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Journal Club: Efficacy of Tocilizumab in Early Systemic Sclerosis–Related Interstitial Lung Disease

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INTRODUCTION

Interstitial lung disease (ILD) is one of the major reasons for increased morbidity and mortality in patients with systemic sclerosis. The patients with diffuse cutaneous disease, positivity for anti-SCL-70 antibody, elevated inflammatory markers, hypothyroidism, cardiac involvement, elevated creatinine phosphokinase values, and African American ethnicity seem to be at higher risk of developing progressive ILD (1,2). The available treatment options, including mycophenolate, cyclophosphamide, and nintedanib, are only modestly effective at stabilizing lung function in such patients. Tocilizumab is a humanized anti-interleukin-6 (IL-6) receptor antibody that has been successfully used to treat various rheumatological disorders such as rheumatoid arthritis, giant cell arteritis, and Castleman disease, to name a few. Levels of IL-6 are also elevated in patients with systemic sclerosis, and initial studies suggested that blockade of IL-6 activity in the mouse model improved skin disease (3). A phase 2 randomized controlled trial, safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate) (4), using weekly tocilizumab did not show a significant change in the skin disease. Still, it highlighted the possible role of IL-6 inhibitor tocilizumab in improving lung function in ILD related to systemic sclerosis. The tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial investigated the efficacy and safety of tocilizumab in systemic sclerosis–associated skin disease and ILD.

PATIENTS AND METHODS

The focuSSced trial enrolled patients with early systemic sclerosis who had risk factors for the development of progressive disease. The presence of lung disease was not required for enrollment. Patients meeting 2013 American College of Rheumatology/European League Against Rheumatism criteria for systemic sclerosis were enrolled.

Inclusion criteria. Participants met the inclusion criteria if they had a disease duration of 60 months or less; a modified Rodnan skin score (mRSS) of 10 to 35 units, the presence of active disease with more than one of the following characteristics: disease duration of 18 months or less, mRSS increase of at least three units or involvement of one new body area, and mRSS increase of at least two units, or involvement of two new body areas and at least one tendon friction rub; and at least one of the elevated acute phase reactants (C-reactive protein [CRP] >6 mg/L, erythrocyte sedimentation rate > 28 mm/h, or platelet count >330 $\times$ 10^9).

Exclusion criteria. Participants were excluded if the predicted forced vital capacity (FVC) was less than 55% or if the diffusing capacity for carbon monoxide (DLCO) was less than 45%

Baseline characteristics. Eighty-one percent of the participants were female, with a mean age of 48.2 years and a disease duration of less than 2 years, with comparable distribution in the placebo in the tocilizumab group. The mRSS was 20.4 in the placebo group compared with 20.3 in the tocilizumab group. Sixty-five percent of the participants had ILD on high-resolution computed tomography (HRCT) at baseline. The frequency of ILD was similar in the placebo and the tocilizumab group.

Of the patients with baseline ILD on HRCT, 77% of the enrollees had a quantitative ILD (QILD) score of more than 10%, but quantitative lung fibrosis (QLF) was less than 2.8% in 67% of the enrollees, signifying limited fibrosis in a majority of the participants. In addition, patients with ILD at baseline had lower FVC percentage and DLCO, higher CRP level, and anti-SCL-70 antibody positivity, and this correlated with QILD and QLF scores.

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Study design. The focuSSced study was a phase 3, randomized, double-blind, and placebo-controlled trial conducted at multiple sites in 20 countries across the globe. The primary outcome was a change in mRSS at Week 48, and a key secondary endpoint was a change in baseline of FVC percentage predicted at Week 48. mRSS, FVC, and quantitative HRCT were performed at baseline and then at regular intervals. Patient global assessment and physician global assessment were included as secondary endpoints. Some of the exploratory endpoints included a decline (at least 10%) in observed FVC and FVC percentage predicted, change in FVC at Week 24, change in DLCO with at least 15% decline at Week 40, and change in the QLF of the most affected lobe at Week 48. A post hoc analysis (5) was also done with quantitative HRCT to calculate the QILD of the whole lung and QLF of the whole lung. The QILD score refers to the summation of ground glass opacities, honeycombing, and fibrotic reticulation, whereas the QLF score refers to quantitative fibrosis alone. Both scores range from 0% to 100% involvement of the whole lung. All scans had QILD and QLF measurements. QILD scores were categorized as minimal (≤5%), mild (>5-10%), moderate (>10-20%), or severe (>20%), and QLF was organized in tertiles according to the range (0.1-18.5%) of fibrotic involvement.

