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BRIEF REPORT

Impact of Scleroderma-Associated Autoantibodies on Clinical Outcome Assessments: Post Hoc Analysis From a Randomised, Double-blind, Placebo-controlled, Phase 3 Trial of Tocilizumab in Scleroderma

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Objective. Scleroderma-associated autoantibodies (SSc-Abs) are specific in participants (pts) with systemic sclerosis and are associated with organ involvement. Our objective was to assess the influence of baseline SSc-Abs on the trajectories of the clinical outcome assessments (COAs) in a phase III randomized controlled trial.

Methods. We used data on both the groups who received placebo (Pbo) and tocilizumab from the focuSSced trial. The SSc-Ab panel was assessed centrally. We analyzed four groups with SSc-Abs: anti–topoisomerase 1 antibody (ATA), anti–RNA polymerase 3 antibody (RNAP3), anti-centromere antibody, and negative for all three (triple negative). We assessed the impact of baseline SSc-Abs on six COAs: modified Rodnan skin score (mRSS), forced vital capacity (FVC%), Health Assessment Questionnaire Disability Index, patient and clinical global assessments, and American College of Rheumatology (ACR) Composite Response Index in Systemic Sclerosis (CRISS).

Results. We observed that all COAs, except for FVC%, improved for the group who received Pbo during the 48-week period. For mRSS, pts with RNAP3 showed the largest Pbo effect (7.20 per year, n = 14) and smallest for ATA (3.28 per year, n = 49). This trend was also seen for the ACR CRISS (0.00–1.00 scale), with median improvement at week 48 of 0.94 for RNAP3 versus 0.01 for ATA. ATA enriched for FVC% decline of 7.34% per year versus 2.54% per year for RNAP3. In the group who received tocilizumab, similar changes were seen in the mRSS and ACR CRISS with preservation of lung function, irrespective of SSc-Ab type.

Conclusion. Our result shows a differential effect of SSc-Abs on the trajectories of COAs over 48 weeks in group who received Pbo. These findings highlight the importance of incorporating SSc-Abs in trial design, either as a stratification factor or limiting the SSc-Abs that are included in the trials.

INTRODUCTION

Systemic sclerosis (SSc) is a rare autoimmune disorder characterized by progressive fibrosis of the skin and internal organs, vasculopathy, often leading to significant morbidity and mortality.[1] One of the intriguing aspects of SSc is heterogeneity of the disease, both at presentation and over time, and the presence and role of different autoantibodies implicated in the pathogenesis of this disease.[2] Antinuclear antibodies (ANAs) are identified in over 95% of individuals affected by SSc, and they can be detected several years before the onset of the disease.[2] Within this group of antibodies, three prominent and distinctive scleroderma-associated autoantibodies (SSc-Abs) that are universally assessed are as follows: anti-centromere antibody (ACA), anti–topoisomerase 1 antibody (ATA), and anti–RNA polymerase 3 antibody (RNAP3).[2] These SSc-Abs have been linked to diverse clinical manifestations and outcomes or clinical outcome assessments (COAs) in patients with SSc. A COA is a measure that

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describes or reflects how a patient feels, functions, or survives. In clinical trials and observational cohorts, there are clear differences in outcome for skin, lung, and other complications among the subgroups with ANAs that are largely mutually exclusive. However, this likely reflects treatment response and natural history of disease. Clinical trial cohorts such as focuSSced present a convincing opportunity to scrutinize these distinctions. The availability of patients observed over 48 weeks without any background treatment uniquely defines differences in natural history. In this analysis, we aim to assess the impact of baseline SSc-Abs on the trajectories of the modified Rodnan skin score (mRSS), forced vital capacity (FVC%), Health Assessment Questionnaire Disability Index (HAQ-DI), patient global assessment (PGA) of disease, clinician global assessment (CGA) of disease, and the American College of Rheumatology (ACR) Composite Response Index in Systemic Sclerosis (CRISS) in a phase III randomized controlled trial (RCT).

In recent years, there has been increased focus to explore the relationship between SSc-Abs and the COAs. The published data from different clinical cohorts show that the presence of these SSc-Abs has differential effects on these COAs.[3] For example, the ACA is protective against progressive skin and interstitial lung disease (ILD) but increased risk for pulmonary arterial hypertension. On the contrary, RNAP3 and ATA are both associated with high likelihood of diffuse cutaneous SSc (dcSSc), but RNAP3 is associated with rapid skin worsening and risk for scleroderma renal crisis, whereas ATA is associated with progressive skin thickening and progressive ILD.

Recent trials in early SSc continue to show lack of efficacy on COAs, including mRSS, FVC%, and the ACR CRISS. These negative studies have been attributed to lack of efficacy of novel agents and/or poor performance of the COAs, but another key aspect is the heterogeneity in SSc (as influenced in part by SSc-Abs) that may impact the clinical course of these COAs. With increased interest in novel therapies in SSc, there is a critical need to design trials that have a more predictable course of COAs in the group who received placebo (Pbo).

PATIENTS AND METHODS

Patients and data. We used the data from the group who received Pbo and the active group (received tocilizumab) from the focuSSced trial.[4] In this double-blind, Pbo-controlled, phase III trial, participants (pts) included adults with dcSSc for ≤60 months and an mRSS of 10 to 35 at screening and elevated acute-phase reactants who were randomly assigned (1:1) to receive subcutaneous 162 mg tocilizumab or Pbo weekly for 48 weeks, stratified by interleukin-6 levels. No background immunosuppressive therapy was allowed. The primary endpoint was the difference in change from baseline to week 48 in the mRSS. FVC% predicted at week 48 was a key secondary endpoint. The primary endpoint of mRSS was not met. Findings for the secondary endpoint of FVC% predicted indicate that tocilizumab preserves lung function in people with early scleroderma-associated ILD (SSc-ILD). Safety was consistent with the known profile of tocilizumab.

The SSc-Ab panel was performed centrally at the RDL Laboratories (now part of LabCorp) at the screening visit and included tests for the following antibodies using enzyme-linked immunosorbent assay (ELISA): RNAP3 (positive ≥ 20 U/mL) and ATA (positive ≥ 20 U/mL). For the ATA, positive ELISA was confirmed by the immunodiffusion. The ACA (positive ≥ 1:40 dilution) was performed using the immunofluorescence.

