Treatment of Systemic Sclerosis–associated Interstitial Lung Disease

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SLS-II

- Randomized trial, ***142 patients*** with SSc-ILD,
- ***FVC<80 percent, but >45 percent of predicted***, exertional dyspnea, GGO on HRCT with or without reticular opacities, and onset of the first non-Raynaud symptom of SSc within the prior seven years.
- MMF 1500 mg twice daily for 24 months or oral CYC titrated up to a maximum daily dose of 1.8 to 2.3 mg/kg for 12 months.
- Improvement in FVC from baseline to 24 months: ***2.19 percent*** (95% CI 0.53-3.84) in the ***MMF*** group and ***2.88 percent*** (95% CI 1.19-4.58) in the ***cyclophosphamide*** group, a nonsignificant difference. Dyspnea improved in both groups based on the Transition Dyspnea Index.
- MMF was better tolerated than cyclophosphamide based on a longer time to patient withdrawal and a lower incidence of leukopenia and thrombocytopenia.

Lancet Respir Med 2016; 4:708

Rituximab versus intravenous cyclophosphamide in patients with connective tissue disease-associated interstitial lung disease in the UK (RECITAL): a double-blind, double-dummy, randomised, controlled, phase 2b trial

*Toby M Maher, Veronica A Tudor, Peter Saunders, Michael A Gibbons, Sophie V Fletcher, Christopher P Denton, Rachel K Hoyles, Helen Parfrey, Elisabetta A Renzoni, Maria Kokosi, Athol U Wells, Deborah Ashby, Matyas Szigeti, Philip L Molyneaux, on behalf of the RECITAL Investigators**

