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4 **Title: Tocilizumab and rituximab for systemic sclerosis interstitial lung disease: a real-**
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6 **world cohort analysis**
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Abstract:**Objectives:**

Systemic sclerosis (SSc)-interstitial lung disease (ILD) is one of the leading causes of mortality in SSc. Data from randomised controlled trials (RCTs) supports rituximab and tocilizumab monotherapy but there is limited data regarding their use for those who fail standard immunomodulatory therapies.

Methods:

SSc patients treated with rituximab or tocilizumab were retrospectively identified in a single centre cohort. Linear mixed effect models were used to analyse before and after treatment lung function trajectory and identify patient characteristics associated with treatment response.

Results:

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4 127 patients were included for analysis. 51 of 94 (51.4%) and 13 of 33 (39.4%) of the
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6 rituximab and tocilizumab cohorts respectively were receiving concurrent mycophenolate
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8 mofetil. Pre-treatment decline in absolute change %FVC/year and %DLCO/year respectively,
9
10 was similar in both cohorts (-3.2% and -4.0% rituximab and -3.2% and -3.6% tocilizumab).
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12 Both treatments resulted in lung function stabilisation (%FVC/year and %DLCO/year: 1.2%
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14 and +0.2% rituximab cohort, 1.0% and 1.0% tocilizumab cohort). Anti-topoisomerase
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16 antibody (ATA) positive patients had a significant response on %FVC/year to tocilizumab
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18 compared to ATA negative patients. Gender had a significant impact on %FVC/year response
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20 to rituximab, with males responding to a greater degree than females. Age, ILD extent and
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22 skin subset had no impact on treatment response.
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31 **Conclusion:**

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33 Combination rituximab or tocilizumab with background immunosuppressive therapy is
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35 associated with stabilisation in lung function trajectory among those who remain refractory
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37 to standard immunosuppressives. Specific patient characteristics have an impact on lung
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39 function response. Improved FVC response among ATA patients receiving tocilizumab
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41 validate data from RCTs.
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48 **Key Words:**

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50 Anti-topoisomerase antibody, Interstitial lung disease, Rituximab, Systemic Sclerosis,
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53 Tocilizumab
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58 **Key Messages:**

- This real world data demonstrates improvement in %FVC trajectory following treatment with rituximab and tocilizumab in systemic sclerosis interstitial lung disease
- Specific patients characteristics including anti-topoisomerase-I antibody positivity and gender impact response to treatment
- This data complements recent RCTs and supports the use of biologics in a more diverse patient cohort with severe SSc-ILD.

Introduction:

Interstitial lung disease (ILD) is a leading cause of mortality in systemic sclerosis (SSc)[1].

Male gender, older age, African American race, diffuse skin disease and anti-topoisomerase-I antibody (ATA) positivity are reported risk factors for ILD development and progression [2]. Low baseline forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO), CT disease extent over 20% and FVC decline of at least 10% are associated with progressive ILD [2]. However, the majority of studies do not consider predictors of progressive ILD treatment response.

Evidence from clinical studies support immunological approaches in SSc-ILD. The Scleroderma Lung Studies (SLS) indicate cyclophosphamide and mycophenolate mofetil (MMF) reduce ILD progression [3,4]. Autologous stem cell transplant (aSCT) also provides supportive evidence [5]. Although initially mixed results, randomised controlled trials (RCTs) demonstrated improvement in FVC with rituximab, a chimeric monoclonal antibody against human CD20 [6,7]. A study with smaller SSc-ILD numbers showed short-term benefit with

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4 combination rituximab and MMF compared to MMF alone [8]. Tocilizumab, a monoclonal
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6 antibody targeting the interleukin-6 (IL6) receptor, monotherapy was beneficial in arresting
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8 lung function decline in early-stage diffuse SSc [9,10]. Post-hoc analysis of the phase III study
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10 confirmed early disease duration (< 2 years), ATA positivity and male gender were predictive
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12 of tocilizumab response [11].
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19 Real-world evidence can complement RCT evidence in treatment algorithms development
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21 and help understand if treatment benefits found in RCTs may extend to a broader SSc
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23 cohort. We therefore performed a retrospective cohort study to assess trajectory of ILD
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25 following treatment with rituximab or tocilizumab in SSc patients from our single centre
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27 cohort, assessing differential response in subgroups based on patient characteristics.
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33 **Methods:**

