Meta-analysis of Change in Lung Capacity and Skin Thickening for Interstitial Lung Disease (ILD) with Mixed Connective Tissue Disorders

Madison Snyder, Carlos Sepulveda, and Sima Ahadieh
Pfizer, Inc.

ACoP14, Nov 5 to Nov 8, 2023, National Harbor, Maryland

INTRODUCTION

Interstitial Lung Disease (ILD) is a group of disorders that cause lung inflammation and scarring, making it difficult to breathe and transfer oxygen into the bloodstream. Clinical presentation, severity, and prognosis can vary broadly, but cases are universally progressive in nature. While diagnosis of ILD has increased in the last decade, current effectiveness of treatments has not been widely studied. Here, we performed a meta-analysis of drug performance for key patient endpoints to determine the efficacy of currently approved or in pipeline ILD drugs. The meta-analysis will help summarize the efficacy of current or in pipeline drugs in ILD and will inform benchmark estimates for future drug development and decision making.

METHODS

A literature search and systematic review of randomized clinical trials for ILD patients with mixed connective tissue disorders was conducted using Medline, Embase, and Biosis databases. Both monotherapy and drugs in combination studies were included in the search. Clinical trials were selected relating to the use of nintedanib, tociluzumab, rituximab, lenabasum, prednisolone, pirfenidone, cyclophosphamide, and mycophenolate mofetil. Only Phase 2/3 randomized, placebo or active controlled studies were included in the search.

PICOS		
Population	Demographics	Adults; mixed connective tissue diseases. Exclude pulmonary hypertension
	Disease	Interstitial lung disease (ILD)with mixed connective tissue disease. Excluding exposure
	Sub Populations	RA, Scleroderma, Mixed Connective Tissue Disease, Polymyositis, Dermatomyositis,
	Covariates	corticosteroids, methotrexate, rituximab, mycophenolate mofetil, cyclophosphamide,
Interventions	Primary	corticosteroids, methotrexate, mycophenolate mofetil, cyclophosphamide,
	Secondary	oxygen
	Background	
	Prior	
	Post Search Interventions	
Comparators	Placebo/SoC/Drug of Interest	Placebo, SoC, nintedanib, MEDI-551, BIBF 1120, actemra, tociluzumab, rituximab,
Outcomes	Main Outcomes	(FVC or "forced vital capacity" or mRSS or "modified Rodnan Skin Score" or DLCO or "diffusing capacity of the lung for carbon monoxide" or CRP or C-reactive protein or hsCRP or hs-CRP or "High-sensitivity C-reactive protein" or ESR or "erythrocyte sedimentation rate" or survival or "Kaplan Meier plot").mp
	Primary Endpoints	serum surfactant protein-D, serum KL-6, tissue biopsy, FACIT-Fatigue, HAQ-DI
	Secondary Endpoints	ACR-CRISS, St. George's Respiratory Questionnaire, high resolution CT scan changes,
Study Designs		Phase 2 and 3, randomized, double-blind, placebo controlled

Fig 1. PICOS summary showing the inclusion/exclusion criteria used for population, interventions, comparators, outcomes, and study design.

Endpoints of Interest

The quantitative meta-analysis only included studies with one or more of the following endpoints:

FVC

Forced vital capacity (FVC) is the amount of air that can be forcibly exhaled from your lungs after taking the deepest breath possible (measured in milliliters (mL) of air). An increase in FVC is considered beneficial.

mRSS

Skin thickness is quantified using the modified Rodnan measurement method (mRSS), with a scale that ranges from 0 (no skin involvement) to a maximum of 51. The reported skin score is determined by a clinical assessment of skin thickness, which is performed by a trained reader, and represents the sum of individual assessments that are made in each of 17 body areas. Each area is given a score in the range of 0-3 (0 = normal; 1= mild thickness; 2 = moderate; 3 = severe thickness). A higher score represents more severe skin involvement, meaning a decrease in mRSS is considered beneficial.

DLCO

The DLCO measures the ability of the lungs to transfer gas from inhaled air to the red blood cells in pulmonary capillaries (measured in % change from baseline). An increase in DLCO is considered beneficial.

Change from baseline was the primary response used to compare drugs for all three endpoints of interest. Missing values were calculated as the difference between baseline and post treatment primary timepoint measurements and all values were normalized to a standard unit per endpoint (e.g.: mL for FVC, weeks for all timepoints). Primary timepoints for each study ranged from 4-8 weeks post treatment. Additionally, missing standard deviations were imputed using median SD. Forest plots were used to visualize mean difference from placebo in change from baseline by drug and endpoint. In these plots, study mean difference points were weighted by standard error. In addition, random effects weighted averages and 95% confidence intervals were calculated over all drugs and for individual drugs which were trialed in more than one study. Endpoint data was analyzed using the *meta* package and the internal resource *metatools* in R Version 4.1.3.

