National Jewish Health
Breathing Science is Life.

JOURNAL CLUB

Article Summary by: Liudmila Kastsianok, MD, RhMSUS & Rebecca Keith, MD

ARTICLE

Tocilizumab in systemic sclerosis: a randomized, double-blind, placebo-controlled, phase 3 trial (focuSSed). Lancet Respir Med 2020 Oct;8(10):963-974. https://pubmed.ncbi.nlm.nih.gov/32866440/

CLINICAL QUESTION

Implication of tocilizumab in systemic sclerosis interstitial lung disease, a new kid on the block?

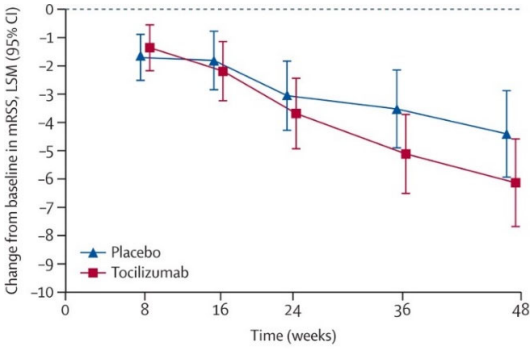
SUMMARY

FocuSSed was a multicenter, international, randomized, double-blind, placebo-controlled, phase 3 trial to investigate the safety and efficacy of tocilizumab, an anti-interleukin-6 antibody, in the treatment of systemic sclerosis. Adults with diffuse cutaneous systemic sclerosis for 60 months/5 years or less and a modified Rodnan skin score (mRSS; mRSS is a measure of skin thickness that has been used in clinical trials of diffuse cutaneous systemic sclerosis) of 10-35 at the screening were randomly assigned to receive subcutaneous tocilizumab 162mg or placebo weekly for 48 weeks, stratified by IL-6 levels. Patients were recruited between November 20, 2015 and February 14, 2017.

The primary endpoint was the difference in change from baseline to week 48 in mRSS. Secondary endpoints were percentage of predicted forced vital capacity (FVC% predicted) at week 48, time to treatment failure, and patient-reported and physician-reported outcomes.

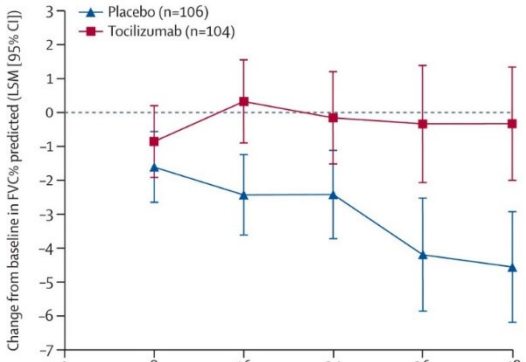
A total of 210 patients were recruited. 210 patients were randomly assigned to receive tocilizumab (N 104) or placebo (N 106). Least square mean (LSM) change from baseline to week 48 in mRSS was -6.14 for tocilizumab and -4.41 for placebo (adjusted difference -1.73 [95% CI -3.70 to 0.32], p=0.10). The sift in distribution of change from baseline in FVC% predicted at week 48 favored tocilizumab with the difference in LSM of 4.2 (95% CI 2.0-6.4; nominal p=0.0002), as did time to treatment failure (hazard ratio 0.63 [95% CI 0.37-1.06], nominal p=0.08). Changes in LSM from baseline to week 48 in Health Assessment Questionnaire-Disability Index and in patient-global and physician global visual analogue scale assessments were not different from tocilizumab and placebo.

The primary skin fibrosis endpoint was not met. Findings for the secondary endpoint of FVC% predicted indicate that tocilizumab might preserve lung function in people with early SSc-ILD and elevated acute phase reactants.