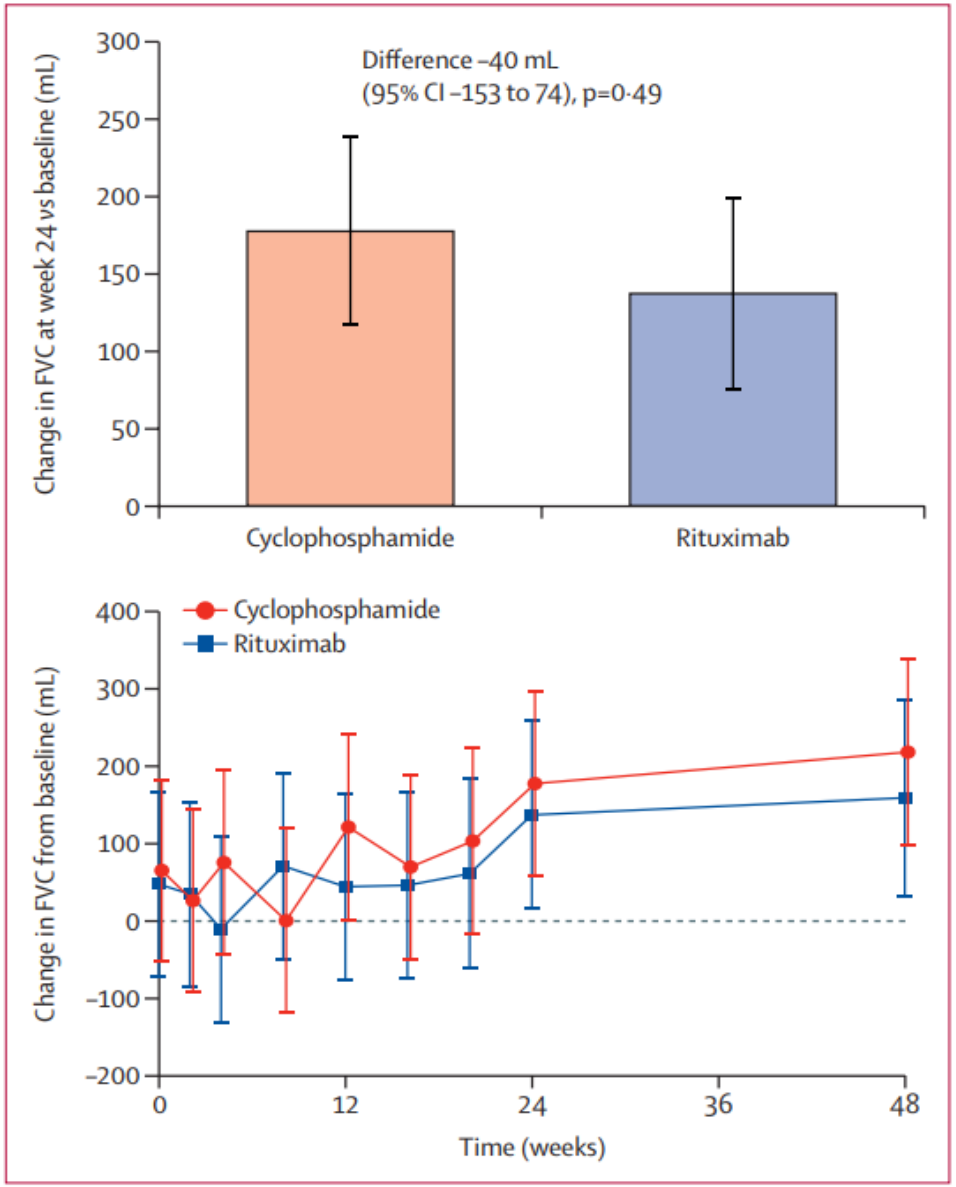
Lancet Respir Med 2023; 11: 45–54

- Randomised, double-blind, phase 2b trial , 11 centres in the UK
- To assess the superiority of rituximab compared with cyc.
- with severe or progressive ILD related to scleroderma, idiopathic inflammatory myositis, or mixed CTD .

- Randomly assigned (1:1) to receive rituximab, ***48*** (1gr at weeks 0 and 2 iv) or cyclophosphamide, ***49*** (600 mg/m^2 every 4 wk iv for six doses).
- The primary endpoint: rate of change in FVC at 24 weeks compared with baseline.

	Cyclophosphamide group (n=48)	Rituximab group (n=49)
Connective tissue disease type		
Idiopathic inflammatory myositis	22 (46%)	22 (45%)
Systemic sclerosis	19 (40%)	18 (37%)
Mixed connective tissue disease	7 (15%)	9 (18%)
Years since onset of connective tissue disease	4·8 (6·2)	4·5 (7·6)
FVC, L	2·23 (0·85)	2·25 (0·77)
FVC, % of predicted	71% (20)	68% (17)
DL_{CO}, mL/min per kPa	3·35 (1·42), n=46	3·46 (1·33), n=45
DL_{CO}, % of predicted	40% (14), n=46	40% (14), n=45
SpO_2 on room air, %	96% (2)	97% (2)
6 min walk distance, m	363 (111)	356 (126)
EQ-5D score	55 (20)	58 (22)
GDA score	5·03 (1·76), n=40	4·58 (1·97), n=38
KBILD score	46·1 (20·3)	51 (21·2)
SGRQ score	55·8 (20·0), n=47	52·1 (17·6), n=45

Baseline characteristics in the modified intention-to-treat population



Adjusted rate of change in FVC in the cyclophosphamide and rituximab groups at week 24 and adjusted change in FVC from baseline to week 48

Interpretation

- No significant differences in secondary endpoints were identified between the treatment groups.
- Rituximab was not superior to cyclophosphamide to treat patients with CTD-ILD, although participants in both treatment groups had increased FVC at 24 weeks, in addition to clinically important improvements in patient-reported quality of life.
- Rituximab was associated with fewer adverse events.

RHEUMATOLOGY

Rheumatology 2020;00:1–11
doi:10.1093/rheumatology/keaa550

Systematic review and meta analysis

Rituximab in the treatment of systemic sclerosis–related interstitial lung disease: a systematic review and meta-analysis

Rudra P. Goswami [1], Animesh Ray[2], Moumita Chatterjee[3], Arindam Mukherjee[4], Geetabali Sircar [5] and Parasar Ghosh[5]

- A total of ***20 studies*** (2 randomized controlled trials, 6 prospective studies, 5 retrospective studies and 7 conference abstracts) were included ***(n=575).***
- RTX improved ***FVC*** from baseline by 4.49% (95% CI 0.25, 8.73) at 6 months and by 7.03% (95% CI 4.37, 9.7) at 12 months.
- Similarly, RTX improved ***DLCO*** by 3.47% (95% CI 0.99, 5.96) at 6 months and 4.08% (95% CI 1.51, 6.65) at 12 months.
- In the two studies comparing RTX with other immunosuppressants, improvement of FVC by 6 months in the RTX group was 1.03% (95% CI 0.11, 1.94) greater than controls.
- Patients treated with RTX had a lower chance of developing ***infections*** compared with controls [odds ratio 0.256 (95% CI 0.104, 0.626).

Conclusions

- Treatment with RTX in SSc-ILD was associated with a ***significant improvement of both FVC and DLCO*** during the first year of treatment.
- RTX use was associated with ***lower infectious adverse events***.