RESULTS

A total of 212 participants were randomized 1:1 to the weekly tocilizumab (n = 105) versus weekly placebo (n = 107) for 48 weeks. Background immunomodulatory therapy was not allowed at the beginning of this study. The earliest such medications could be added was the sixteenth week of this study for more than 10% decline in percentage predicted FVC or after 24 weeks for worsening skin fibrosis. The primary endpoint was not met, as the least square means (LSM) change at Week 48 between the tocilizumab and the placebo group was only 1.7 with a *P* value of 0.1. However, tocilizumab-treated participants maintained preservation of their baseline lung function. Only 5% of the participants in the tocilizumab group had an absolute decline in FVC of at least 10% compared with 17% in the placebo group. In systemic sclerosis (SSc)-ILD subgroup, the mean change in the baseline FVC was -14 ml in the tocilizumab group and -251 ml in the placebo group at Week 48, with an LSM change of 241 ml. Moreover, the change in the baseline of FVC percentage in the tocilizumab group was only −0.4 compared with −4.6 in the placebo group. In the post hoc analysis, moderate to severe involvement of the whole lung with a QILD score of greater than 10% was found in 77% of the ILD population, but the fibrosis score was low at less than 2.8%. An inverse relationship was noted between FVC percentage and QILD and QLF, with a correlation coefficient of −0.36. No difference was noted between the placebo and the tocilizumab groups in terms of other secondary and exploratory endpoints. Infections were the most common adverse events in both groups, with serious adverse events in 13% of the participants in the tocilizumab arm compared with 17% in the placebo arm. Four patients died, with three deaths in the placebo group being primarily due to cardiac reasons compared with the one death in the tocilizumab arm, which was labeled as an "unknown cause." The outcomes are summarized in Table 1.

Table 1. Summary of major outcomes

Outcomes	Tocilizumab	Placebo	*P* Value
Change in mRSS	−6.1	−4.4	0.10
Percentage change in FVC	−0.4	−4.6	0.002
Absolute change in FVC(ml)	−24	−190	0.0001
Change in HRCT QILD median	−0.9	0.4	0.04
Change in HRCT QLF median	0.0	0.1	0.005
Change in HRCT QLF-LM median	0.3	0.0	0.02
Change in HAQ-DI	−0.11	−0.06	0.45
Treatment failure, %	22	35	0.08
>10% decrease in pFVC, %	13	24	0.08
Serious adverse events, %	13	17	NA
Number of deaths	1	3	NA

Abbreviations: FVC, forced vital capacity; HAQ-DI, health assessment questionnaire-disability index; HRCT, high-resolution computed tomography; mRSS, modified Rodnan skin score; NA, not applicable; pFVC, predicted forced vital capacity; QILD-WL, quantitative interstitial lung disease of the whole lung; QLF-WL, quantitative lung fibrosis of the whole lung; QLF-Wm, quantitative lung fibrosis-most affected lobe.

DISCUSSION

The primary endpoint for the focuSSced trial was not met, as the change in skin thickness (mRSS) from baseline to 48 weeks between the tocilizumab group and the placebo group did not reach statistical significance. However, change from baseline in FVC at Week 48 was significant. The focuSSced trial enrolled patients with early SSc who had poor prognostic features with regard to development and worsening of ILD. Sixty-five percent of the enrolled population in the focuSSced trial had ILD at baseline, and 77% of the patients with ILD were noted to have more than 10% lung involvement as determined by the burden of QILD. It is worth noting that more than 20% of lung involvement on HRCT has been shown to be associated with significant morbidity and mortality (6). In this study, a disconnect was noted between FVC in the total enrolled (82.1 ± 14.8) and those with ILD (79.6 ± 14.5), suggesting the presence of asymptomatic ILD. Thus, the observations from the focuSSced trial provide a therapeutic rationale for obtaining an HRCT scan in any patient with SSc at baseline.

Currently, significant variability exists in screening for ILD in patients with SSc. A global survey (7) observed that only half of the general rheumatologists and two-thirds of scleroderma experts routinely obtained a chest HRCT scan in patients with

