, 9) three-way interaction of treatment arm, study time point, and baseline QILD/QLF group. We obtained least squares means (LSM) from the models, and plotted the LSM to show the FVC change trend. No data were imputed. All analyses were done via SAS software (Version 9.4).

Results

Baseline characteristics of participants with ILD

Supplemental Figure 1 shows the distribution of patients as it relates to their treatment arm and baseline radiographic assessments. Two hundred and ten participants were randomized and received treatment: 106 to the placebo arm and 104 to the TCZ arm. Of these participants, 136 were confirmed by a thoracic radiologist to have ILD on HRCT done at baseline. Table 1 shows the baseline characteristics of the overall population (n= 210) compared to the subset of participants with ILD (n=136). Three participants had ILD based on baseline visual assessment of HRCT, however their percent quantity of ILD (including QILD and QLF) were missing. Compared to those without ILD, the remaining 133 participants with ILD had numerically lower %pFVC and

%pDLco, higher CRP, and a greater percentage of anti-topoisomerase-1 antibody positivity. ILD participants had a mean (SD) %pFVC of 79.6 (14.5) and 18.7% (11.1) QILD with most of that being ground-glass opacities (14.9% (8.3)); QLF accounted for a mean (SD) of 3.0% (3.6)).

Majority of ILD participants had moderate-to-severe whole lung involvement with limited fibrosis

The baseline QILD of 133 participants were stratified into 4 quartiles corresponding to minimal (≤5%), mild (>5-10%), moderate (>10-20%), and severe (>20%) lung involvement. The majority of participants (77%, or 102/133) with ILD had moderate or severe lung involvement, as defined by QILD of >10% (range 10.2 -52.6, Table 2). Higher degrees of QILD scores were associated with increasing mRSS, percentages of anti-topoisomerase-1 antibody positivity, lower baseline %pFVC and %pDLco, and higher percentages of QLF. Table 2 also shows ILD participants stratified by QLF into tertiles (0.1-1.0%, 1.1-2.7%, 2.8-18.5%), with approximately 2/3rds of participants having ≤2.8% fibrosis (89/133 or 67%). Similar to QILD, increasing QLF% was associated with higher percentages of anti-topoisomerase-1 antibody positivity and QILD, and lower baseline %pFVC and %pDLco.

QILD and QLF Inversely Correlates with the Forced Vital Capacity

Figure 1 demonstrates an inverse relationship between the baseline %pFVC and degree of QILD (Panel A); baseline %pFVC significantly declined with each escalating QILD cutoff point. The mean baseline %pFVC for those with severe QILD was significantly lower (mean 73.6, SD 12.9) when compared to those with minimal (mean 88.4, SD 18.3, p=0.01), mild (mean 85.4, SD 13.1, p=0.0004), and moderate QILD (mean 81.1, SD 14.4, p=0.007). There is an inverse correlation between the baseline %pFVC and QILD, with a correlation coefficient of -0.36, p<0.0001. Figure

1 also demonstrates a similar inverse relationship of the baseline %pFVC with QLF (Panel B), with the mean baseline %pFVC significantly higher in the first tertile compared to the third tertile (p=0.0004). The Spearman correlation was also -0.36 (p=<0.0001).

TCZ Stabilizes FVC Over 48 Weeks for Baseline Mild-to-Severe QILD and All Ranges of Baseline QLF

The TCZ arm demonstrated preserved %pFVC over 48 weeks: the least squared means (LSM) of FVC change was -0.1% for TCZ, and -6.3% for PBO. The difference between treatment group was 6.2% (P<0.0001). Figure 2 shows the mean trend over 48 weeks of the %pFVC change, accounting for covariates listed in methods; the results are separated by treatment arm (TCZ vs PBO) and stratified by the extent of QILD. As there were only 2 and 4 evaluable patients in the PBO and TCZ groups, respectively, with $\leq$5% QILD over 48 weeks, they were excluded from Figure 1. Specifically, those with >5% QILD in the TCZ group showed %pFVC stabilization over 48 weeks; this preservation was not influenced by the escalating degree of QILD involvement. For mild, moderate, and severe QILD, the mean change in the %pFVC in the TCZ arm at 48 weeks were -4.1 (SD: 2.5), N=11, 0.7 (SD: 1.9), N=19, 2.1 (SD: 1.6), N=26 and in the placebo group was -10.0 (SD: 2.6), N=11, -5.7 (SD: 1.6), N=26, -6.7 (SD: 2.0), N=16, respectively. A pairwise comparison at week 48 in the TCZ arm showed no significant differences between the mild, moderate, or severe QILD strata. Those with >5% QILD in the PBO arm showed worsening %pFVC decline, also with no significant pairwise differences in the trajectory of the decline by QILD severity.