AMERICAN THORACIC SOCIETY DOCUMENTS

Treatment of Systemic Sclerosis–associated Interstitial Lung Disease: Evidence-based Recommendations

An Official American Thoracic Society Clinical Practice Guideline

Ganesh Raghu, Sydney B. Montesi, Richard M. Silver, Tanzib Hossain, Madalina Macrea, Derrick Herman, Hayley Barnes, Ayodeji Adegunsoye, Arata Azuma, Lorinda Chung, Gregory C. Gardner, Kristin B. Highland, Marie Hudson, Robert J. Kaner, Martin Kolb, Mary Beth Scholand, Virginia Steen, Carey C. Thomson, Elizabeth R. Volkmann, Fredrick M. Wigley, Dee Burlile, Karen A. Kemper, Shandra L. Knight, and Marya Ghazipura; on behalf of the American Thoracic Society Assembly on Clinical Problems

Am J Respir Crit Care Med Vol 209, Iss 2, pp 137–152, Jan 15, 2024

Recommendation 3

- We suggest using rituximab to treat patients with SSc-ILD ***(conditional recommendation, very low quality evidence)***.
- The committee noted from clinical experience that the use of rituximab for SSc-ILD is often as rescue therapy in individuals with evidence of SSc-ILD progression despite treatment with mycophenolate.

Am J Respir Crit Care Med Vol 209, Iss 2, pp 137–152, Jan 15, 2024

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nintedanib for Systemic Sclerosis–Associated Interstitial Lung Disease

Oliver Distler, M.D., Kristin B. Highland, M.D., Martina Gahlemann, M.D., Arata Azuma, M.D., Aryeh Fischer, M.D., Maureen D. Mayes, M.D., Ganesh Raghu, M.D., Wiebke Sauter, Ph.D., Mannaig Girard, M.Sc., Margarida Alves, M.D., Emmanuelle Clerisme-Beaty, M.D., Susanne Stowasser, M.D., Kay Tetzlaff, M.D., Masataka Kuwana, M.D., and Toby M. Maher, M.D., for the SENSCIS Trial Investigators*

May 20, 2019

- Randomized, double-blind, placebo-controlled trial, A total of ***576 patients*** across ***32 countries***.
- To investigate the ***efficacy and safety*** of nintedanib in patients with ILD associated with systemic sclerosis.
- Patients who had SSc with an onset of the first non-Raynaud's symptom within the past 7 years and a HRCT scan that showed ***fibrosis affecting at least 10% of the lungs.***
- Randomly assigned, in a 1:1 ratio, to receive 150 mg of nintedanib, administered orally twice daily, or placebo.
- The primary end point: the ***annual rate of decline in FVC***, assessed over a ***52-week period.***
- Secondary end points: absolute changes from baseline in the modified ***Rodnan skin score*** and in the total score on the St. George's Respiratory Questionnaire ***(SGRQ)*** at week 52.

- primary end-point: the adjusted annual rate of change in FVC was −52.4 ml per year in the nintedanib group and −93.3 ml per year in the placebo group (difference, 41.0 ml per year; 95% confidence interval [CI], 2.9 to 79.0; P=0.04).
- Secondary end point: ***mRSS*** and the total score on the ***SGRQ*** at week 52 ***did not differ significantly*** between the trial groups.
- Safety: ***Diarrhea***, the most common adverse event, was reported in ***75.7%*** of the patients in the nintedanib group and in ***31.6%*** of those in the placebo group.
- Nintedanib increased the risk of ***nausea*** (2.3 times), ***vomiting*** (2.4 times), ***diarrhea*** (2.4 times), ***weight loss*** (2.8 times), and adverse events leading to ***treatment discontinuation*** (1.8 times) but decreased the risk of ***cough*** as an adverse event by 35%

Combination therapy

- For SSc-ILD, it is unknown if combining therapies with different mechanisms of action is preferable to individual agents and, if dual therapy is preferred, what is the combination of choice.
- The use of mycophenolate has demonstrated improvement in the absolute FVC % predicted over time, whereas nintedanib has been shown to reduce the rate of disease progression compared with placebo in patients with SSc-ILD.

Combination therapy

- The second study was a ***post hoc subgroup analysis*** of the SENSCIS trial that examined the efficacy and safety of patients treated with mycophenolate and nintedanib.
- This study reported results for four groups— combination therapy, mycophenolate plus placebo, nintedanib plus placebo, and placebo only—and provided the majority of data for the systematic review.

Results

- There were ***no significant differences in the annual rate of decline in FVC or FVC % predicted*** between combination therapy and mycophenolate or combination therapy and nintedanib,
- But the ***risk of FVC decrease from baseline by >5%*** was about one-third less in the combination therapy arm when compared with either mycophenolate alone or nintedanib alone.
- There were ***no differences*** identified in ***mRSS*** between combination therapy with nintedanib plus mycophenolate versus placebo, mycophenolate only, or nintedanib only.

QOL

- There were ***no differences*** identified in ***SGRQ*** scores between combination therapy with nintedanib plus mycophenolate to placebo, mycophenolate only, or nintedanib only.