34 **Cohort Selection:**

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36 Patients from the Royal Free Hospital (London, UK) Scleroderma Cohort (SMART) who
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38 fulfilled the ACR/EULAR 2013 diagnostic criteria for SSc and had received ≥ 1 dose of
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40 rituximab (1000mg at weeks 0 and 2) and/or ≥ 3 months tocilizumab with at least 1
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42 pulmonary function test within 24 months before and after treatment were included [12].
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45 Relevant demographic and clinical data were extracted from records.
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53 The study was approved by London-Fulham NHS Research Ethics Committee (IRAS ID
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55 279682) and all patients have provided written informed consent. This study complied with
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57 the ethical standards of the Declaration of Helsinki.
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Demographics, Disease Characteristics and Outcomes.

Disease onset was defined as time of first non-Raynaud's manifestation of SSc. Early disease as ≤ 60 months since disease onset. Skin disease subtype by presence of skin involvement proximal or distal to the elbow or knees. Overlap syndromes were recorded. ILD was confirmed on HRCT. Pulmonary hypertension (PH), cardiac scleroderma, gastrointestinal involvement and scleroderma renal crisis were defined from previous SMART cohort studies [13]. Auto-antibody data were collected. If patients were positive for >1 antibody they were included in the antibody group specific to SSc.

All available pulmonary function tests were collected and included in analysis. The closest C-reactive protein (CRP) prior to but within 12 months of starting biologic therapy was recorded. Elevated CRP was defined as ≥ 5 mg/L. Available CT scans of the chest performed within 12 months prior to starting treatment were scored using the Goh et al. extent of disease staging system by 2 independent assessors (NG + VO) [14]. Extensive disease was defined as $\geq 20\%$ involvement.

If rituximab and tocilizumab had been given to the same patient, data was analysed for the first biologic only. Response to therapy was considered stabilisation or improvement of lung function.

Statistical Analysis:

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4 Linear mixed effects models were used to describe the changes in absolute %FVC and
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6 %DLCO over 24-months pre and post-treatment start. All available patient lung function
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8 within 24 months pre and post biological treatment were included. Patient characteristics
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10 and their interactions with time were included in the models as covariates to assess their
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12 effect on absolute %FVC and %DLCO change over time. For each effect we present β co-
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14 efficients, p-values and 95% confidence intervals (CI). P-value of ≤ 0.05 was deemed
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16 significant. Age was assessed as a continuous variable centered at 50 years. Statistical
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18 analysis was performed using Stata14.
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26 **Results:**

27 **Description of study cohort:**

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29 We identified 127 SMART cohort patients who received rituximab and/or tocilizumab. 87
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31 had been treated with rituximab only, 32 tocilizumab only, and 8 received both biologics (7
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33 rituximab initially and 1 tocilizumab initially). Mean number of available lung function per
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35 patient over the study period was 5.16 (range 2–13) and 4.45 (range 2–8) for the rituximab
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37 and tocilizumab group respectively. Patients commenced rituximab between 2008 and 2021
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39 and tocilizumab between 2013 and 2021.
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48 43.6% (n=41) and 45.5% (n=15) of the rituximab and tocilizumab patients respectively were
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50 ATA positive. At the time of biologic treatment, patients were relatively evenly split
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52 between early and late disease in both treatment groups (early disease: 45.7% (n=43)
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54 rituximab, 57.6% (n=19) tocilizumab). The majority of patients received concurrent
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56 immunosuppression with their biologic therapy (rituximab: DMARD(s) 74.5% (n=70),
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4 prednisolone 74.5% (n=70), neither 5.3% (n=5), tocilizumab: DMARD(s) 60.6% (n=20),
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6 prednisolone 36.4% (n=12), neither 27.3% (n=9) with MMF the predominant DMARD used.
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8 Prior cyclophosphamide had been given to 43.6% (n=41) of the rituximab and 18.2% (n=6) of
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10 the tocilizumab cohort. 1 patient receiving tocilizumab had undergone aSCT for SSc. Of CT
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12 scans available (53 rituximab and 20 tocilizumab cohort), 26 (49.1%) of the rituximab and 3
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14 (15%) of the tocilizumab patients had extensive disease pre-treatment. Additional cohort
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16 baseline characteristics are shown in **Table S1**.
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24 **Biologics impact on lung function trajectory:**