Figure 3 shows a similar preservation effect in the TCZ arm, not present in the PBO arm when stratified by QLF severity. The mean trend over time of the %pFVC change, accounting for

covariates listed in methods, separated by treatment arm (TCZ vs PBO) do not differ by the extent of QLF for either the TCZ or the PBO arms.

TCZ Stabilizes QILD and QLF Over 48 Weeks for All Ranges of Baseline QILD and QLF

Table 3 reports QILD and QLF scores at 48-week follow-up stratified by the baseline QILD and QLF cutoff points, for each treatment arm (TCZ vs. PBO). As expected, higher baseline QILD and QLF have higher QILD and QLF values at 48 weeks. In the TCZ arm, there was a significant improvement in QILD at 48 weeks whereas there was statistically significant worsening of QLF in the PBO group in 1st and 2nd tertile.

Discussion

In this post-hoc analysis of the FocuSSced trial, we analyzed the effect of TCZ in an early progressive skin disease cohort with elevated acute phase reactants, an enriched cohort with high prevalence of early SSc-ILD. A majority (77%) of participants had moderate-to-severe extent QILD (defined as >10% involvement), despite approximately half of patients having none-to-mild restrictive lung physiology (mean (SD) FVC was 79.6% (14.5)). Participants treated with TCZ showed preservation of their FVC (average of -13.5mL/year, or approximately 0.2% decline in %pFVC), while those in the placebo arm had a clinically meaningful FVC decline (average of -228mL/year, or approximately 5.8% decline in %pFVC) at 48 weeks. The preservation of FVC in the TCZ arm did not vary by the degree of QILD or QLF, which emphasizes the importance of early intervention to retard progression for those with mild to severe lung involvement in this enriched cohort.

The pathobiology of SSc-ILD is complex, but may be understood in two distinct phases: the antecedent repetitive alveolar endothelial and epithelial cell injury (from environmental triggers, infectious pathogens, or inflammation) promoting innate and adaptive immune system responses, activating fibroblasts, and the consequent differentiation of fibroblasts to myofibroblasts with subsequent lung fibrosis(25). Laboratory analysis linked to the FaSScinate trial investigated the effect of TCZ on the molecular, functional, and genomic properties of explanted fibroblasts from FaSScinate trial participants(15). In this gene expression analysis, it was demonstrated that fibroblasts from treated with TCZ showed attenuated functional properties of SSc fibroblasts (e.g., protein production, contractility, migration), and inhibition of the key pathological pathways associated with SSc(15). The gene expression of those fibroblasts treated with TCZ was downregulated for both the IL-6 pathway and the M2 macrophage, evidence of interruption of IL-6's influence of switching macrophage polarization towards a pro-fibrotic pathway.

IL-6 is an important mediator in the pathogenesis of SSc-ILD and the preservation of FVC in the treatment arm likely represents an intervention interrupting inflammation that would lead to resident fibroblast transformation(26). IL-6 has been shown to be a prognostic biomarker early in SSc-ILD, especially in patients with mild restrictive lung disease (FVC >70%); elevated IL-6 may signal the onset of a progressive disease phase(13) and a window of opportunity to treat mild disease before progressive disease advances. Our hypothesis is supported by data from Phase II TCZ data and is conceptually similar to the recently published data with abatacept in early dcSSc(27, 28). Later disease may be a predominantly fibrotic process which may have less beneficial response to immunomodulatory or anti-inflammatory therapy but respond better to

anti-fibrotic therapies. The ongoing Scleroderma Lung Study III is testing the hypothesis of upfront combination therapy(29).