ADVERSE EVENTS

- Combination therapy was associated with a ***sevenfold*** higher risk of ***decreased appetite***, more than ***2.5-fold*** higher risk of ***diarrhea***, and about ***threefold*** higher risk of ***nausea, vomiting, and/or fatigue*** compared ***with placebo***.
- Combination therapy was also associated with nearly ***twice*** the risk of ***diarrhea, nausea, and vomiting*** compared with ***mycophenolate*** only.
- Combination therapy was associated with a ***1.65-fold*** increase in ***serious adverse events*** compared with ***mycophenolate*** only.
- Interestingly, combination therapy was associated with a ***60% lower*** risk of ***liver test abnormalities*** compared with ***nintedanib*** only.

Recommendation 5 & 6

- We suggest using nintedanib to treat patients with SSc-ILD ***(conditional recommendation, very low quality evidence)***

- We suggest using the combination of nintedanib plus mycophenolate to treat patients with SSc-ILD

(conditional recommendation, very low quality evidence)

The Journal of Rheumatology

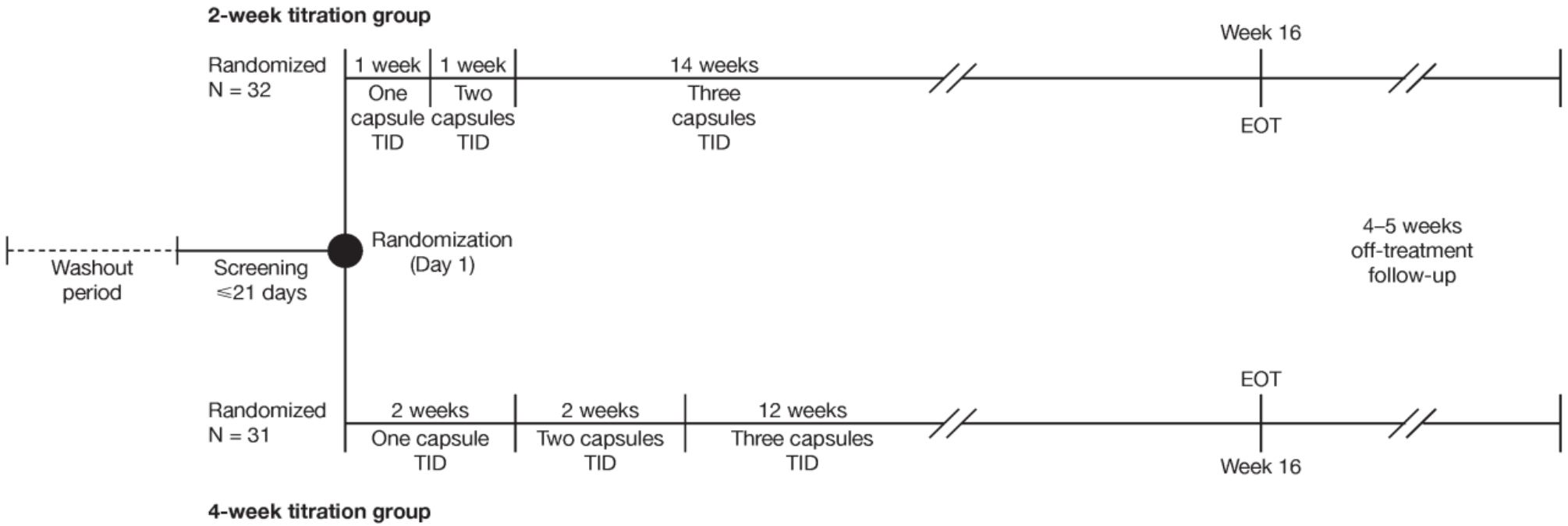
The Journal of Rheumatology

An Open-label, Phase II Study of the Safety and Tolerability of Pirfenidone in Patients with Scleroderma-associated Interstitial Lung Disease: the LOTUSS Trial

Dinesh Khanna, Carlo Albera, Aryeh Fischer, Nader Khalidi, Ganesh Raghu, Lorinda Chung, Dan Chen, Elena Schiopu, Margit Tagliaferri, James R. Seibold and Eduard Gorina

The Journal of Rheumatology 2016; 43:9; doi:10.3899/jrheum.151322

LOTUSS study design



Results

- 96.8% experienced a TEAE
- More patients reported TEAE ***during the titration*** versus the maintenance period.
- The most commonly reported TEAE were consistent with those observed for ***pirfenidone in IPF (nausea, headache, fatigue)*** and were similar regardless of titration schedule.
- More patients discontinued treatment because of TEAE in the ***2- versus 4-week*** titration group ***(5 vs 1, respectively)***
- Mycophenolate mofetil (MMF), taken by 63.5% of patients in addition to pirfenidone, ***did not appear to affect tolerability***.
- Conclusion: Pirfenidone showed an ***acceptable tolerability*** profile in SSc-ILD, although a ***longer titration*** may be associated with better tolerability.
- Tolerability was not affected by concomitant MMF.

