

Manuscript title

**Real-world experience of Tocilizumab in systemic sclerosis: potential benefit on lung function for anti-topoisomerase (ATA) positive patients**

Authorship list

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**Rheumatology key message:** Tocilizumab administration stabilises lung function test decline in systemic sclerosis patients with positive anti-topoisomerase antibody.

*Dear Editor,*

In the Phase II faSScinate [1] and Phase III focuSSced [2] clinical trials, tocilizumab, an anti-IL-6 receptor antibody, demonstrated consistent and clinically meaningful benefit on lung function decline in diffuse cutaneous systemic sclerosis (SSc) assessed by change in forced vital capacity (FVC), a validated measure of SSc associated interstitial lung disease (SSc-ILD). This was despite both studies showing only a trend in benefit in the primary endpoint of modified Rodnan skin score (mRSS). In the focuSSced trial the impact on FVC was particularly seen in those patients with evidence of SSc-ILD on baseline chest CT scan, with quantitative analysis of fibrosis showing statistically significant benefit compared with placebo. The focuSSced trial results also suggested that patients with anti-topoisomerase-1 autoantibody (ATA, also known as anti-Scl-70) show greater treatment benefit for FVC compared to other autoantibody subgroups [3]. This is notable because ATA is associated with a very high risk of early progressive lung fibrosis in SSc that is independent of disease subset [4].

Tocilizumab is licensed for treatment of inflammatory arthritis and giant cell arteritis. It has been used in our tertiary connective tissue disease centre for patients with SSc and overlap inflammatory arthritis, who have not responded to standard DMARD therapy. We report here our real-world experience of tocilizumab in SSc, and its impact on the lung function of these patients.

We carried out a retrospective study of all SSc patients treated with tocilizumab. Data from patients receiving tocilizumab while enrolled in the faSScinate trial were excluded, however,

we did include results for those receiving it on a compassionate basis following the focuSSced trial. A comparator group not receiving tocilizumab matched for ANA subtype and SSc diagnosis was also examined. Statistical analysis was carried out using the median values and the Wilcoxon rank sum test.

47 patients were identified as being initiated on tocilizumab in our cohort and 31 had serial lung function data available to compare FVC and DLCO before and after initiation of treatment. 71% of these patients (n=22) had a diagnosis of diffuse SSc, with 77% (n=24) being female. 35.4% of patients were ATA positive. 45.2% (n=14) had known interstitial lung disease. Median age of disease onset was 37 years and median disease duration prior to initiation of tocilizumab was 6 years. 6 patients received tocilizumab on a compassionate basis following completion of the open label phase of the focuSSced clinical trial whilst the remainder had a diagnosis of overlap inflammatory arthritis.

To standardise results, annualised change rate in FVC and DLCO was calculated (% predicted change/year). Across the tocilizumab treated cohort, median predicted FVC prior to initiation of treatment was 92.4%, and predicted DLCO was 63.0%. Overall median change in % predicted FVC was -1.3% (IQR=0.1787) and median change in % predicted DLCO was 1.54% (IQR=0.2275). The average change in FVC was significantly greater in the non-tocilizumab comparator group (n=31) with median -4.1% (IQR 5.8%), p=0.016).

Subgroup analysis revealed a significant difference between autoantibody groups and change in FVC while on tocilizumab (p=0.044) (Fig. 1). Median FVC in the ATA prior to initiation of tocilizumab 87% (IQR 79.6% - 94%), and in the non-ATA group was 97% (88.0 - 102.6%). Median change in predicted FVC over 12 months was 0% in the ATA group (IQR 4.04%), and was -3.5% in the non-ATA group (IQR 8.58%). There was no significant difference in FVC

