ILDsym®, a Quantitative Systems Pharmacology (QSP) Platform, Successfully Simulates the Pathophysiology of Systemic Sclerosis-Interstitial Lung Disease (SSc-ILD) and Inter-patient Variability

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PURPOSE

Systemic sclerosis (SSc) is a rare connective tissue and autoimmune disease associated with inflammation of the skin and internal organs. Interstitial lung disease (ILD), a frequent complication of SSc, is associated with increased risk of morbidity and mortality [1]. The course of SSc-ILD is highly variable; some patients remain stable while others progress rapidly. The two current FDA-approved treatments for SSc-ILD patients, nintedanib and tocilizumab (TCZ), demonstrate efficacy but do not reverse disease [2]. Mechanistic, mathematical modeling approaches can support the development of new drug treatments by improving understanding of disease pathophysiology, identifying mechanistic drivers of SSc-ILD, interpreting clinical treatment results, and assessing efficacy for novel treatments as monotherapies or in combination with existing treatments.

OBJECTIVE

Develop mechanistic representation of SSc-ILD pathophysiology capable of representing responses to existing and novel treatments.

METHODS

ILDsym, a QSP model of SSc-ILD, was developed based on publicly available data. Applications combine predicted drug exposure in the lung with drug pharmacodynamic (PD)properties (mechanism of action) to modulate SSc-ILD pathophysiology and predict efficacy of novel therapeutics. To facilitate evaluating the effects of inter-individual patient variability on predicted treatment response, a simulated population (SimPops™) of SSc-ILD patients was generated reflecting variability in disease pathophysiology. Patients were screened by assessing simultaneous consistency with multiple clinical data sets, including lung function, disease extent, cell populations, biomarkers, and standards of care.

RESULTS

ILDsym dynamically captures changes to lung architecture, susceptibility to inflammation and/or fibrosis, and several key clinical outcome measures such as forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO). Over 700 simulated patients were generated to represent SSc-ILD patients at various stages of disease (mean ± standard deviation for baseline % predicted FVC and % predicted DLCO values of 74.3% ± 12.2% and 54.8% ± 19.1%, respectively), and the simulated patients span appropriate ranges of alveolar epithelial cells, endothelial cells, macrophages, and myofibroblasts, mediators and biomarkers in accordance with published data for SSc-ILD patients; a selection of these validation results are shown. Over a one-year simulation, lung function remains stable in some patients and declines in others, with average FVC losses of -0.142 ± 0.112 L/year. Simulated patients were sub-selected (i.e., SimCohorts generation) to match the baseline lung function characteristics of clinical patients in phase 3 trials for nintedanib [3] and TCZ [19]. Simulations of compound exposure and PD effects in SimCohorts resulted in lesser lung function decline and stabilized lung function, respectively, consistent with clinical data.

CONCLUSIONS

ILDsym is well-positioned to support SSc-ILD drug development by providing a dynamic representation of SSc-ILD disease progression. The flexible framework of ILDsym enables its use in exploring novel targets and therapies as needed. ILD SimPops capture expected clinical inter-patient variability and can be utilized to optimize clinical trial protocols, explore mechanistic hypotheses, and evaluate combination therapies in addition to monotherapies.

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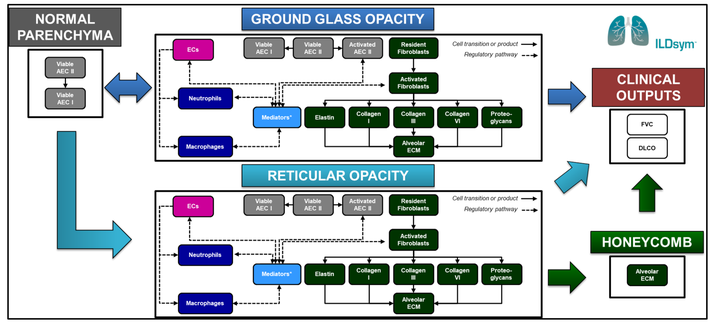
QSP model captures pathophysiology of SSc-ILD and inter-patient variability