COAs. The mRSS is a measure of skin thickness and has been used as a primary or secondary outcome measure in clinical trials of dcSSc. Skin thickening was assessed by palpation of the skin in 17 areas of the body using a 0 to 3 scale. Total skin score can range from 0 (no thickening) to 51 (severe thickening). This trial conducted a skin scoring certification to standardize the mRSS assessments, and it was required that each pt be assessed by the same assessor to reduce variability. FVC% was measured in a standardized manner using the American Thoracic Society guidelines at baseline and follow-up and the National Health and Nutrition Examination Survey III reference values were used to calculate the FVC% predicted.[5] Presence of ILD was determined by a high-resolution computed tomography scan with confirmation by a thoracic radiologist at baseline for all pts. HAQ-DI is a self-reported questionnaire covering 20 items in eight domains related to measuring difficulty in performing activities of daily living. PGA and CGA were assessed as a single item (0–10 with higher score associated with more severe disease) and asked the respondents to rate their/patient overall disease severity on a 11-point Likert scale. ACR CRISS is a weighted score and includes five core set measures: mRSS, FVC% predicted, HAQ-DI, PGA, and CGA. It is scored on a 0.00 to 1.00 scale.[6]

Statistical analysis. Demographics, baseline characteristics, and week 48 efficacy measurements were tabulated by SSc-Abs. Pairwise group comparison was conducted for each two antibody groups. We performed *t*-test for numeric variables that followed normal distribution, Wilcoxon rank-sum test for numeric variables that did not follow normal distribution, chi-square or Fisher exact test for categorical variables. Efficacy measurements included six COAs: mRSS; FVC% overall and in those with ILD, HAQ-DI, PGA, and CGA; and the ACR CRISS. For each COA, except for the ACR CRISS, a linear mixed-effect model was fitted using change in measurement from baseline as outcome, baseline value, SSc-Ab type, age, sex, race, disease duration, study week, and interaction of antibody group and study week as covariates. For FVC% predicted, we adjusted for baseline value, SSc-Ab type, disease duration, study week, and interaction of antibody group and study week as covariates. Least-square mean (LSM) with 95% confidence interval (CI) at week 48 for each group with SSc-Abs and LSM (with 95% CI) of group difference between each two groups were obtained. Line charts of LSM over time were plotted. For ACR CRISS, mean (±SD) and median (interquartile range) were reported; dichotomized CRISS data (≥0.6) and revised CRISS (two or more COAs improved and up to one COA worsened with threshold of improvement/worsening 25% for mRSS, HAQ-DI, CGA, PGA, and 5% for FVC% predicted) was reported as count and percent. Relationship among five COAs (except ACR CRISS) was assessed using Pearson correlation coefficient at baseline and changed scores over 48 weeks. All analyses were conducted using SAS (version 9.4), and figures were created using RStudio (version 4.3.2).

RESULTS

In the focuSSced trial, the majority of pts were female (80.3%) and White (83.3%). The mean (±SD) age was 48.0 (±12.4) years, and the mean disease duration was 22.7 (±16.2) months. The mean (±SD) mRSS score was 20.5 (±6.9) units, mean HAQ-DI scores was 1.0 (±0.7), and mean FVC% predicted was 82.6% (±14.8%). For SSc-Abs, 50.5% were ATA positive, 15.7% were RNAP3 positive, 8.1% were ACA positive, and 25.8% were negative for all three SSc-Abs. At baseline, ILD was present in 64.1% of pts (among which 68.5% were ATA, 11.8% were RNAP3, 0.8% were ACA and 18.9% were triple negative). Among the group who received Pbo, 49.5% were ATA positive, 14.1% were RNAP3 positive, 9.1% were ACA positive, and 27.3% were negative for all three SSc-Abs (triple negative). In the group who received tocilizumab, 51.5% were ATA positive, 17.2% were RNAP3 positive, 7.1% were ACA positive, and 24.2% were triple negative.

In the group who received Pbo, we observed that all the COAs, except for FVC%, improved during the 48-week trial versus baseline. For mRSS, the pts with RNAP3 had a higher baseline mean mRSS (23.9 units) versus those with ATA, triple negative, and ACA (20.7, 20.4, and 16.0 units; Table 1). During the longitudinal follow-up, an improvement versus baseline was seen in the mRSS for all groups with LSM change of 5.38 units per year (P = 0.0002). Among the pts with ATA, there was an improvement of 4.89 per year, RNAP3 had an improvement of 7.20 units per year, triple negative showed an improvement of 6.16 units per year, and ACA had an improvement of 4.89 per year (Figure 1; Table 1).

An overall decline in FVC% was observed in all pts and in those with ILD, characterized by a significant decline of 3.40% per year and 5.02% per year, respectively, regardless of their SSc-Ab profile ($P < 0.001$ and P = 0.0007, respectively; Table 1). In those with ILD, among pts with ATA, there was a decline of 7.78% per year ($P < 0.0001$), RNAP3 exhibited a decline of 6.08% per year (P = 0.0861), and triple negative exhibited a decline of 1.19% per year (P = 0.5899). RNAP3 in the group with ILD had a large decline of 6.08% per year, largely due to the small number of patients in this group (n = 5). ACA was not included when we explored FVC% decline among pts with ILD due to the small sample size (n = 1).

For the HAQ-DI score, there was an overall improvement of 0.15 per year, irrespective of SSc-Ab profile. Among the pts with ATA, there was no improvement in the HAQ-DI score, and in pts with RNAP3, there was an improvement of 0.19 per year in HAQ-DI score. In pts with triple negative and ACA, improvements of 0.20 per year and 0.23 per year, respectively, were observed (Figure 1; Table 1). None of the changes was statistically significant. For the PGA, there was an overall improvement in all groups, and the improvement was similar in all groups with SSc-Abs (Figure 1; Table 1).