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

ABSTRACT NUMBER: 0520

Combination Therapy of Mycophenolate Mofetil and Pirfenidone vs. Mycophenolate Alone: Results from the Scleroderma Lung Study III

Dinesh Khanna[1], Cathie Spino[2], Elana Bernstein[3], Jonathan Goldin[4], Donald Tashkin[4], Michael roth[4] and On Behalf of SLS III Investigators[2], [1]Division of Rheumatology, Department of Internal Medicine, Scleroderma Program, University of Michigan, Ann Arbor, MI, [2]University of Michigan, Ann Arbor, MI, [3]Columbia University, New York, NY, [4]University of California Los Angeles, Los Angeles, CA

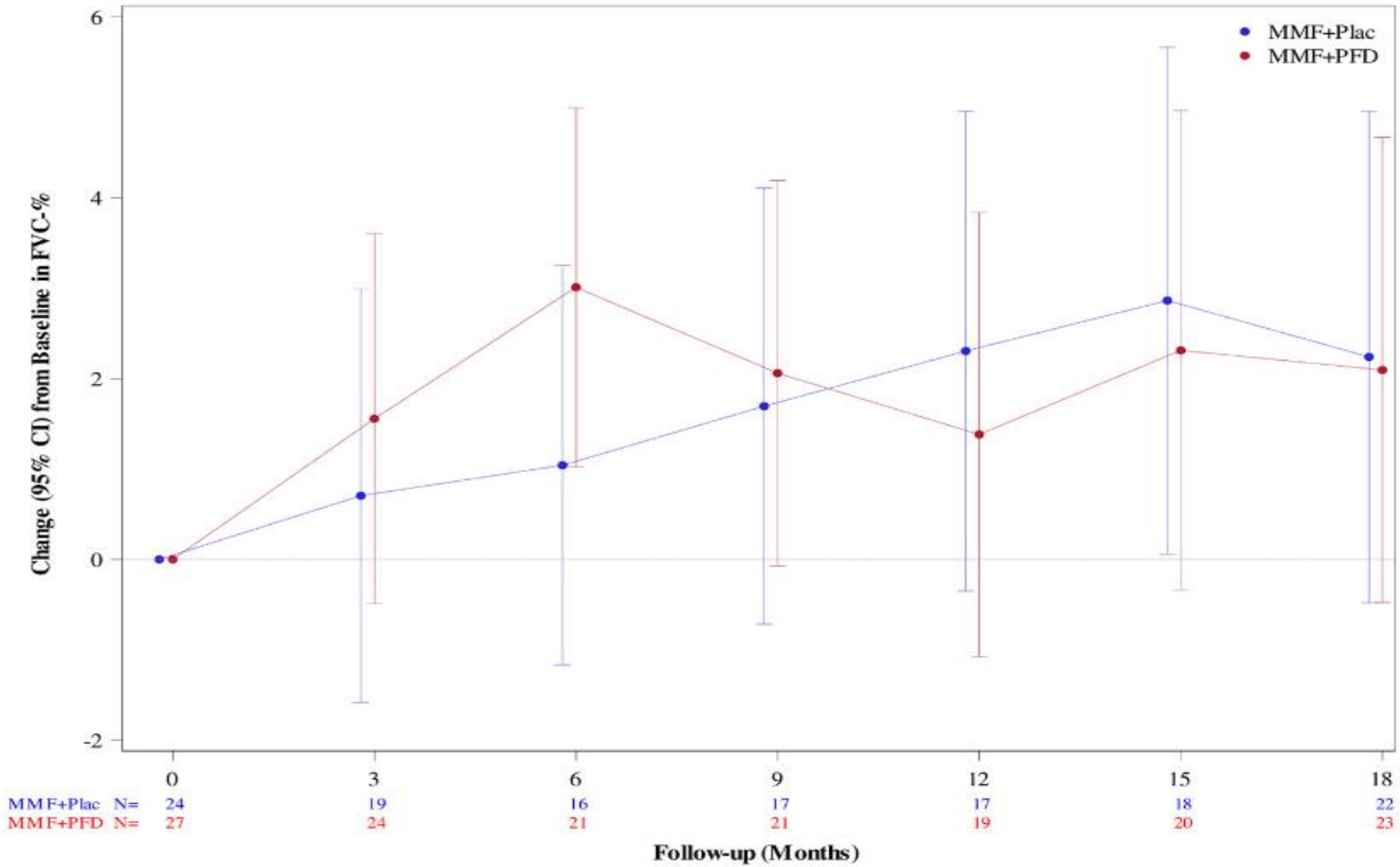
Meeting: ACR Convergence 2022

Methods

- Multi-center, double-blind, placebo-controlled Phase II trial
- Evaluated ***MMF+PFD*** vs ***MMF+PLA*** in those with SSc-ILD.
- FVC% ≤ 85% predicted, disease duration ≤7 yrs, and any GGO on HRCT.
- The primary endpoint was the change from baseline in the mean FVC% over the course of the 18-month treatment period.