RESULTS

62 manuscripts were identified in the literature search. However, after systematic review, **19** studies representing **2070** subjects and **7** mixed connective tissue disorder subpopulations were included in the meta-analysis. Given the limited number of studies investigating ILD at the clinical trial level, the overall dataset was sparse but novel in its findings.

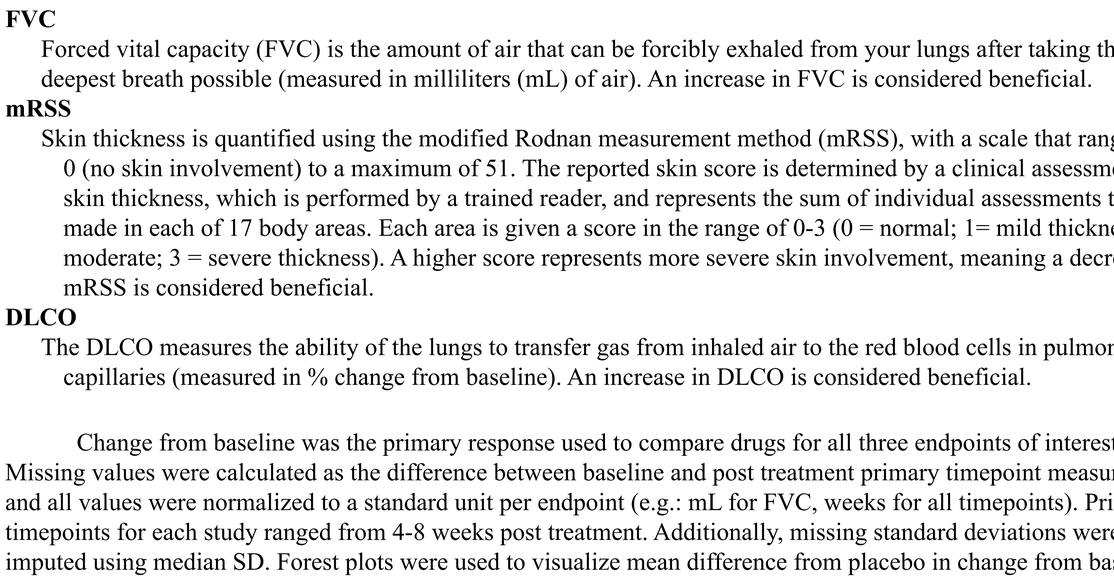

Fig 2. Mean Difference in Drug Performance compared to Placebo for Forced Vital Capacity (FVC) by drug. A 95% confidence interval was used and a random effects weighted average was calculated using mean differences weighted by standard error.

The results for FVC demonstrate that among the trials, the drugs tocilizumab, nintedanib, pirfenidone, and lenabasum show improvement in FVC over placebo. Tocilizumab shows the largest magnitude of improvement with a mean difference of 160.59 ml (95% CI 105.53, 215.65), well above the average for the group of 80.49 ml (95% CI 15.94, 145.03). Notably, lenabasum shows a lack of efficacy, with an average decrease in FVC of 27.00 ml (95% CI -100.39, 46.39). Overall, existing drug products do show efficacy in improving FVC for patients.

RESULTS

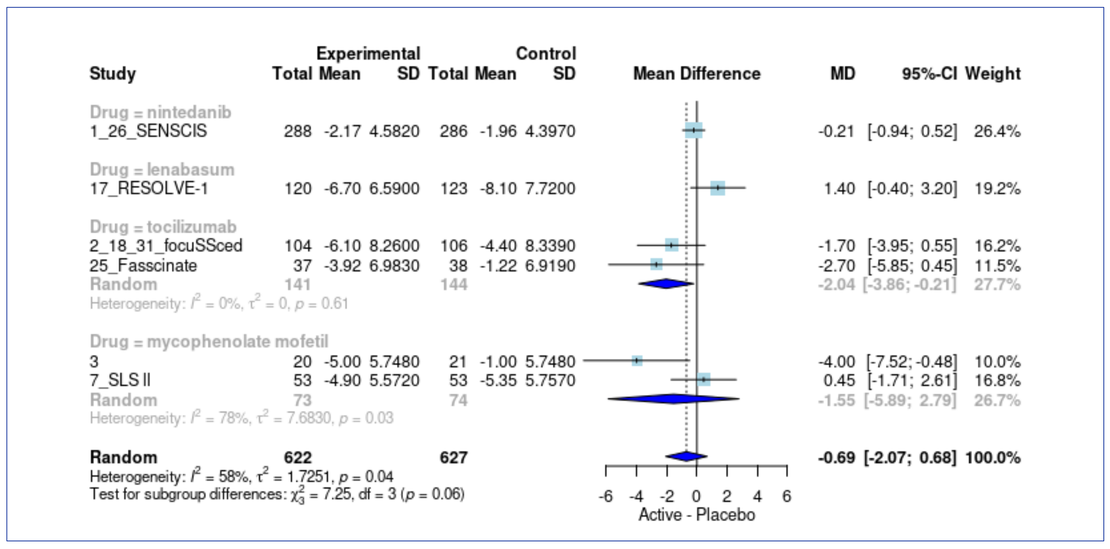

Fig 3. Mean Difference in Drug Performance compared to Placebo for Modified Rodnan Skin Score (mRSS) by drug. A 95% confidence interval was used and a random effects weighted average was calculated using mean differences weighted by standard error.