At week 48 follow-up, ACR CRISS had a median score of 0.29 (0.00–0.99). Among the pts with ATA, the median score was 0.01, RNAP3 had 0.94, and triple negative and ACA had median scores of 0.76 and 0.75, respectively. When we assessed for revised CRISS, which is the proportion of pts who improved in two or more COAs and did not worsen in more than one COA (improvement and worsening in mRSS, HAQ-DI, CGA, and PGA by ≥25% and FVC% by ≥5%), we observed that in the overall group, 53.3% of pts met revised CRISS. Out of all the SSc-Abs, ATA had the smallest proportion of pts who met the revised CRISS (47.4%) compared to others (61.1% for triple negative, 62.5% for ACA, and 54.5% for RNAP3).

Group who received tocilizumab. In the group who received tocilizumab, the changes in COAs were largely similar in four groups with SSc-Abs (Figure 2; Table 2). An overall improvement was seen in the mRSS of 8.03 units, with similar improvements in the four groups with SSc-Abs (8.05 units in ATA, 8.99 units in RNAP3, 6.37 units in ACA, and 8.72 units in triple negative). At week 48 follow-up, ACR CRISS had a median score of 0.85 (0.12–1.0) in the group who received tocilizumab. Among the pts with ATA, the median score was 0.89, RNAP3 was 1.00, and triple negative and ACA had median scores of 0.84 and 0.52, respectively. When we assessed for revised CRISS, we observed that in the overall group, 66.7% pts met revised CRISS. The proportion of 61.9% of pts with ATA who met revised CRISS was similar to 78.9% for triple negative and 76.9% for RNAP3.

An overall improvement was seen in HAQ-DI, PGA, and CGA of 0.18 units, 1.15 units, and 2.74 units, respectively. A decrease was seen in FVC% predicted of 0.30% in the whole cohort and 0.42% in the pts with ILD. These changes were similar across SSc-Ab types(Figure 2; Table 2).

Relationships among five COAs were assessed at baseline and as changed scores. In the group who received Pbo, the relationships at baseline were largest for CGA with mRSS and PGA and PGA with HAQ-DI (Supplementary Table 1), and the relationships for changed scores were largest for mRSS with HAQ-DI and CGA. In the group who received tocilizumab, the relationships at baseline were largest for CGA with PGA and HAQ-DI and PGA

Table 1. Changes in the COAs in a phase III clinical trial over 48 weeks, stratified for the overall group who received placebo and four scleroderma-associated autoantibodies*

COA	Overall (n = 99)	Triple negative (n = 27)	ACA (n = 9)	ATA (n = 49)	RNAP3 (n = 14)	Group differences: ACA vs triple negative	ATA vs triple negative	RNAP3 vs triple negative	ACA vs ATA	ACA vs RNAP3	ATA vs RNAP3
Baseline mRSS, 0–51 (n = 99)	20.6 (±7.1)	20.4 (±7.6)	16.0 (±5.4)	20.7 (±6.1)	23.9 (±9.0)	*P* = 0.1528	*P* = 0.8473	*P* = 0.2016	***P* = 0.0338**	***P* = 0.0345**	*P* = 0.2359
LSM change in mRSS (n = 98)	−5.38 (−6.89 to −3.88); *P* < 0.0001	−6.16 (−8.55 to −3.77); *P* < 0.0001	−4.89 (−8.98 to −0.79); *P* = 0.0195	−3.28 (−5.11 to −1.46); *P* = 0.0005	−7.20 (−10.52 to −3.88); *P* < 0.0001	1.28 (−3.46 to 6.01); *P* = 0.5965	2.88 (−0.13 to 5.89); *P* = 0.0605	−1.03 (−5.13 to 3.06); *P* = 0.6200	−1.60 (−6.09 to 2.89); *P* = 0.4826	2.31 (−3.03 to 7.65); *P* = 0.3954	3.91 (0.13–7.70); ***P* = 0.0428**
Baseline FVC% predicted (n = 99)	84.3 (±15.1)	86.1 (±13.4)	92.4 (±16.3)	80.6 (±16.3)	88.3 (±10.0)	*P* = 0.2532	*P* = 0.1412	*P* = 0.5947	*P* = 0.0515	*P* = 0.4688	*P* = 0.1019
LSM change in FVC% predicted (n = 98)	−3.40 (−5.05 to −1.74); *P* < 0.0001	−1.05 (−3.69 to 1.60); *P* = 0.4379	−2.66 (−7.14 to 1.82); *P* = 0.2436	−7.34 (−9.40 to −5.29); *P* < 0.0001	−2.54 (−6.11 to 1.03); *P* = 0.1632	−1.61 (−6.81 to 3.58); *P* = 0.5417	−6.30 (−9.65 to −2.94); ***P* = 0.0003**	−1.49 (−5.93 to 2.95); *P* = 0.5096	4.68 (−0.28 to 9.64); *P* = 0.0640	−0.12 (−5.82 to 5.58); *P* = 0.9663	−4.81 (−8.94 to −0.67); ***P* = 0.0229**
Baseline FVC% predicted among ILD (n = 63)	81.9 (±15.0)	84.6 (±11.7)	111.0 (–)	80.2 (±15.8)	82.8 (±10.9)	–	*P* = 0.3460	*P* = 0.8170	–	–	*P* = 0.7235
LSM change in FVC% predicted among ILD (n = 61)	−5.02 (−7.88 to −2.16); *P* = 0.0007	−1.19 (−5.53 to 3.15); *P* = 0.5899	–	−7.78 (−10.32 to −5.24); *P* < 0.0001	−6.08 (−13.04 to 0.87); *P* = 0.0861	–	−6.59 (−11.63 to −1.55); ***P* = 0.0106**	−4.90 (−13.09 to 3.30); *P* = 0.2402	–	–	−1.70 (−9.10 to 5.71); *P* = 0.6518
Baseline HAQ-DI, 0–3 (n = 97)	1.1 (±0.7)	1.2 (±0.7)	1.2 (±0.6)	1.1 (±0.7)	1.1 (±0.5)	*P* = 0.7889	*P* = 0.3493	*P* = 0.4183	*P* = 0.5465	*P* = 0.5899	*P* = 0.8660
LSM change in HAQ-DI (n = 96)	−0.15 (−0.26 to −0.05); *P* = 0.0040	−0.20 (−0.37 to −0.03); *P* = 0.0194	−0.23 (−0.52 to 0.06); *P* = 0.1134	0.01 (−0.12 to 0.14); *P* = 0.8721	−0.19 (−0.42 to 0.03); *P* = 0.0842	−0.03 (−0.36 to 0.30); *P* = 0.8651	0.21 (0.00–0.42); ***P* = 0.0495**	0.01 (−0.27 to 0.29); *P* = 0.9635	−0.24 (−0.55 to 0.07); *P* = 0.1306	−0.04 (−0.40 to 0.33); *P* = 0.8485	0.21 (−0.05 to 0.46); *P* = 0.1142
Baseline PGA, 0–10 (n = 97)	6.1 (±2.0)	6.2 (±2.0)	5.9 (±2.6)	6.1 (±2.1)	5.9 (±1.6)	*P* = 0.7344	*P* = 0.8305	*P* = 0.6363	*P* = 0.8193	*P* = 0.9247	*P* = 0.7529
LSM change in PGA (n = 96)	−1.04 (−1.55 to −0.53); *P* < 0.0001	−1.13 (−1.96 to −0.31); *P* = 0.0073	−1.07 (−2.48 to 0.33); *P* = 0.1325	−1.13 (−1.75 to −0.51); *P* = 0.0004	−0.82 (−1.91 to 0.26); *P* = 0.1371	0.06 (−1.57 to 1.69); *P* = 0.9417	0.00 (−1.03 to 1.04); *P* = 0.9934	0.31 (−1.05 to 1.68); *P* = 0.6512	0.06 (−1.48 to 1.59); *P* = 0.9427	−0.25 (−2.03 to 1.52); *P* = 0.7787	−0.31 (−1.56 to 0.94); *P* = 0.6269
Baseline CGA, 0–10 (n = 93)	5.9 (±1.6)	5.9 (±1.7)	5.5 (±1.3)	6.2 (±1.6)	5.4 (±1.2)	*P* = 0.4930	*P* = 0.4207	*P* = 0.3136	*P* = 0.1778	*P* = 0.6141	*P* = 0.0659
LSM change in CGA (n = 91)	−2.41 (−2.93 to −1.90); *P* < 0.0001	−2.65 (−3.52 to −1.78); *P* < 0.0001	−3.19 (−4.54 to −1.83); *P* < 0.0001	−1.95 (−2.57 to −1.32); *P* < 0.0001	−1.87 (−3.00 to −0.74); *P* = 0.0013	−0.54 (−2.15 to 1.07); *P* = 0.5108	0.70 (−0.37 to 1.77); *P* = 0.1978	0.78 (−0.65 to 2.20); *P* = 0.2848	−1.24 (−2.74 to 0.26); *P* = 0.1040	−1.31 (−3.07 to 0.44); *P* = 0.1424	−0.07 (−1.38 to 1.23); *P* = 0.9104
ACR CRISS, 0.00–1.00 (n = 75)[a]	0.29 (0.00–0.99); *P* = 0.0003	0.76 (0.01–1.00); *P* = 0.3465	0.75 (0.15–0.99); *P* = 1.0000	0.01 (0.00–0.95); *P* < 0.0001	0.94 (0.00–1.00); *P* = 0.7002	*P* = 1.0000	***P* = 0.0208**	*P* = 1.0000	*P* = 0.1197	*P* = 0.8365	***P* = 0.0474**
ACR CRISS, 0.00–1.00 (n = 75)[a]	0.46 (±0.45)	0.55 (±0.45)	0.60 (±0.43)	0.35 (±0.44)	1.00 (±0.61)	–	–	–	–	–	–