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26 Model-estimated mean %FVC and %DLCO at the time of treatment were lower in the
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28 rituximab-treated group compared to the tocilizumab-treated group (rituximab: %FVC 70.7,
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30 %DLCO 41.4. tocilizumab: %FVC 88.2%, %DLCO 60.5%) (**Table S2**). Pre-treatment lung
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32 function decline was similar for both cohorts with change in %FVC/year and %DLCO/year in
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34 the rituximab cohort of -3.2% and -4% respectively, and in the tocilizumab cohort of -3.2%
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36 and -3.6% respectively (**Figure 1a, Table S3**). Both treatments were associated with lung
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38 function stabilisation with post-treatment change in %FVC/year and %DLCO/year
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40 respectively +1.2% and +0.2% for the rituximab cohort and +1.0% and +1.0% for the
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42 tocilizumab cohort (**Table S3**).
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51 **Impact of clinical characteristics on treatment response**

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53 Compared to females, males had a numerically greater pre-treatment decline in %FVC/year
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55 and lower %FVC on treatment initiation (**Table 1, Table S2 & Figure 1b**). However, males
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4 demonstrated a greater improvement in %FVC with either biologic compared to females
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6 and responded better to rituximab compared with tocilizumab (**Table 1**).

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11 Diffuse compared to limited skin subset was associated with numerically lower absolute
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13 levels of %FVC and a significantly greater rate of decline pre-treatment in the tocilizumab
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15 cohort (**Table 1 & S2**). However, no effect of skin subset on treatment response was
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17 observed (**Table 1 & S4**). Similarly, age did not impact response to either therapy (data not
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19 shown).

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26 Overlap inflammatory arthritis did not associate with %FVC or %DLCO values on treatment
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28 initiation or response to therapy. Disease duration did not appear to associate with either
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30 absolute %FVC levels or %FVC treatment response to rituximab or tocilizumab (**Figure S1a**).

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33 Early disease was associated with significantly faster decline in %DLCO pre-treatment in the
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35 rituximab group but not response to either treatment.

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41 ATA positive patients had significantly lower %FVC and %DLCO on treatment initiation
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43 compared to ATA negative patients (**Table S2**). While pre-treatment %FVC decline did not
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45 associate significantly with ATA positivity, treatment response did, with significantly greater
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47 response to tocilizumab and numerically greater but not statistically significant response to
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49 rituximab in %FVC in ATA positive patients treated with rituximab compared to ATA
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51 negative (**Figure 1c**). The significantly greater %FVC response to tocilizumab in ATA positive
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53 compared to ATA negative patients was maintained when age and gender were included in
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55 the mixed effects model ($\beta=5.8$, $p=0.03$, 95%CI 0.45–11.09).

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7 Patients who had received prior cyclophosphamide had a significantly lower starting %FVC
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9 **(Table S2)**. A numerically greater response was seen in tocilizumab patients who had
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11 received cyclophosphamide previously however this was a small patient subset **(Table 1)**.
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13 Concurrent MMF use on biologic initiation was significantly associated with increased %FVC
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15 response to tocilizumab, but not rituximab **(Figure 1d)**. CRP level had no significant effect on
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17 response to either biologic **(Figure S1b)**.
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24 As expected, patients with global extent of disease >20% on CT had a lower %FVC on
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26 treatment initiation **(Table S2)**, although treatment response did not differ from those with
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28 less extensive disease.
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33 **Discussion:**