	Placebo n=106	Tocilizumab n=104	
LSM change from baseline at week 48 (primary outcome)	-4·4	-6·1	-1·7 (95% CI -3·8 to 0·3); p=0·10
LSM change from baseline at week 24 (exploratory outcome)	-3·1	-3·7	-0·6 (95% CI -2·3 to 1·0); nominal p=0·45

Figure 1: Mean change from baseline in mRSS



	Placebo n=106	Tocilizumab n=104	
LSM change from baseline at week 48	-4·6	-0·4	4·2 (95% CI 2·0 to 6·4); nominal p=0·0002

Figure 2: Mean change from baseline for FVC% predicted at week 48

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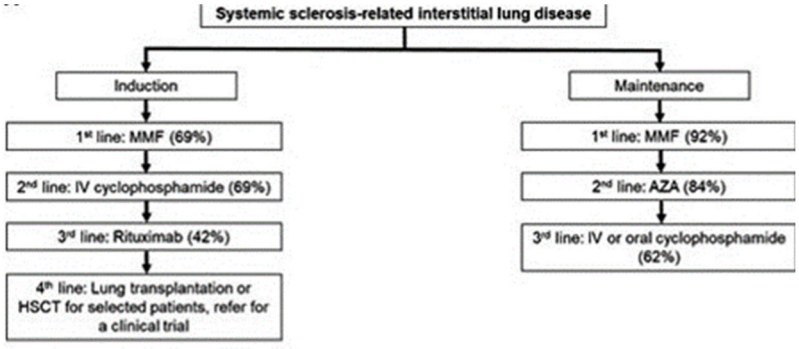
GROUP OPINION

Interstitial lung disease (ILD) is one of the leading causes of death in patients with SSc. Factors associated with progression of ILD in SSc include diffuse cutaneous phenotype, anti-SCL-70 (anti-topoisomerase I) positivity, elevated acute phase reactants, and ethnicity (1). It is one of the challenging manifestations to treat. There are limited options available for SSc-ILD treatment available.

ILD treatment in SSc (2)



IV cyclophosphamide vs rituximab were assessed for systemic sclerosis skin and ILD (3), showed that RTX is a safe and effective alternative to CYC in the primary therapy of skin and lung manifestations of scleroderma.
SENSCIS trial of nintedanib in SSc, nintedanib slowed the progression of established lung fibrosis in a large cohort participant with SSc-ILD (4).

The focuSSed trial recruited patients with early diffuse cutaneous disease, comparing to SENSCIS trial.

IL-6 effect on myofibroblasts via inhibition of STAT3 have been reported previously, a putative link between IL-6 and TGF-b intracellular signaling (5,6,7). Circulating IL-6 levels are elevated in patients with SSc (8) and are associated with the development of skin fibrosis and SSc-ILD (9,10,11). Inhibition of IL-6 signaling via IL-6 receptor blockade with tocilizumab might reduce skin fibrosis in patients with SSc (12, 13). faSSinate, a phase 2, randomized controlled trial, investigated the efficacy and safety of tocilizumab in SSc (14). Data from faSSinate trial and the need for effective treatment for SSc with severe skin and lung manifestations, supported investigation of tocilizumab in a phase 3 trial, focuSSed.

Participants in faSSinate and focuSSed trials had early disease and mild lung involvement, which limits comparison with other trials; however, it provides new data that support further investigation.

FDA approval of tocilizumab in March 2021 is a promising move, however further investigation is needed to determine the role of tocilizumab in SSc-ILD. Our clinical group favors MMF and CYC for clinically and radiologically significant ILD (HRCT involvement >10%). In cases of progression fibrosis in SSc-ILD, our group favors adding nintedanib to baseline immunosuppression. Tocilizumab seems to have a role for use in patients with SSc who present with inflammatory arthritis with synovitis and/or erosions and limited ILD. There may also be a role for adding tocilizumab to MMF in patients with ongoing inflammation and autoimmunity as a driver of progressive fibrosis. We look forward to additional studies in this area.

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ILD Journal Club dates and times: ***njhealth.org/ILDJournalClub***

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