(Continued)

Table 1. *(Cont'd)*

COA	Overall (n = 99)	Triple negative (n = 27)	ACA (n = 9)	ATA (n = 49)	RNAP3 (n = 14)	Group differences					
						ACA vs triple negative	ATA vs triple negative	RNAP3 vs triple negative	ACA vs ATA	ACA vs RNAP3	ATA vs RNAP3
ACR CRISS ≥ 0.6 (n = 75), n (%)[a]	35 (46.7)	10 (55.6)	5 (62.5)	13 (34.2)	7 (63.6)	*P* = 1.0000	*P* = 0.1294	*P* = 0.7167	*P* = 0.2316	*P* = 1.0000	*P* = 0.0965
Revised CRISS (n = 75), n (%)[b]	40 (53.3)	11 (61.1)	5 (62.5)	18 (47.4)	6 (54.5)	*P* = 1.0000	*P* = 0.3365	*P* = 1.0000	*P* = 0.6995	*P* = 1.0000	*P* = 0.6750

Note: Bold indicates statistically significant values $P < 0.05$.
*The values given are mean (±SD) or median (interquartile range) unless otherwise indicated. ACA, anti-centromere antibody; ACR, American College of Rheumatology; ATA, anti-topoisomerase 1 antibody; CGA, clinician global assessment; COA, clinical outcome assessment; CRISS, Composite Response Index in Systemic Sclerosis; FVC%, forced vital capacity; HAQ-DI, Health Assessment Questionnaire Disability Index; ILD, interstitial lung disease; LSM, least-square mean; mRSS, modified Rodnan skin score; PGA, patient global assessment; RNAP3, anti–RNA polymerase 3 antibody.
[a]The median ACR CRISS in each group is tested with $H_0 = 0.6$.
[b]Given is the proportion of participants who improved by two or more COAs and not worsened by more than one COA (improvement and worsening in mRSS, HAQ-DI, CGA, and PGA by ≥25% and FVC% ≥5%).

with HAQ-DI (Supplementary Table 2), and the relationships for the changed scores were largest for HAQ-DI with PGA and CGA.

DISCUSSION

To better understand the impact of SSc-Abs on the trajectories of COAs, we analyzed the group who received Pbo and the active group from the focuSSced trial, a pivotal trial that assessed the efficacy and safety of tocilizumab versus Pbo in patients with early dcSSc and led to the approval of tocilizumab for SSc-ILD. We observed an overall improvement in the COAs (except for FVC%) over the course of 48 weeks in the group who received Pbo. In addition, there was a differential effect of SSc-Ab on the trajectory of the COAs. Of the four SSc-Ab types, ATA showed the smallest improvement in the mRSS, greatest decline in FVC %, and no change in the HAQ-DI. On the contrary, both the RNA3P, triple negative, and ACA SSc-Abs exhibited a large improvement in the mRSS, small decline in the FVC%, and large improvement in the HAQ-DI. In contrast, the patients who received tocilizumab had similar effect on the COAs, irrespective of SSc-Ab type. The largest differential effect between tocilizumab and Pbo was seen in the group with ATA, with large improvements in the mRSS (8.05 vs 3.28 for Pbo), preservation of FVC % (predicted 0.63% vs a decline of 7.34% for Pbo), and large ACR CRISS response (0.89 vs 0.01 for Pbo).