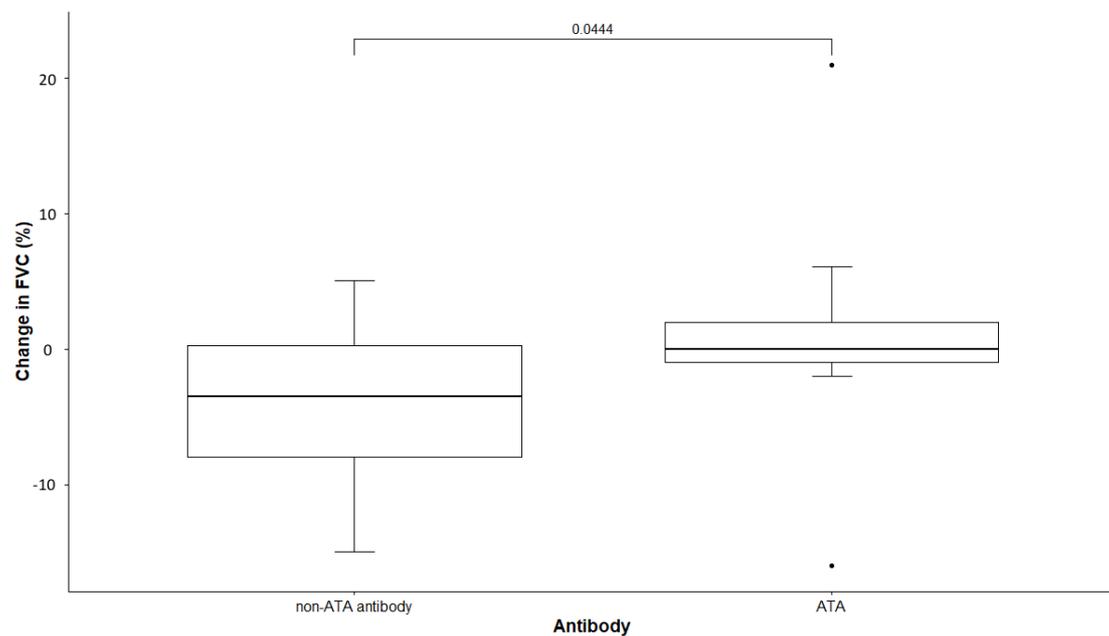
change for patients with ILD prior to initiation of treatment and those without ( $p=0.11$ ) or for patients on a DMARD in combination with tocilizumab, compared with tocilizumab alone ( $p=0.78$ ). There was no difference between early and late stage disease at time of tocilizumab initiation, as defined by  $<5$  years disease duration ( $p=0.952$ ).

In the non-tocilizumab comparator group, annualised decline in FVC was numerically greater for non-ATA (-5.63%, IQR 6.06%) than in the ATA subgroup (-2.32%, IQR 2.97%), but this was not significant ( $p=0.057$ ). Whilst these comparative data need cautious interpretation, being retrospective and not randomised, it is notable that for both ATA and non-ATA cases the average decline in FVC was lower in tocilizumab treated patients, although the difference was statistically significant only for ATA positive cases ( $p=0.0058$ ), suggesting that tocilizumab may have greater benefit in this subgroup.

Our study supports potential benefit of tocilizumab on lung function in SSc patients in a real world setting, especially for ATA positive cases. This includes patients with more established disease than those included in the faSScinate or focuSSced clinical trials. Since many were receiving tocilizumab for arthritis it is also relevant that other investigators have recently described a risk score (SPAR) for progressive lung fibrosis in SSc suggesting presence of arthritis as a predictor of increased risk of lung function decline and this may be relevant in identifying cases of SSc most likely to benefit from tocilizumab [5]. Our findings provide further support for considering tocilizumab as a treatment for SSc-ILD.

## Figures

**Fig. 1**



### Change in forced vital capacity (FVC) by anti-topoisomerase antibody (ATA) status

**Fig.1:** Median percentage change in predicted FVC over 12 months was 0% in the ATA group (-1% to 2%), and -3.5% in the non-ATA group (-8% to 0.25%) whilst on Tocilizumab. Significant p-value included.

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