Table 2. Characteristics of a few major SSc-ILD clinical trials

Clinical Trial (Yr)	Trial Description	Patient Population	Therapeutic Intervention	Treatment Outcome
SLS 1 (2006)	158 patients in a double-blind, multicenter, and randomized trial	Patients with limited and diffuse SSc and ILD	Oral CYC vs placebo for one year	FVC decline −1% in the CYC group vs −2.6% in the placebo group
SLS 2 (2016)	126 patients in a double-blind, multicenter, and randomized trial	Patients with limited and diffuse SSc and ILD	Oral CYC for one year and then placebo for 1 year vs MMF for 1 year	Predicted FVC improvement of 2.19% in the MMF vs 2.88 in the CYC group
SENSCIS (2019)	576 patients in a double-blind, multicenter, and randomized trial	Patients with limited and diffuse SSc and ILD	Nintedanib with or without MMF vs placebo with or without MMF	FVC decline rate of −1.4% per year in the nintedanib group vs −2.6% per year in MMF
faSScinate (2016)	87 patients in phase 2, randomized, double-blind, and multicenter trial	Patients with progressive SSc of 5 years' duration or less	Weekly TCZ vs placebo	FVC decline of 10% in TCZ group vs 21% in the placebo group at Week 48

Abbreviations: CYC, cyclophosphamide; faSScinate, safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis; FVC, forced viral capacity; ILD, interstitial lung disease; MMF, mycophenolate; SENSCIS, safety and efficacy of nintedanib in systemic sclerosis; SLS-1, Scleroderma Lung Study I; SLS-2, Scleroderma Lung Study II; SSc, systemic sclerosis; TCZ, tocilizumab.

newly diagnosed SSc. This finding also mirrors the observation in other trials (8,9), which showed patients having a normal physical examination and pulmonary function test despite the presence of significant ILD on the HRCT scan. Another notable aspect of these findings was the presence of substantial ILD in the relatively early phase of the disease, with the mean duration of SSc as only 23.1 months in the placebo group and 22.2 months in the tocilizumab group. The focuSSced study reiterated the findings from other trials (10), which showed early severe organ involvement in patients with SSc. In addition, these patients also had a high rate of lung disease progression, with an absolute decline in FVC of at least 10%. Seventeen percent of the participants in the placebo group had an FVC decline of at least 10% compared with only 5% in the group receiving tocilizumab. This has important therapeutic implications, as the treatment guidelines for SSc-related ILD are unclear, and these results support the idea of intervening early.

The tocilizumab intervention's efficacy was also evident, with 21% of the placebo arm participants needing rescue immunomodulatory therapy as opposed to only 9% of the participants in the tocilizumab arm. Moreover, only 10% of the tocilizumab group participants suffered an absolute reduction in the FVC percentage compared with 23% in the placebo arm. An important finding was also related to the tocilizumab's efficacy in preserving lung function regardless of the baseline ILD burden. The presence of ILD was not a prerequisite to participate in this trial, which makes it unique among the SSc-ILD–related trials safety and efficacy of nintedanib in systemic sclerosis (SENSCIS) (11), Scleroderma Lung Study 1 (12), Scleroderma Lung Study 2 (13), and fibrosing alveolitis in scleroderma trial (FAST) (14), which only enrolled patients with established ILD. This limits a comparative analysis of these trials, but these studies' characteristics are summarized in Table 2.

Strengths and limitations. The strengths of this study include that it is a well-organized multicenter, randomized, double-blind, and placebo-controlled trial; there was no requirement for the presence of ILD at baseline for enrollment in the study; quantitative HRCT was used to define the extent of fibrosis and other components of ILD; and no background immunomodulatory therapy was used at enrollment. There were also a few limitations. Ideally, as the primary endpoint was not met, the secondary endpoints should also be considered to have not reached significance. The post hoc analysis should be considered to be hypothesis-generating rather than conclusive. There was minimal representation of the minimal (<5%) QILD group. DLCO could not be included in the analysis, as this was measured using investigators' own equipment.

Application to clinical practice. From this study, a few things can be applied to clinical practice, such as an emphasis on screening for ILD with HRCT in all patients with SSc. This study also opens up the discussion on the cost-effectiveness and the real-world use of quantitative HRCT in evaluating patients with SSc. Tocilizumab could be a viable option to treat SSc-ILD if mycophenolate is not tolerated or contraindicated. It could also be considered as the first-line treatment in patients with early subclinical SSc-ILD associated with the risk factors for disease progression. Finally, this study is a possible backbone for immunomodulatory therapy in the early immunoinflammatory phase of the SSc-ILD.

In conclusion, the focuSSced trial did not show improvement in the SSc-related skin disease with tocilizumab therapy but demonstrated its efficacy in patients with SSc-ILD, regardless of the degree of ILD at the baseline. The United States Food and Drug Administration's approval of tocilizumab is based on the findings of the focuSSced trial, subsequent post hoc analysis, and the faSScinate trial. However, it is not clear how tocilizumab fits in the current treatment strategy for SSc-ILD. Whether it would complement mycophenolate and other treatment options in all patients with SSc-ILD or it would have its niche for a select group of patients as in this trial remains unanswered.

AUTHOR CONTRIBUTIONS

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.

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