Subgroups with ANAs have been analyzed extensively in clinical cohorts and are associated with skin subsets, frequency of organ-based complications, and death. The impact on the skin is a significant component of morbidity in SSc, and a considerable number of clinical trials have employed the mRSS as a primary endpoint. SSc-Abs are associated with different trajectories in mRSS, with patients who received RNAP3 tending to reach their peak mRSS earlier than other patients.[7] In the focuSSced patients, this peak was much higher than for patients with other or no SSc-Abs, whereas those with ATA tended to have more slow progressive worsening and softening, whereas ACA was and is generally protective for progressive skin and ILD.[7] In addition, some pts with ATA can continue to have high mRSS beyond the five-year duration and worsening of mRSS after achieving improvement.[8] In a single-center cohort, 3% of patients with dcSSc were ACA positive and had more insidious skin and organ impact.[9] For SSc-ILD, ACA provides protection against progressive ILD, whereas ATAs are linked to the highest ILD incidence and progression, regardless of cutaneous subset.[3] Others have shown that pts with RNAP3 tend to experience ILD later in the progression of the disease in contrast to those with ATA, for whom ILD manifests as an early complication.[10] An exploratory clustering analysis from an Indian registry showed lower average FVC%s were comparable across the three predominant ATA clusters (59.7, 66.5, and 59.3, respectively). However, in cluster 4, which was predominantly ACA, there was a notably higher

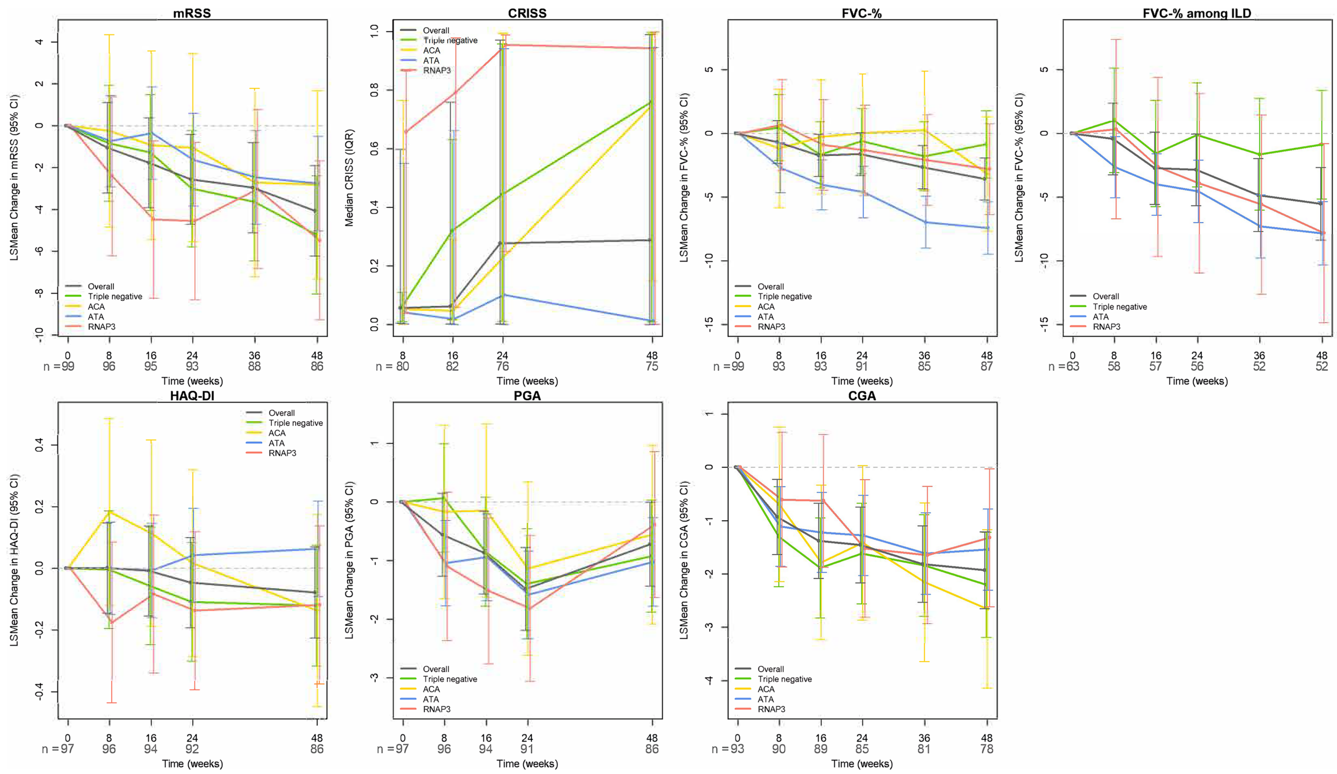

Figure 1. Impact of four scleroderma-associated autoantibodies on clinical outcome assessments in the group who received placebo. ACA, anti-centromere antibody; ATA, anti–topoisomerase 1 antibody; CGA, clinician global assessment; CI, confidence interval; CRISS, Composite Response Index in Systemic Sclerosis; FVC-%, forced vital capacity; HAQ-DI, Health Assessment Questionnaire Disability Index; ILD, interstitial lung disease; IQR, interquartile range; LSMean, least-square mean; mRSS, modified Rodnan skin score; PGA, patient global assessment; RNAP3, anti–RNA polymerase 3 antibody.

mean FVC% (83.8%) and the lowest percentage of patients with ILD (12.9%).[11]