The results for mRSS show that among trials for the drugs nintedanib, lenabasum, tocilizumab, and mycophenolate mofetil, tocilizumab shows the largest magnitude of improvement (2.04 point decrease (95% -3.86, -0.21)). Interestingly, lenabasum shows a negative change in skin thickening with a 1.40 point increase in mRSS (95% CI -0.40, 3.2). There is a limited change in mRSS in either direction for these drugs.

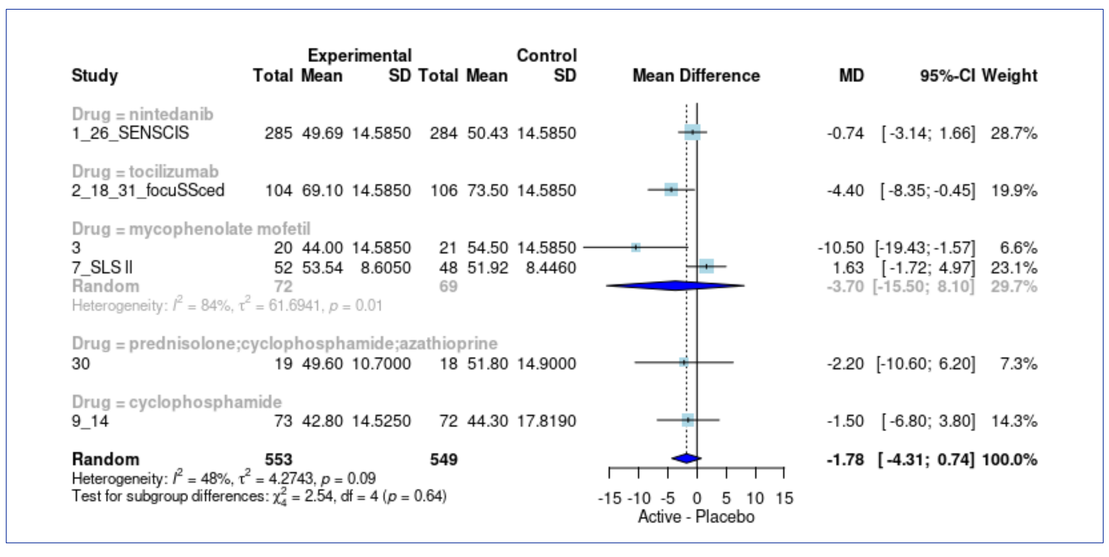

Fig 4. Mean Difference in Drug Performance compared to Placebo for Diffusing capacity of the lung carbon monoxide (DLCO) by drug. A 95% confidence interval was used and a random effects weighted average was calculated using mean differences weighted by standard error.

The results for DLCO show that among trials for the drugs nintedanib, tocilizumab, myophenolate mofetil, prednisolone in combination with cyclophosphamide and azathioprine, and cyclophosphamide alone, the majority of drugs show a small negative change in DLCO (-1.78% change, 95% CI -4.31%, 0.74%). The only drug to show a small improvement in DLCO was mycophenolate mofetil in the 7_SLS II study (1.63% increase in DLCO, 95% CI -1.72%, 4.97%). When averaged with the other trial, mycophenolate mofetil does not show efficacy.

For both FVC and mRSS, **tocilizumab showed the greatest magnitude of efficacy** with a mean difference in FVC of 160.59 ml (95% CI 105.53, 215.65) and a mean difference in skin thickening score points of -2.04 (95% CI -3.86, -0.21). In contrast, **lenabasum studies showed a negative change** in FVC and mRSS, suggesting poor patient outcomes in these areas.

CONCLUSION

Although study information on ILD drugs is sparse, results from this meta-analysis provide a novel overview of the current drug landscape in ILD studies.

Overall, ILD drugs show clinically relevant improvement for FVC. However, impact on dermatological endpoints and oxygen transfer endpoints is marginal.

These findings suggest that there is marked room for improvement in ILD drug efficacy relating to FVC, mRSS and DLCO. Benchmarks identified for ILD endpoints are a valuable resource in the decision-making process for future drug development and clinical trial design.

REFERENCES

Balduzzi S, Rücker G, Schwarzer G (2019). "How to perform a meta-analysis with R: a practical tutorial." *Evidence-Based Mental Health*, 153–160.

Shah Gupta, R., Koteci, A., Morgan, A., George, P. M., & Quint, J. K. (2023). " Incidence and prevalence of interstitial lung diseases worldwide: a systematic literature review." *BMJ open respiratory research*, *10*(1), e001291. https://doi.org/10.1136/bmjresp-2022-001291