Results

- 51 participants were randomized with 27 to MMF+PFD and 24 to MMF+PLA.
- Recruitment was prematurely stopped due to COVID-19 and the impact of prior drug treatment on eligibility.
- Overall, a similar magnitude of improvement in FVC% over 18 months occurred in both arms ***(2.24% MMF+PLA vs. 2.09% MMF+PFD; P=0.93)*** with a more rapid improvement noted in the MMF+PFD arm over 6 months.
- Trends favouring the PFD arm in HRCT QLF and QILD as well as in, SGRQ-activity scale, all meeting/exceeding minimally important differences.
- ***74.1%*** of subjects on MMF+PFD vs ***29.2%*** on MMF+PLA had adverse events of special interest; the difference primarily related to ***gastrointestinal disorders*** (55.6% vs. 20.8%) and ***photosensitivity*** (14.8% vs 0%).



Change from baseline in the mean FVC% over the course of the 18-month treatment period

Recommendation 7 & 8

- We recommend further research into the safety and efficacy of pirfenidone to treat patients with SSc-ILD.

- We recommend further research into the safety and efficacy of pirfenidone plus mycophenolate combination therapy to treat patients with SSc-ILD.

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Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial

Dinesh Khanna, Celia J F Lin, Daniel E Furst, Jonathan Goldin, Grace Kim, Masataka Kuwana, Yannick Allanore, Marco Matucci-Cerinic, Oliver Distler, Yoshihito Shima, Jacob M van Laar, Helen Spotswood, Bridget Wagner, Jeffrey Siegel, Angelika Jahreis, Christopher P Denton*, for the focuSSced investigators†*

Lancet Respir Med 2020

Methods

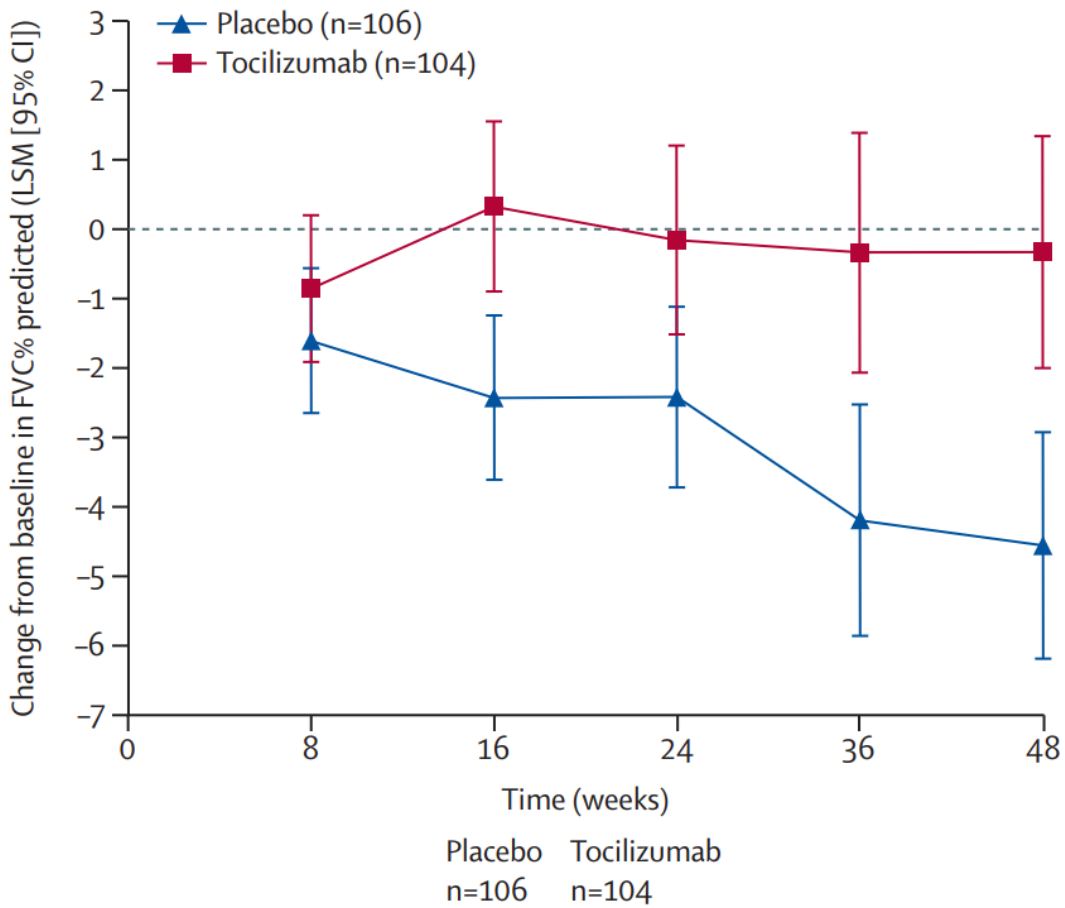
- Multicentre, randomised, double-blind, placebo-controlled, phase 3
- 75 sites in 20 countries across Europe, North America, Latin America, and Japan.
- Adults with diffuse SSc for 60 months or less and a mRSS of 10–35 at screening were randomly assigned (1:1).
- Tocilizumab 162 mg or placebo weekly for 48 wks, stratified by IL-6 levels.
- primary endpoint : the difference in change from baseline to week 48 in mRSS.
- Secondary endpoints: Percentage of predicted FVC% predicted at week 48.