Our data add to the published literature and highlight the variable impact of SSc-Abs on the COAs in early SSc clinical trials. First, despite an enrichment for earlier active and progressive skin disease and elevated acute-phase reactants, on average, pts improved on the COAs (except FVC%) at week 48 in the group who received Pbo. One striking feature was the differential effects on the COAs among the pts who were ATA positive and with other SSc-Abs; the group who was ATA positive had minimal impact of mRSS and HAQ-DI, but there was a large decline in FVC% in the group who received Pbo. The effect in the group who was ATA positive on SSc-ILD was consistent with the cohort studies, in which ATA positivity is associated with progressive ILD.[12] In review of the published post hoc analyses from previous trials, our data contradict the effect of ATA positivity on mRSS and FVC% predicted in two trials with well-established ILD (Scleroderma Lung Study [SLS]-I and SENSCIS) in which these associations were not noticed.[13,14] The differences in the design of these Pbo-controlled trials (focuSSced vs SLS-I and SENSCIS) highlight fundamental differences in the patients recruited in these trials—focuSSced recruited pts with an earlier phase of the disease with less extensive lung involvement, when immunoinflammatory drivers are strongly implicated, and SLS-I and SENSCIS enrolled a cohort with more fibrotic disease with more extensive underlying ILD (and both limited and dcSSc). In addition, SENCSIS allowed for background immunosuppressive therapies.

Second, improvements in the group who received Pbo and who were RNAP3 positive were seen within the first 8 weeks in mRSS, PGA, and HAQ-DI, which influenced the median ACR CRISS of >0.6 in the first 8 weeks with a median ACR CRISS score of 0.94 at 48 weeks (Figure 1). In the group who received tocilizumab, RNAP3 also showed a large effect on the mRSS and other COAs, which translated into a median ACR CRISS of 1.00 at week 48 and a lack of clinically meaningful difference in the ACR CRISS between tocilizumab versus Pbo at week 48. Similar effect was seen in the group who was triple negative in the ACR CRISS between tocilizumab versus Pbo at week 48. ATA positivity differentiated the two groups who received Pbo and tocilizumab at week 48 with a large effect seen in the group who received tocilizumab. In the group who was ACA positive, the overall effect favored the group who received Pbo over tocilizumab (median ACR CRISS scores of 0.52 in the group who received tocilizumab versus 0.75 in the group

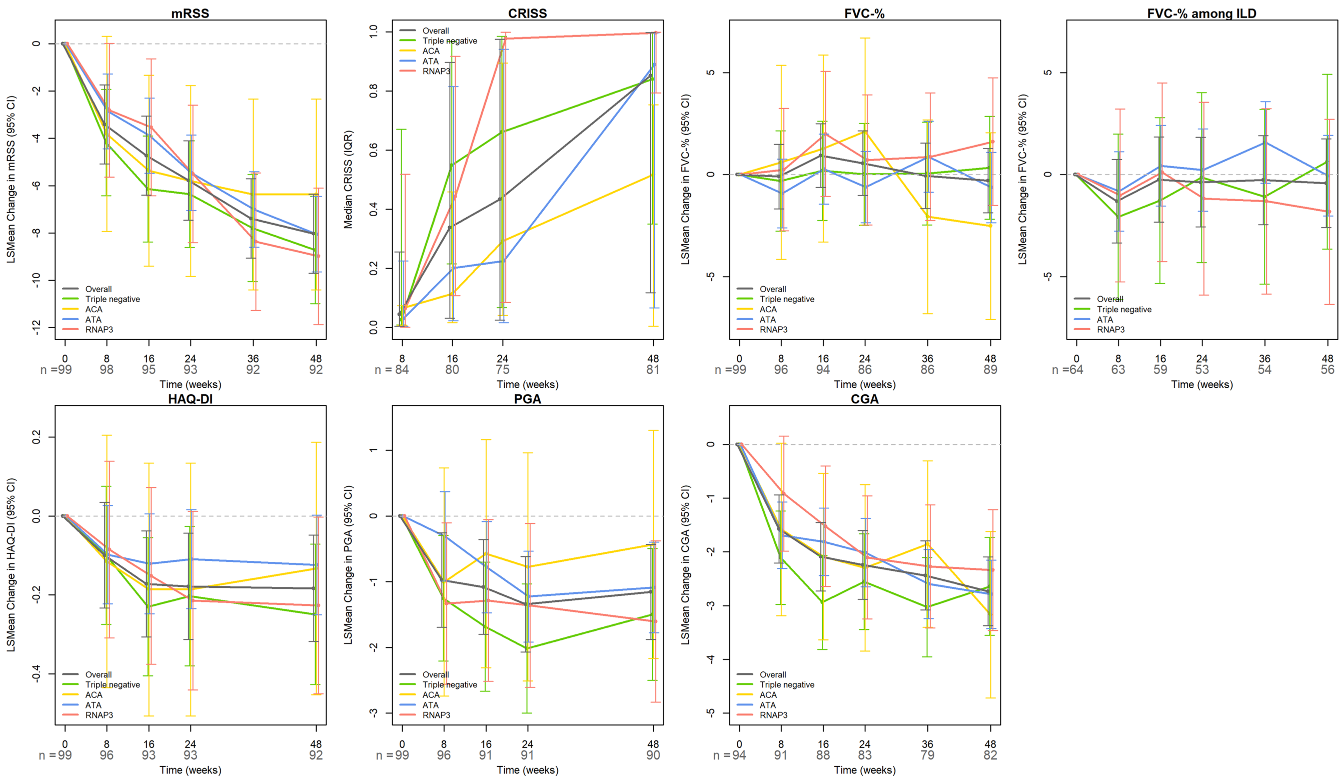

Figure 2. Impact of four scleroderma-associated autoantibodies on clinical outcome assessments in the group who received tocilizumab. ACA, anti-centromere antibody; ATA, anti–topoisomerase 1 antibody; CGA, clinician global assessment; CI, confidence interval; CRISS, Composite Response Index in Systemic Sclerosis; FVC-%, forced vital capacity; HAQ-DI, Health Assessment Questionnaire Disability Index; ILD, interstitial lung disease; IQR, interquartile range; LSMean, least-square mean; mRSS, modified Rodnan skin score; PGA, patient global assessment; RNAP3, anti–RNA polymerase 3 antibody.

who received Pbo, but the number of pts was small in the group who was ACA positive).