In our current analysis, a few key contextual factors are important. First, this analysis focuses on a population at high risk for progressive disease with potentially poor outcomes. A recent large retrospective analysis identifying predictors of disease worsening in dcSSc found that those patients with elevated CRP and the presence of lung fibrosis had a median time to severe organ-based dysfunction or death of 1.53 years, compared to 4.48 years for patients without any risk factors(30). Our cohort represents a uniquely early-stage immuno-inflammatory, rather than advanced-stage fibrotic SSc-ILD populations studied in previous SSc-ILD trials. Four key prior studies (e.g., the Scleroderma Lung Study I(18) and II(19), FAST(31), and the SENSCIS(20) trials) included participants with both limited and diffuse cutaneous SSc, with a median disease duration of ≤ 7 years, and enriched for clinical ILD based on respiratory symptoms (at least grade 2 exertional dyspnea according to baseline Mahler Dyspnea Index in the SLS-I and SLS-II studies), and fibrosis (≥10% of the lungs) in the SENSCIS trial. Participants in these trials had moderate-to-severe fibrotic disease: SLS-II had an average (SD) QLF of 8.6% (6.9) and SENSCIS reporting a visual fibrosis score of 36.8 (21.8) in the treatment arm and 35.2 (20.7) in the placebo arm(19, 20) . With the exception of the FAST trial (%pFVC of 80.1% and 81.0% in the treatment and placebo arms, respectively), the studies' participants had %pFVC impairment: 68.1% in SLS-I, 66.5% in SLS-II, and 72% in SENSCIS(18–20). TCZ Phase III trial participants were chosen for their worsening skin disease in diffuse distribution with mild mean (SD) QLF of 3.0% (3.6), and relatively preserved baseline lung function(27, 28). Second, placebo-controlled trials and observational cohort studies inform our understanding of the

natural progression of SSc-ILD; our data have an important role in understanding the pathogenesis of SSc-ILD progression in our enriched group(32–36). The resulting average rate of decline (SD) of FVC in the FocuSSced placebo group was 228.2 mL (394.2) over 48 weeks, or a p%FVC of about 6.5% and considerably higher than those previously reported: the FAST trial(31) had an average decline of 3.0%, which was similar to that of the SLS-I trial (2.6%), and the SENSCIS cohort showed a decline of 2.6%, or 93.3 mL (13.5) over 52 weeks(18, 20). As such, our current analysis may influence trial design by providing a template to target early ILD, where the participants may have none-to-minimal respiratory symptoms, and enrich for progressive fibrotic ILD where treatment impact may be easier to detect(37).

There is considerable variability in screening for SSc-ILD with HRCT(38). Some have argued that only certain subsets, such as dcSSc or those with symptoms or impairment in pulmonary physiology should get HRCT to diagnosis SSc-ILD. These data support patients with early dcSSc obtaining HRCT at the time of diagnosis. PFTs are not sensitive enough to accurately assess the presence of ILD and delays in treatment initiation may lead to irreversible disease(39, 40). Recently, Fleischner Society Writing Committee for Position Paper on interstitial lung abnormalities published consensus statement on interstitial lung abnormalities (ILAs)(41). They acknowledged that abnormalities identified during screening for ILD in high-risk groups (e.g., those with systemic sclerosis) are not considered as ILAs because they are not incidental. In addition, they agreed that the ILAs as non-dependent abnormalities affecting more than 5% of any lung zone (upper, middle, and lower lung zones are demarcated by the levels of the inferior aortic arch and right inferior pulmonary vein)(41). Analysis of our data shows that participants with >5% QILD involvement (majority of whom had involvement of their lower zones) was

associated with a large decline in FVC% in the PBO group over 48 weeks, that 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 work by Hoffman-Vold 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, 26, 42). As evidence accumulates for treatment effects in subsets of SSc-ILD, practice guidelines may favor targeted immunomodulatory therapies in early disease vs. anti-fibrotic therapy in later disease.

Strengths of our post-hoc 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 TCZ's lung preservation effect. This study serves as an example of the use of quantitative HRCT measurements in understanding SSc-ILD pathophysiology and its response to treatment(21, 43).

The analysis is not without limitations. The analysis is post-hoc and should be considered as hypothesis generating. The FVC is a measurement of expiration and is an indirect measure of the flow-resistive properties of the lung(44). The reduction in vital capacity reflects having fewer functional alveolar units(45), but 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). The FVC were standardized in the randomized

clinical trial and our data is supported by stabilization of HRCT findings at week 48 in the TCZ arm and progression in placebo arm.