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36 In this analysis, rituximab and tocilizumab are associated with significant improvement in
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38 %FVC trajectory, including in those who remain refractory to standard immunosuppression
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40 extending data from recent RCTs [7,9,10]. ATA positivity and male gender significantly
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42 impacted %FVC treatment response to tocilizumab and rituximab respectively. Two recent
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44 studies of real-world cohorts of tocilizumab in SSc reported a consistent but not significant
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46 effect on stabilisation of %FVC, however, neither study identified predictors of treatment
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48 responsiveness [15,16]. We showed lung function stabilised in all patient subgroups
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50 independent of skin subset, disease duration, gender, inflammatory arthritis and
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52 inflammatory response.
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4 In our cohort, baseline CRP was not predictive of response to tocilizumab and this is
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6 consistent with the focuSSced trial where high CRP level was prognostic for lung function
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8 decline but not predictive of treatment response [11]. A recent study reported
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10 immunosuppression stabilised lung function trajectory in patients with persistently elevated
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12 CRP, but worsened lung function decline in non-inflammatory patients. However, in this
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14 analysis, small numbers of patients were receiving MMF or rituximab and no patients were
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16 receiving tocilizumab [17].
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24 Our data on differential response of ATA positive patients to tocilizumab is consistent with
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26 data from focuSSced post-hoc analysis. Of note however treatment response to both
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28 rituximab and tocilizumab occurred irrespective of ATA status in our cohort [11]. The
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30 differential response to rituximab in the ATA positive subgroup was not specifically
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32 addressed in the recent SSc-ILD rituximab monotherapy RCT [6].
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38 Although we demonstrate a greater response among males only to rituximab, it should be
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40 noted that our tocilizumab analysis is underpowered. Post-hoc analyses from SLS I and II
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42 demonstrated men had a worse outcomes than women despite MMF or cyclophosphamide
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44 [18]. EVER-ILD RCT did not report differential gender response with combination MMF and
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46 rituximab [8]. However, data from focuSSced showed that male gender predicted response
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48 to tocilizumab [11]. It is well established that male gender is associated with progressive
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50 SSc-ILD and along with ATA positive patients rapid progressors may particularly benefit from
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52 additional biological therapies.
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4 Few ILD therapeutic trials have evaluated outcomes with combination approaches. Upfront
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6 combination rituximab and MMF was associated with greater benefit on FVC change at six
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8 months compared to MMF alone in a cohort of patients with non-specific interstitial
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10 pneumonia, including a small number of SSc-ILD patient. Infection rates were higher with
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12 combination MMF and rituximab however infections were predominantly non-serious viral
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14 infections [8]. The majority of our patients were on background DMARD therapy and we
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16 showed combination MMF with either rituximab or tocilizumab is beneficial. Notably the
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18 FVC response to tocilizumab-MMF was significant compared to tocilizumab treatment
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20 alone. The addition of tocilizumab may potentiate the effect of MMF and the timely
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22 introduction of a second agent may be particularly relevant in high-risk patients however we
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24 are not aware of any published data regarding infection risk with combination therapy in
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26 SSc and this needs further research.
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36 A high proportion, particularly of the rituximab-treated patients, had received prior
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38 cyclophosphamide. Despite previous cyclophosphamide, patients responded to treatment
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40 with rituximab and tocilizumab suggesting additive benefit of biologic treatment in patients
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42 with continued decline. Due to their recent approval no patients were receiving anti-
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44 fibrotics.
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50 The lack of effect of CT disease extent with biologic may relate to the small numbers.
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52 However, data on impact of disease extent on treatment response in SSc-ILD has not been
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54 consistent. *Post-hoc* analysis of SLS I suggested patients with more severe reticular changes
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56 on HRCT may have a greater response to cyclophosphamide [19]. However, *post-hoc*
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4 focuSSced study analysis found no influence of quantitative ILD and fibrosis scores on
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6 baseline CT in tocilizumab response [20].
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11 There are a number of study limitations. This is a single centre retrospective data set,
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13 however, this reflects a large well-characterised SSc cohort. Lung function testing frequency
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15 was variable and subject to clinical judgment, some characteristics were under-represented
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17 and there were a number of missing data points. It was not possible to clarify rituximab
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19 repeat doses therefore the initial dose of rituximab was taken as rituximab start time. We
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21 were unable to reliably collect data on treatment complications.
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29 Real-world treatment choice takes into account extrapulmonary conditions and patient
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31 comorbidities and include a more diverse patient cohort including patients with early and
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33 late disease, both skin subsets and of diverse ethnic backgrounds. Our data suggests
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35 stabilisation of lung function decline with both rituximab and tocilizumab in a real-world SSc
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37 cohort. We propose tocilizumab in combination with MMF may be of particular benefit in
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39 patients who are ATA positive. However, both biologic therapies appear to stabilise lung
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41 function decline in patients with both early and late disease who may have failed initial
42
43 therapy.
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50
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9