Findings

- The differences in mean absolute change from baseline in FVC between the tocilizumab (n=104) and placebo (n=106) arms were ***118 ml less at 24 weeks (p=0·008), 241 ml less at 48 weeks (p<0·0001) in favour of tocilizumab***
- The mean change in ***DLCO %*** predicted from baseline to 48 weeks was 1.5% less in the tocilizumab arm
- At 48 weeks, the change in ***QILD and QLF*** scores across all categories favoured the tocilizumab group.
- The ***mRSS*** change from baseline at 72 weeks was 4.1 better in the tocilizumab arm when compared with placebo.

Conclusion

- 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.

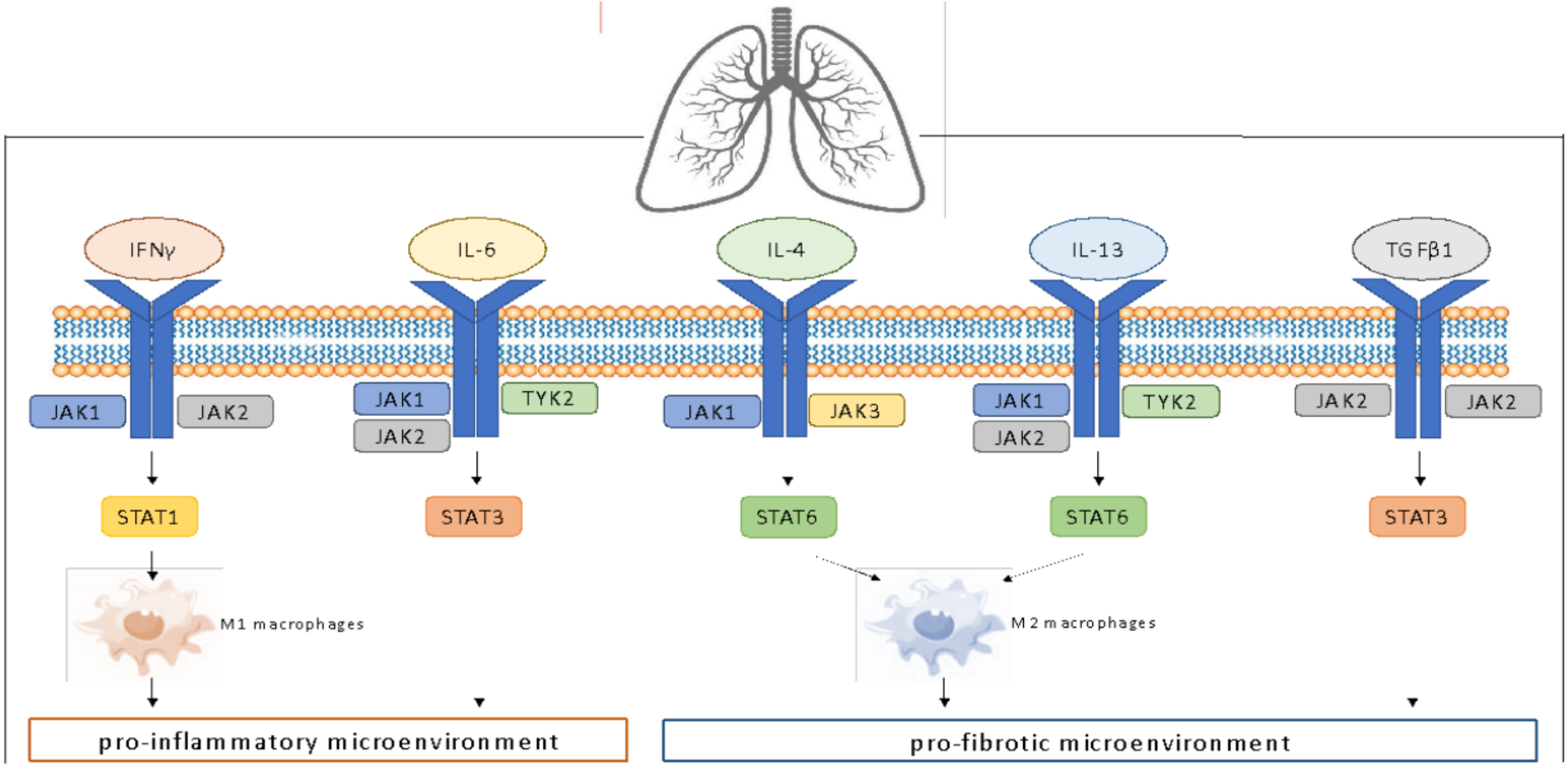

Placebo (n=106)
Tocilizumab (n=104)
Change from baseline in FVC% predicted (LSM [95% CI])
3
2
1
0
−1
−2
−3
−4
−5
−6
−7
0
8
16
24
36
48
Time (weeks)
Placebo n=106
Tocilizumab n=104

Recommendation 4

- Recommendation 4: We suggest using tocilizumab to treat patients with SSc-ILD

(conditional recommendation, very low quality evidence)

Am J Respir Crit Care Med Vol 209, Iss 2, pp 137–152, Jan 15, 2024



Schematic depiction of the main JAK/STAT pathways involved in developing pro-inflammatory and pro-fibrotic microenvironments

Retrospective comparative study of the efficacy of JAK inhibitor (tofacitinib) in the treatment of systemic sclerosis-associated interstitial lung disease

Zhou Junfei [1], Gao Meihua [2], Zhang Shuai [3], Lu Xiangting [3], Lei Zhidan [4], Cheng Tianming [4], Liu Yajing [5], Tianshu Chu [6], Shi Lipu [7]

Clin Rheumatol, 2023 oct;42(10):2823-2832

- 9 patients who received tofacitinib for at least 6 months and a matched group of 35 SSc-ILD patients treated with conventional therapy.
- Tofa-group showed :
- Amelioration in decreased DLCO (62.05 ± 9.47 vs. 66.61 ± 12.39, p = 0.046),