In conclusion, early dcSSc is associated with high prevalence of ILD, with 77% having moderate-to-severe ILD (defined as QILD>10%). TCZ was effective in preserving the lung function, irrespective of the degree of QILD and QLF at baseline. This likely represents an interruption of the immuno-inflammatory, early fibrotic phase of the disease 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. Finally, our findings are important in establishing TCZ's role in the treatment algorithm for SSc-ILD.

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Table 1: Baseline characteristics of the overall FocuSSced population and those with ILD on HRCT

	All Patients N=210	**ILD** N=136
Demographics		
Females, %	81.4	79.4
Age, mean years (SD)	48.2 (12.4)	48.1 (12.9)
Duration of SSc months, (SD)	22.6 (16.5)	22.8 (16.8)
Disease Features		
Total mRSS, units (SD)	20.3 (6.8)	20.8 (7.0)
CRP, mg/L, (SD)	7.9 (13.1)	9.6 (15.4)
ANA positive, n/N (%)	183/198 (92.4)	124/128 (96.9)
Anti-topoisomerase positive, n/N (%)	103/202 (51.0)	90/131 (68.7)
Anti-RNA polymerase positive, n/N (%)	35/202 (17.3)	19/131 (14.5)
Anti-centromere positive, n/N (%)	17/202 (8.4)	2/131 (1.5)
Baseline Pulmonary Function Assessments		
FVC, in ml, (SD)	2996.7 (836.8)	2885.4 (835.8)
%pFVC, % (SD)	82.1 (14.8)	79.6 (14.5)
%pDL_{CO}, % (SD)	75.6 (18.9); n=208	70.4 (16.9); n=135
Baseline Quantitative ILD Measurements, Whole Lung %*		
HRCT QILD, % (SD)	15.9 (11.4); n=202	18.7 (11.1); n=133
GGO, % (SD)	13.0 (8.8); n=202	14.9 (8.3); n=133
QLF, % (SD)	2.3 (3.3); n=202	3.0 (3.6); n=133
HC, % (SD)	0.40 (1.2); n=202	0.43 (1.3); n=133

*: Three subjects had ILD based on baseline visual assessment of HRCT, however their percent quantity of ILD (including QILD and QLF) were missing.

SSc= Systemic Sclerosis; mRSS= Modified Rodnan Skin Score; CRP= C-Reactive Protein; ANA= Antinuclear Antibody; FVC- Forced Vital Capacity; pFVC= Predicted Forced Vital Capacity; pDLco= Predicted Diffusing Capacity for carbon monoxide corrected for haemoglobin; HRCT = High resolution CT; QILD= Total ILD (ground glass opacities, honeycombing, reticulations) on computer quantification; GGO = Ground glass opacities; QLF= Lung fibrosis (reticulations) on computer quantification; HC = Honeycombing

Table 2: ILD Participants, Stratified by Quantitative Interstitial Lung Disease and Lung Fibrosis involving the Whole Lung

	ILD	**Quantitative Interstitial Lung Disease (QILD) by Ascending Severity**				**Quantitative Lung Fibrosis (QLF) by Ascending Severity**		
Severity Cut-Off	-	Minimal ≤5%	Mild >5-10%	Moderate >10-20%	Severe >20%	1st Tertile 0.1-1.0%	2nd Tertile 1.1-2.7%	3rd Tertile 2.8-18.5%
N	n = 133*	n = 6	n = 25	n = 54	n = 48	n = 45	n = 44	n = 44
Demographics								
Females, %	79.0	66.7	76.0	83.3	77.1	77.8	81.8	77.3
Age, years (SD)	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)
Disease Duration, months (SD)	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 (SD)	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/L (SD)	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 n/N (%)	121/125 (96.8)	6/6 (100)	24/24 (100)	48/50 (96.0)	43/45 (95.6)	42/43 (97.7)	40/41 (97.6)	39/41 (95.1)
Anti-topoisomerase positive n/N (%)	88/128 (68.8)	4/6 (66.7)	15/24 (62.5)	33/50 (66.0)	36/48 (75.0)	28/43 (65.1)	26/41 (63.4)	34/44 (77.3)
Anti-RNA polymerase positive n/N (%)	19/128 (14.8)	1/6 (16.7)	3/24 (12.5)	5/50 (10.0)	10/48 (20.8)	4/43 (9.3)	9/41 (22.0)	6/44 (13.6)
Anti-centromere positive n/N (%)	2/128 (1.6)	0/6 (0.0)	1/24 (4.2)	1/50 (2.0)	0/48 (0.0)	1/43 (2.3)	1/41 (2.4)	0/44 (0.0)
Baseline Pulmonary Function Assessments								
FVC, in ml (SD)	2881.4 (833.6)	3483.3 (1079.0)	3268.8 (1031.4)	2945.7 (672.4)	2532.1 (720.8)	3216.4 (908.1)	2817.5 (656.4)	2602.7 (810.8)
%pFVC (SD)	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)
%pDL_{CO} (SD)	70.4 (17.1); n=132	88.5 (19.7)	85.3 (17.2)	67.3 (12.9)	63.6 (14.9); n=47	75.9 (17.4)	70.9 (17.0)	64.0 (14.9); n=43
Baseline Quantitative ILD Measurements								
HRCT QILD, % (SD)	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)