We further explored the relationships among different COAs because improvements in the mRSS are usually associated with and are predictive of improvements in functional ability and global assessments, as shown by Clements et al.[15] We assessed relationships at baseline and over the 48 weeks in the COAs. We saw small correlation coefficients at baseline between mRSS and three of four COAs (HAQ-DI, PGA, and CGA) but large correlation coefficients between change in the mRSS versus change in the HAQ-DI, PGA, and CGA, highlighting the relationship between the mRSS and measures of feel (PGA) and function (HAQ-DI). In addition, because mRSS is weighted highest in the ACR CRISS formula, a larger improvement is noted in those subgroups with SSc-Abs. ATA showed the smallest Pbo with slowly progressive decline in mRSS, which mirrored the changes in HAQ-DI, CGA, and PGA. However, ATA had a large decline in FVC% over 48 weeks, starting as early as week 8. These data highlight that both patients and physicians rated the changes in the skin and function, which translated into patients feeling better (eg, potentially decreased pruritus and increased range of motion) versus changes in FVC%, which may not be related to symptoms in earlier disease. This highlights the importance of categorizing patients with SSc by autoantibody subtype in clinical trials, potentially elucidating varying COAs seen across subgroups in trials focusing on specific pathogenic mechanisms.

Our study has several strengths. First, a strength is that the group who received Pbo of focuSSced mostly did not receive immunosuppression and was largely treatment naive. It also reflects a population with severe progressive SSc. Such a cohort is unlikely to be available in the future due to routine reception of mycophenolate mofetil or other background immunosuppressive therapy and the poor outcomes observed in the groups who received Pbo of both tocilizumab trials. We acknowledge that current trials allow background immunosuppressive therapies. We do not consider this as a limitation, as highlighted by differential effects on the COAs in this trial versus more fibrotic established population (such as SLS-I and SENSCIS) and incorporation of the lessons learned in the multicenter trials enrichment for acute-phase reactants/stratification for autoantibodies.[16] Second, we used a well-characterized RCT that assessed SSc-Abs using a central laboratory and used standardized methodology to assess

Table 2. Changes in the COAs in a phase III clinical trial over 48 weeks, stratified for the overall group who received tocilizumab and four scleroderma-associated autoantibodies*

COA	Overall (n = 99)	Triple negative (n = 24)	ACA (n = 7)	ATA (n = 51)	RNAP3 (n = 17)	Group difference: ACA vs triple negative	ATA vs triple negative	RNAP3 vs triple negative	ACA vs ATA	ACA vs RNAP3	ATA vs RNAP3
Baseline mRSS, 0–51 (n = 99)	20.3 (±6.7)	17.1 (±4.8)	18.9 (±7.9)	20.5 (±6.7)	24.8 (±6.4)	*P* = 0.4671	***P* = 0.0273**	***P* < 0.0001**	*P* = 0.5469	*P* = 0.0917	***P* = 0.0258**
LSM change in mRSS (n = 99)	−8.03 (−9.70 to −6.36); *P* < 0.0001	−8.72 (−10.99 to −6.45); *P* < 0.0001	−6.37 (−10.40 to −2.34); *P* = 0.0020	−8.05 (−9.65 to −6.46); *P* < 0.0001	−8.99 (−11.87 to −6.10); *P* < 0.0001	2.35 (−2.03 to 6.73); *P* = 0.2930	0.67 (−1.87 to 3.21); *P* = 0.6061	−0.27 (−3.81 to 3.27); *P* = 0.8818	1.68 (−2.38 to 5.74); *P* = 0.4165	2.61 (−1.95 to 7.18); *P* = 0.2606	0.93 (−2.06 to 3.93); *P* = 0.5405
Baseline FVC% predicted (n = 99)	80.9 (±14.2)	80.7 (±12.8)	92.2 (±10.0)	78.3 (±13.8)	84.2 (±16.8)	***P* = 0.0373**	*P* = 0.4623	*P* = 0.4529	***P* = 0.0127**	*P* = 0.1623	*P* = 0.1489
LSM change in FVC% predicted (n = 99)	−0.30 (−1.88 to 1.28); *P* = 0.7079	0.34 (−2.19 to 2.86); *P* = 0.7938	−2.52 (−7.11 to 2.06); *P* = 0.2794	−0.63 (−2.35 to 1.10); *P* = 0.4740	1.61 (−1.51 to 4.74); *P* = 0.3104	−2.86 (−8.10 to 2.38); *P* = 0.2837	−0.96 (−4.02 to 2.09); *P* = 0.5345	1.28 (−2.76 to 5.32); *P* = 0.5335	−1.90 (−6.83 to 3.04); *P* = 0.4502	−4.14 (−9.65 to 1.37); *P* = 0.1404	−2.24 (−5.85 to 1.36); *P* = 0.2215
Baseline FVC% predicted among ILD (n = 64)	78.2 (±14.0)	82.2 (±13.8)	–	77.1 (±13.7)	78.9 (±16.5)	–	*P* = 0.2942	*P* = 0.6232	–	–	*P* = 0.7141
LSM change in FVC% predicted among ILD (n = 64)	−0.42 (−2.59 to 1.76); *P* = 0.7061	0.63 (−3.66 to 4.92); *P* = 0.7716	–	−0.05 (−2.04 to 1.93); *P* = 9,576	−1.83 (−6.37 to 2.71); *P* = 0.4278	–	−0.69 (−5.42 to 4.05); *P* = 0.7756	−2.46 (−8.69 to 3.77); *P* = 0.4372	–	–	1.78 (−3.21 to 6.77); *P* = 0.4838
Baseline HAQ-DI, 0–3 (n = 99)	0.9 (±0.7)	0.8 (±0.9)	0.7 (±0.5)	0.9 (±0.8)	1.2 (±0.5)	*P* = 0.8677	*P* = 0.4383	*P* = 0.1403	*P* = 0.9427	***P* = 0.0474**	*P* = 0.0562
LSM change in HAQ-DI (n = 98)	−0.18 (−0.32 to −0.05); *P* = 0.0079	−0.25 (−0.43 to −0.07); *P* = 0.0062	−0.13 (−0.45 to 0.19); *P* = 0.4150	−0.12 (−0.25 to 0.002); *P* = 0.0540	−0.23 (−0.45 to −0.003); *P* = 0.0470	0.12 (−0.23 to 0.46); *P* = 0.5048	0.13 (−0.07 to 0.32); *P* = 0.2083	0.02 (−0.24 to 0.29); *P* = 0.8683	−0.01 (−0.33 to 0.31); *P* = 0.9564	0.09 (−0.26 to 0.45); *P* = 0.6034	0.10 (−0.13 to 0.34); *P* = 0.3855
Baseline PGA, 0–10 (n = 99)	5.4 (2.5)	5.4 (2.6)	5.6 (2.7)	5.3 (2.6)	5.5 (1.9)	*P* = 0.8221	*P* = 0.9255	*P* = 0.8067	*P* = 0.7639	*P* = 0.9493	*P* = 0.7228
LSM change in PGA (n = 98)	−1.15 (−1.88 to −0.43); *P* = 0.0019	−1.50 (−2.50 to −0.50); *P* = 0.0035	−0.43 (−2.17 to 1.31); *P* = 0.6257	−1.09 (−1.78 to −0.40); *P* = 0.0022	−1.60 (−2.83 to −0.38); *P* = 0.0106	1.07 (−0.83 to 2.97); *P* = 0.2696	0.41 (−0.70 to 1.52); *P* = 0.4661	−0.11 (−1.59 to 1.38); *P* = 0.8888	0.66 (−1.10 to 2.41); *P* = 0.4621	1.17 (−0.78 to 3.13); *P* = 2,382	0.52 (−0.77 to 1.81); *P* = 0.4295
Baseline CGA, 0–10 (n = 94)	5.9 (±2.0)	5.7 (±1.9)	6.7 (±1.0)	6.1 (±2.1)	5.5 (±2.3)	*P* = 0.2123	*P* = 0.4443	*P* = 0.7297	*P* = 0.4816	*P* = 0.2037	*P* = 0.3116
LSM change in CGA (n = 94)	−2.74 (−3.37 to −2.10); *P* < 0.0001	−2.64 (−3.55 to −1.73); *P* < 0.0001	−3.17 (−4.72 to −1.62); *P* ≤ 0.0001	−2.79 (−3.43 to −2.15); *P* < 0.0001	−2.34 (−3.46 to −1.22); *P* < 0.0001	−0.53 (−2.25 to 1.19); *P* = 0.5435	−0.15 (−1.18 to 0.88); *P* = 0.7787	0.30 (−1.08 to 1.68); *P* = 0.6678	−0.38 (−1.96 to 1.19); *P* = 0.6332	−0.83 (−2.62 to 0.95); *P* = 0.3593	−0.45 (−1.65 to 0.76); *P* = 0.4638
ACR CRISS, 0.00–1.00 (n = 81)[a]	0.85 (0.12–1.00); *P* = 0.7741	0.84 (0.35–1.00); *P* = 0.5949	0.52 (0.005–0.75); *P* = 0.2969	0.89 (0.07–1.00); *P* = 0.5180	1.00 (0.79–1.00); *P* = 0.5288	*P* = 0.1186	*P* = 0.5697	*P* = 0.4659	*P* = 0.1657	*P* = 0.0683	*P* = 0.2544