10
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13
14 Dr Nina R Goldman: declares no conflicts of interest
15

16 Dr Svetlana I Nihtyanova: employee of GSK
17

18 Claire F Beesley: declares no conflicts of interest
19

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21
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23

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25

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31

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45 **Ethics Approval:**
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48 The study was approved by London-Fulham NHS Research Ethics Committee (IRAS ID
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50 279682)
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55 **Data availability statement:**
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4 The data underlying this article will be shared on reasonable request to the corresponding
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6 author.
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16 **Abbreviations:**

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18 ATA = anti-topoisomerase antibody, CRP = C-reactive protein, CTD = connective tissue
19 disease, CT = Computed tomography, DLCO = diffusion capacity for carbon monoxide,
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21 DMARD = disease modifying anti-rheumatic drugs, FVC = forced vital capacity, HRCT = high
22 resolution CT, IL6 = interleukin 6, ILD = Interstitial lung disease, MCID = minimally clinically
23 important difference, MMF = mycophenolate mofetil, PH = pulmonary hypertension, RCT =
24 randomised controlled trial, SLS = scleroderma lung study, SSc = Systemic sclerosis
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Tables and Figures:**Table 1:** Effect of different patient characteristics on the yearly changes in %FVC in the two treatment cohorts pre and post-treatment with rituximab or tocilizumab

Fixed effect parameter	Rituximab						Tocilizumab					
	Pre-Treatment			Post-Treatment			Pre-Treatment			Post-Treatment		
	Effect of characteristic on annual rate of change in %FVC*	P value	95% CI	Effect of characteristic on annual rate of change in %FVC*	P value	95%CI	Effect of characteristic on annual rate of change in %FVC*	P value	95%CI	Effect of characteristic on annual rate of change in %FVC*	P value	95% CI
Male	-4.14	0.08	-8.72, 0.44	3.81	0.03	0.36, 7.27	-3.92	0.46	-14.2, 6.37	1.23	0.74	-5.93, 8.38
dcSSc subset	-2.75	0.14	-6.36, 0.86	-0.03	0.98	-2.95, 2.89	-10.6	0.04	-20.5, -0.69	5.86	0.14	-1.91, 13.64
Inflammatory Arthritis present	1.22	0.53	-2.63, 5.08	1.41	0.35	-1.52, 4.35	6.3	0.09	-0.98, 13.6	3.33	0.21	-1.83, 8.49
ATA positive	-0.37	0.85	-4.16, 3.42	2.37	0.11	-0.51, 5.26	-2.05	0.59	-9.40, 5.30	5.34	0.05	0.02, 10.66
Disease duration at treatment initiation ≤60m	-2.04	0.27	-5.64, 1.57	-0.36	0.81	-3.25, 2.53	-1.75	0.64	-9.15, 5.65	-1.32	0.65	-7.05, 4.41
Concurrent MMF at treatment initiation	-0.22	0.91	-3.94, 3.49	0.91	0.53	-1.92, 3.75	-6.88	0.06	-14.1, 0.37	5.79	0.04	0.33, 11.2
Previous cyclophosphamide	-1.82	0.34	-5.56, 1.92	1.65	0.25	-1.17, 4.4	-2.51	0.58	-11.4, 6.41	6.18	0.08	-0.08, 13.1
Pre-treatment CRP ≥5	-1.76	0.43	-6.13, 2.61	1.71	0.32	-1.62, 5.03	-7.2	0.10	-15.84, 1.45	0.07	0.98	-5.98, 6.11
Global extent on CT ≥20%	0.71	0.77	-4.11, 5.53	2.34	0.23	-1.44, 6.12	-3.49	0.58	-15.82, 8.84	10.45	0.07	-0.93, 21.82