GGO, % (SD)	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, % (SD)	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)
HC, % (SD)	0.43 (1.3)	0 (0)	0 (0)	0.3 (0.9)	0.8 (2.0)	0.1 (0.5)	0.3 (0.9)	0.9 (2.0)

* Three subjects had ILD based on baseline visual assessment of HRCT, however their percent quantity of ILD (including QILD and QLF) were missing.

SSc= Systemic Sclerosis; mRSS= Modified Rodnan Skin Score; CRP= C-Reactive Protein; ANA= Antinuclear Antibody; FVC- Forced Vital Capacity; pFVC= Predicted Forced Vital Capacity; pDLco= Predicted Diffusing Capacity for carbon monoxide corrected for haemoglobin; HRCT = High resolution CT; QILD= Total ILD (ground glass opacities, honeycombing, reticulations) on computer quantification; GGO = Ground glass opacities; QLF= Lung fibrosis (reticulations) on computer quantification; HC = Honeycombing

Table 3: Quantitative ILD and Fibrosis Scores Comparing Baseline to 48 weeks

	Baseline		**48 week Mean (95% CI)**		**Change from Baseline Mean (95% CI)***	
	TCZ	PBO	TCZ	PBO	TCZ	PBO
Whole Lung QILD (TCZ n=55; PBO n=48)						
≤5%; n=4	3.9 (2.2, 5.5); n=3	4.3 (-); n=1	3.6 (0.3, 6.8); n=3	5.9 (-); n=1	-0.3 (-2.7, 2.1); n=3	1.6 (-); n=1
>5-10%; n=19	7.2 (6.3, 8.1); n=9	8.0 (7.2, 8.8); n=10	7.8 (5.5, 10.0); n=9	11.6 (7.5, 15.7); n=10	0.6 (-1.1, 2.3); n=9, p=0.820	3.6 (-0.07, 7.3); n=10, p=0.113
>10-20%; n=43	15.1 (14.0, 16.2); n=19	14.4 (13.4, 15.4); n=24	15.7 (13.2, 18.2); n=19	16.8 (14.6, 19.0); n=24	0.6 (-1.8, 2.9); n=19, p=0.568	2.4 (0.5, 4.3); n=24, p=0.084
>20%; n=37	33.2 (30.1, 36.2); n=24	25.8 (23.2, 28.4); n=13	28.3 (25.1, 31.5); n=24	24.0 (19.3, 28.7); n=13	-4.9 (-7.8, -1.9); n=24, p=0.008	-1.9 (-5.2, 1.5); n=13, p=0.385
Whole Lung QLF (TCZ n=55; PBO n=49)						
1st Tertile; n = 35	0.6 (0.4, 0.7); n=15	0.6 (0.5, 0.7); n=20	0.7 (0.4, 0.9); n=15	1.1 (0.8, 1.4); n=20	0.09 (-0.1, 0.3); n=15, p=1.00	0.5 (0.1, 0.9); n=20, p=0.004
2nd Tertile; n = 36	1.7 (1.5, 1.9); n=18	1.7 (1.5, 1.9); n=18	1.7 (1.2, 2.2); n=18	3.1 (2.2, 3.9); n=18	0.01 (-0.6, 0.6); n=18, p=0.423	1.4 (0.7, 2.1); n=18, p=0.003
3rd Tertile; n = 33	7.6 (5.8, 9.3); n=22	6.3 (3.7, 8.8); n=11	6.3 (4.9, 7.7); n=22	6.4 (3.1, 9.7); n=11	-1.3 (-2.9, 0.4); n=22, p=0.213	0.1 (-1.0, 1.3); n=11, p=1.000