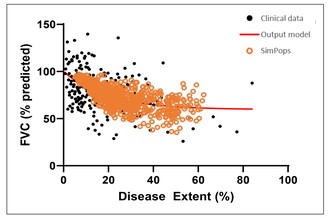
DIAGRAM OF NEWLY DEVELOPED QSP MODEL FOR SSc-ILD

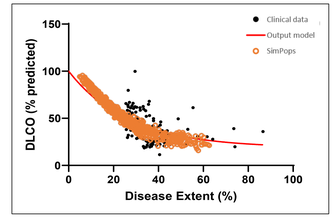


SIMULATED POPULATION CAPTURES CLINICALLY REPORTED RELATIONSHIP BETWEEN DISEASE EXTENT AND CLINICAL OUTPUTS

Key clinical measured FVC and DLCO well-represented

- Baseline relationship developed (red line) captures trend between disease extent and clinical outputs
- SimPops patients (orange circles) designed to span range of clinical data (black circles) [17-18]
- % predicted defined as relative to normal level for person of same gender, height, and age





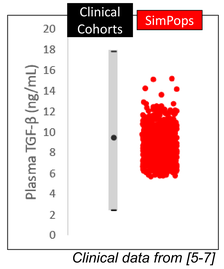
MEDIATOR LEVELS CONSISTENT WITH REPORTED SSc-ILD PATIENT VARIABILITY

Mediators and biomarkers calibrated to represent SSc-ILD patients

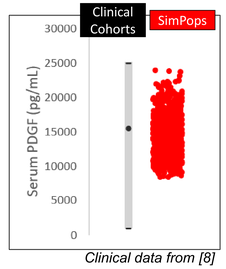
Simulated patients (n=780; red dots represent individual simulated patients) generally consistent with clinical data (range and mean indicated), simultaneously across all data comparisons

- Mediators shown demonstrate key inflammatory and fibrotic regulators; produced by various cell types which are also calibrated to align with clinical data

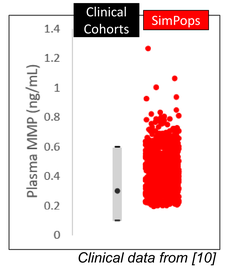
Clinical data from [4]



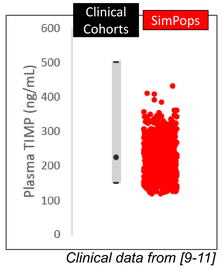
Clinical data from [5-7]



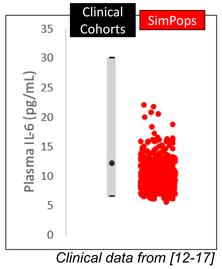
Clinical data from [8]



Clinical data from [10]



Clinical data from [9-11]



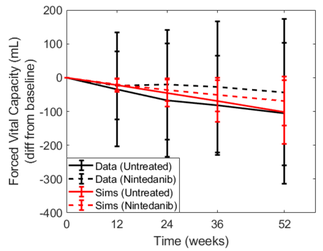
Clinical data from [12-17]

SIMULATED TREATMENT CONSISTENT WITH CLINICAL RESPONSE

Nintedanib treatment response captured by ILDsym

Simulated change in FVC with nintedanib treatment was comparable to clinical data

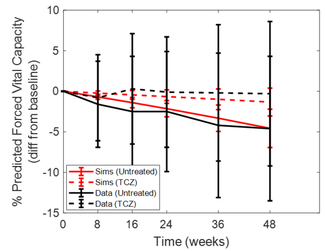
- Clinical untreated and nintedanib groups each composed of n=288 SSc-ILD patients [3]
- ILDsym SimCohorts (n=444) matched to inclusion/exclusion criteria of clinical SSc-ILD patients which were treated with 150 mg BID nintedanib for 52 weeks



Tocilizumab (TCZ) treatment response captured by ILDsym

Simulated change in FVC on TCZ treatment was comparable to intent-to-treat clinical data

- Clinical untreated (n=106) and TCZ (n=104) groups composed of SSc-ILD patients [19]
- ILDsym SimCohorts (n=114) matched to inclusion/exclusion criteria of clinical SSc-ILD patients which were treated with 162 mg SC QW TCZ for 48 weeks



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