Significant values are highlighted in bold
 *β coefficient: Effect of characteristic on annual rate of change in %FVC compared to reference group eg male vs female, dcSSc vs lcSSc, inflammatory arthritis present vs absent, ATA positive vs negative

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3 **Figure 1:** Change in %FVC over time pre and post treatment with rituximab or tocilizumab
4 and interaction of other patient characteristics. Time 0 = time of biologic treatment. *
5 Significant effect of characteristics on annual rate of change in %FVC pre or post treatment
6 compared to reference group (p-value ≤ 0.05). a) Impact of treatment rituximab (RTX) or
7 tocilizumab (TCZ) b) Male or Female c) ATA+ vs ATA-, d) concurrent MMF at treatment
8 initiation vs other/no concurrent immunosuppression at treatment initiation (IS). Linear
9 mixed model data is provided in Table S3 & S5
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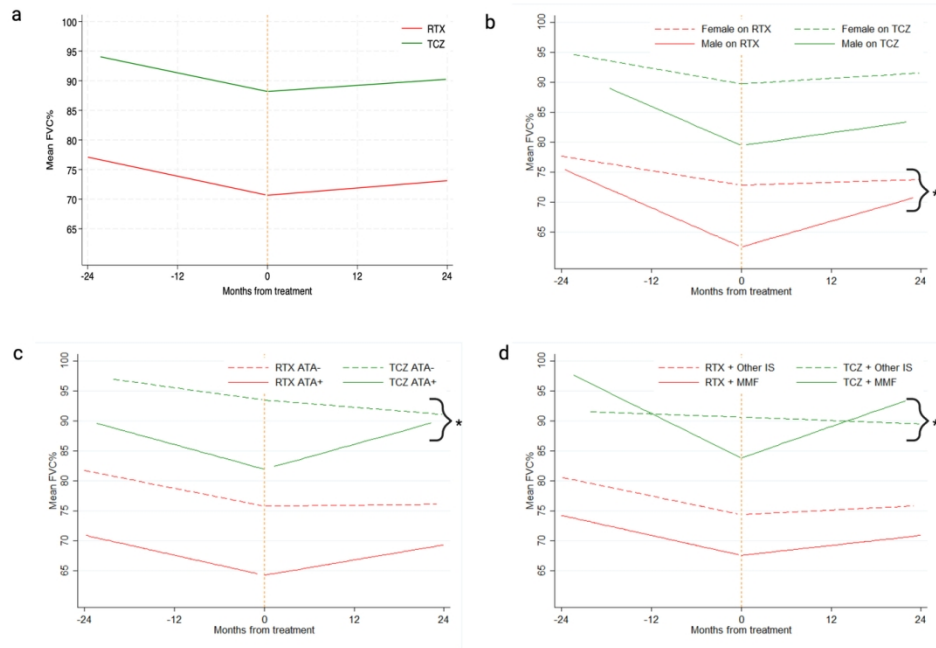


Figure 1: Change in %FVC over time pre and post treatment with rituximab or tocilizumab and interaction of other patient characteristics. Time 0 = time of biologic treatment. * Significant effect of characteristics on annual rate of change in %FVC pre or post treatment compared to reference group (p-value < 0.05). a) Impact of treatment rituximab (RTX) or tocilizumab (TCZ) b) Male or Female c) ATA+ vs ATA-, d) concurrent MMF at treatment initiation vs other/no concurrent immunosuppression at treatment initiation (IS). Linear mixed model data is provided in Table S3 & S5

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