* Negative score denotes improvement; (-) indicates 95% CI cannot be calculated as n=1.
CI=Confidence Interval; QILD= Total ILD (ground glass opacities, honeycombing, reticulations) on computer quantification; QLF= Lung fibrosis (reticulations) on computer quantification

QILD is missing n=33: 19 dropped out between week 0 and 48 (7 in TCZ arm, 12 in PBO arm) and 14 were active through week 48, but had missing data at week 48 (6 in TCZ arm, 8 in PBO arm).

QLF is missing n=32: 19 dropped out between week 0 and 48 (7 in TCZ arm, 12 in PBO arm) and 13 were active through week 48, but had missing data at week 48 (6 in TCZ arm, 7 in PBO arm).

Figure 1: Relationship between forced vital capacity % predicted and increasing severity of baseline QILD (A) and increasing severity of baseline QLF (B). FVC= Forced Vital Capacity, QILD= Quantitative Interstitial Lung Disease, QLF= Quantitative Lung Fibrosis

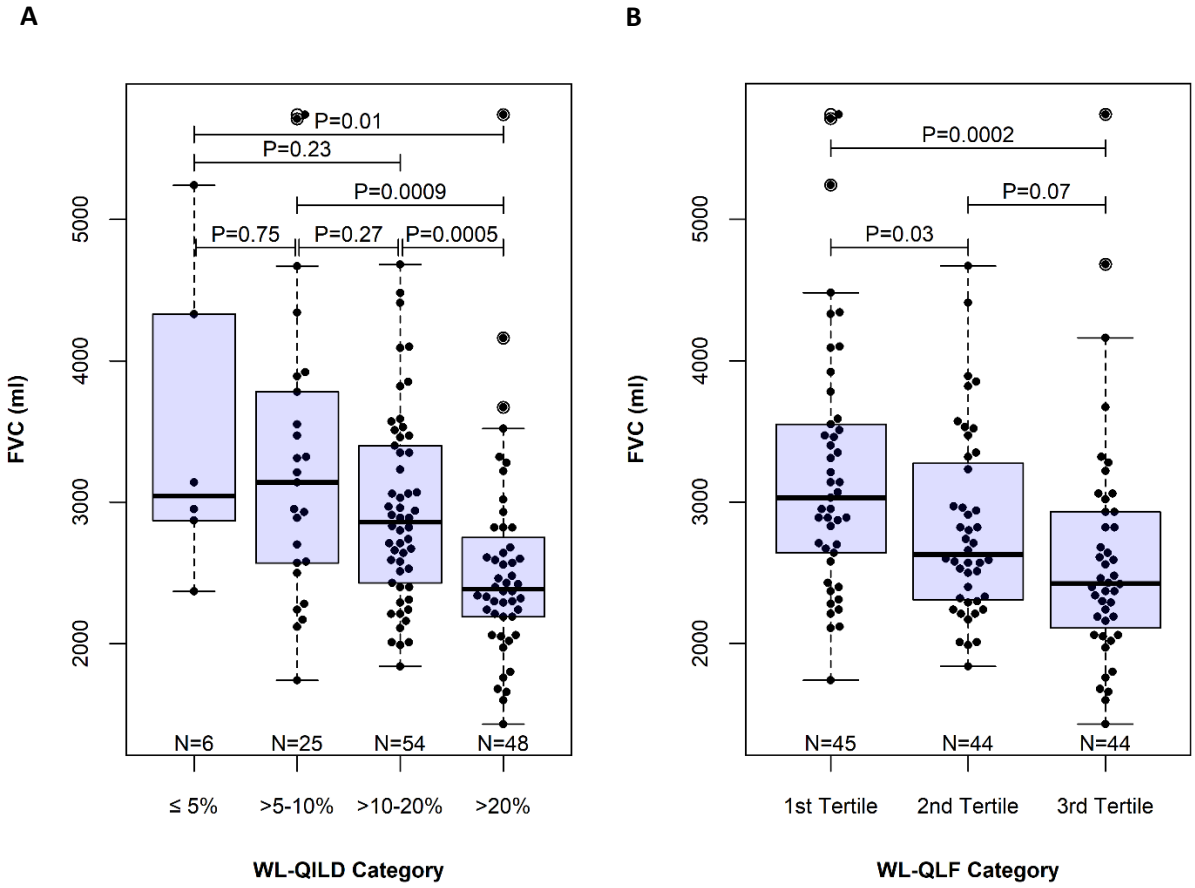
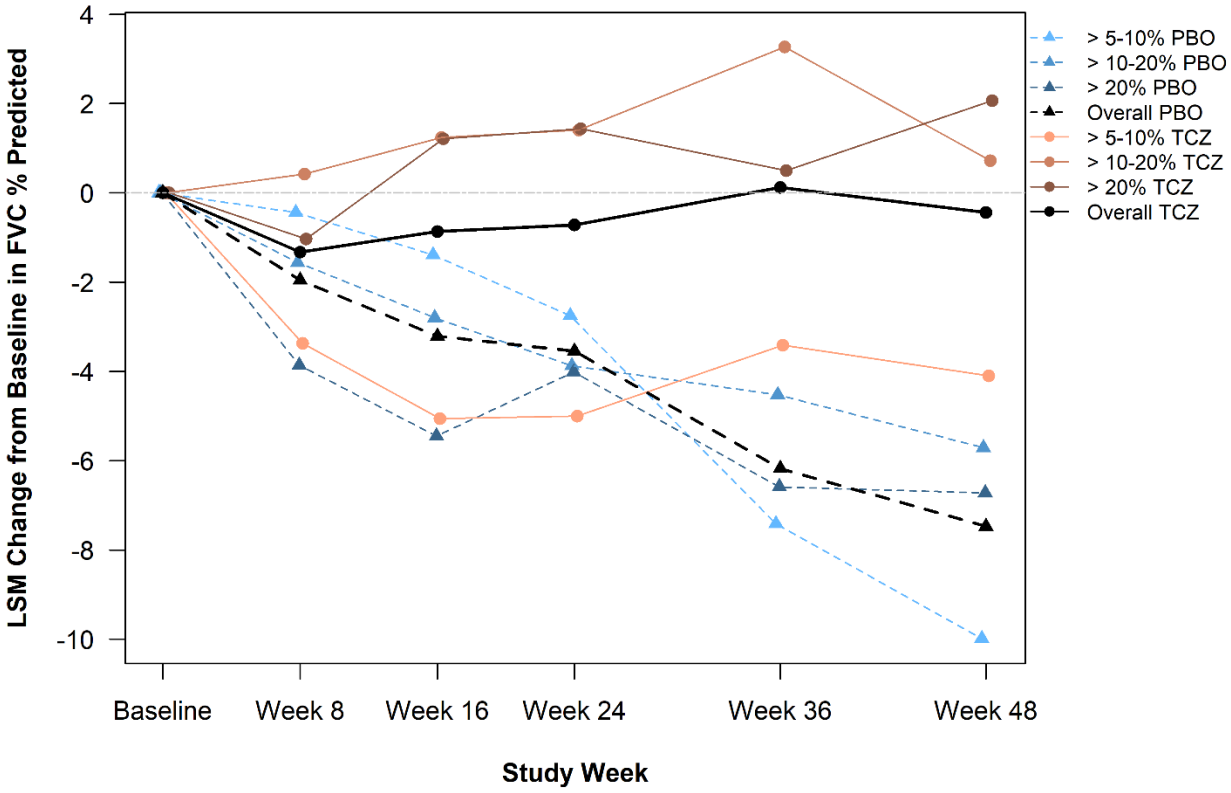
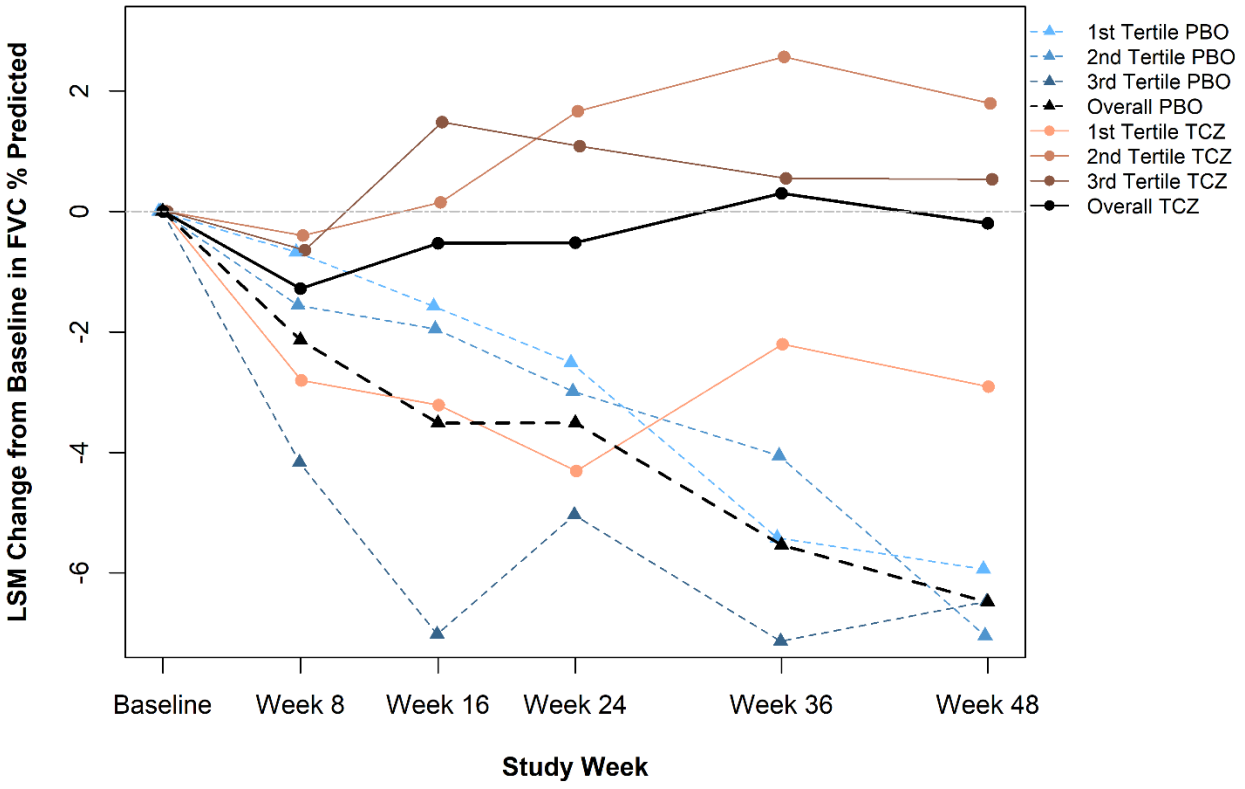