(Continued)

Table 2. *(Cont'd)*

COA	Overall (n = 99)	Triple negative (n = 24)	ACA (n = 7)	ATA (n = 51)	RNAP3 (n = 17)	Group difference: ACA vs triple negative	ATA vs triple negative	RNAP3 vs triple negative	ACA vs ATA	ACA vs RNAP3	ATA vs RNAP3
ACR CRISS, 0.00–1.00 (n = 81)[a]	0.63 (±0.42)	0.67 (±0.38)	0.41 (±0.40)	0.61 (±0.43)	0.74 (±0.43)	–	–	–	–	–	–
ACR CRISS ≥ 0.6 (n = 81), n (%)[a]	49 (60.5)	12 (63.2)	2 (28.6)	25 (59.5)	10 (76.9)	$P = 0.1904$	$P = 0.7879$	$P = 0.4673$	$P = 0.2192$	$P = 0.0623$	$P = 0.3332$
Revised CRISS (n = 81), n (%)[b]	54 (66.7)	15 (78.9)	3 (42.9)	26 (61.9)	10 (76.9)	$P = 0.1490$	$P = 0.1892$	$P = 1.0000$	$P = 0.4221$	$P = 0.1736$	$P = 0.5061$

Note: Bold indicates statistically significant values $P < 0.05$.
*The values given are mean (±SD) or median (interquartile range) unless otherwise indicated. ACA, anti-centromere antibody; ACR, American College of Rheumatology; ATA, anti-topoisomerase 1 antibody; CGA, clinician global assessment; COA, clinical outcome assessment; CRISS, Composite Response Index in Systemic Sclerosis; FVC%, forced vital capacity; HAQ-DI, Health Assessment Questionnaire Disability Index; ILD, interstitial lung disease; LSM, least-square mean; mRSS, modified Rodnan skin score; PGA, patient global assessment; RNAP3, anti-RNA polymerase 3 antibody.
[a]The median ACR CRISS in each group is tested with $H_0 = 0.6$.
[b]Given is the proportion of participants who improved by two or more COAs and not worsened by more than one COA (change improvement and worsening in mRSS, HAQ-DI, CGA, and PGA by ≥25% and FVC% ≥5%).

the COAs. Third, we showed the impact of SSc-Abs on trajectories of COAs in both groups who received tocilizumab and Pbo and focused on a 48-week trial, an accepted trial duration to assess the impact of therapies on COAs. Although the clinical cohorts have shown similar trends, this analysis provides point estimates that can be used for future trial design. Our study has several limitations to consider. First, this was an enriched cohort and is not representative of all patients with early SSc because pts with elevated acute-phase reactants is a limited subset of patients with SSc. Second, the pts did not receive background immunosuppressive therapy, which may augment the impact on the COA trajectories as seen in a recent phase III trial.[17]

In conclusion, our result in an enriched cohort shows a differential effect of SSc-Abs on the trajectories of COAs over a 48-week RCT. These findings, along with previously published data, highlight the importance of incorporating these data in trial design, either as a stratification factor or limiting the SSc-Abs that are included in the trials.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Khanna confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

ROLE OF THE STUDY SPONSOR

Genentech/Roche had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Genentech/Roche.

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