- Reductions in GGO (1.00 ± 0.86 vs. 0.33 ± 0.50, p = 0.024)
- Reduced HRCT scores of pulmonary fibrosis (15.00 ± 3.87 vs. 12.66 ± 4.92, p = 0.009).
- Alleviated modified Rodnan skin score (mRSS) of skin sclerosis (9.22 ± 3.81 vs. 7.11 ± 3.92, p = 0.048)

Rahaghi *et al. Respiratory Research* (2023) 24:6
https://doi.org/10.1186/s12931-022-02292-3

Respiratory Research

RESEARCH Open Access

Expert consensus on the management of systemic sclerosis-associated interstitial lung disease

Franck F. Rahaghi[1*], Vivien M. Hsu[2], Robert J. Kaner[3], Maureen D. Mayes[4], Ivan O. Rosas[5], Rajan Saggar[6], Virginia D. Steen[7], Mary E. Strek[8], Elana J. Bernstein[9], Nitin Bhatt[10], Flavia V. Castelino[11], Lorinda Chung[12], Robyn T. Domsic[13], Kevin R. Flaherty[14], Nishant Gupta[15], Bashar Kahaleh[16], Fernando J. Martinez[3], Lee E. Morrow[17], Teng Moua[18], Nina Patel[9,19], Oksana A. Shlobin[20], Brian D. Southern[21], Elizabeth R. Volkmann[6] and Dinesh Khanna[14*]

Treatment criteria	• FVC <80% and any degree of ILD or symptoms • >20% total lung involvement on HRCT • >10% total lung involvement on HRCT with abnormal PFTs • High-risk patients (early diffuse cutaneous disease) with evidence of mild ILD (<10%) • Worsening HRCT with symptoms or declining PFTs • May consider exertional desaturation on SpO_2
Treatment paradigm	• Initiate therapy with MMF at 2000–3000 mg/day • Consider nintedanib for add-on therapy to MMF/CYC • Use nintedanib in advancing, agressive or progressive ILD/ following failure of immunosupressive therapy • Initiate nintedanib monotherapy in patients with longstanding ILD where immunosuppressive therapy is not recommended • Consider TCZ for patients with early SSc-ILD with elevated acute-phase reactants and for those unable to continue CYC/MMF/antifibrotics due to adverse effects

Thanks For Your Attention