Figure 2: ILD participants showing a mean trend over time of forced vital capacity change by treatment and quantitative ILD of the whole lung. Note: <5% is removed from this model as there were only 2 evaluable patients in the placebo group with <5% QILD over 48 weeks. FVC= Forced Vital Capacity; ILD= Interstitial Lung Disease; QILD= quantitative ILD; PBO= Placebo; TCZ= Tocilizumab



		BSL	WK8	WK16	WK24	WK36	WK48
<=5%	TCZ, N	4	4	3	2	3	3
	PBO, N	2	2	1	2	1	2
> 5-10%	TCZ, N	13	13	11	11	11	11
	PBO, N	12	10	11	11	11	11
> 10-20%	TCZ, N	22	21	21	19	18	19
	PBO, N	32	30	31	29	27	26
> 20%	TCZ, N	28	27	27	24	25	26
	PBO, N	20	19	17	17	16	16

Figure 3: ILD participants showing a mean trend over time of forced vital capacity change by treatment and quantitative lung fibrosis of the whole lung. FVC= Forced Vital Capacity; ILD= Interstitial Lung Disease; PBO= Placebo; TCZ= Tocilizumab



		BSL	WK8	WK16	WK24	WK36	WK48
1st Tertile	TCZ, N	19	19	16	15	15	15
	PBO, N	26	23	23	22	21	22
2nd Tertile	TCZ, N	23	22	21	19	18	21
	PBO, N	21	20	21	21	19	19
3rd Tertile	TCZ, N	25	24	25	22	24	23
	PBO, N	19	18	16	16	15	14