ILDSYM®, A QUANTITATIVE SYSTEMS PHARMACOLOGY (QSP) PLATFORM, SUCCESSFULLY SIMULATES EFFICACY OF KEY TREATMENTS FOR SYSTEMIC SCLEROSIS-INTERSTITIAL LUNG DISEASE

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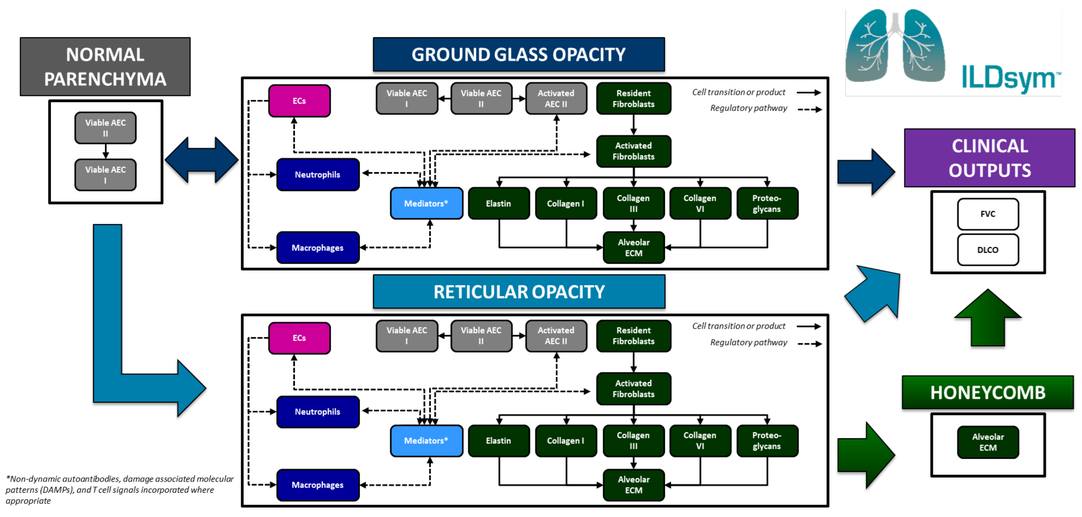
OBJECTIVE

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 with highly variable course, is associated with increased morbidity and mortality risk[1]. Two FDA-approved treatments, anti-inflammatory tocilizumab (TCZ) and anti-fibrotic nintedanib (NIN), demonstrate efficacy in slowing disease progression but do not reverse disease[2]. Anti-inflammatory/anti-fibrotic mycophenolate mofetil (MMF) demonstrates efficacy and may reverse disease[3]. Modeling treatment responses is critical to ensuring model dynamics properly capture physiological responses, lending confidence in the potential to predict novel treatments.

METHODS

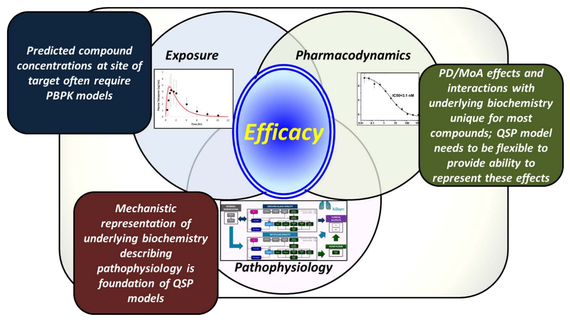
ILDsym is a QSP model of SSc-ILD pathophysiology based on publicly available literature with over 700 simulated patients at various stages of disease[4]. Simulations combine predicted lung drug exposure with drug mechanisms-of-action (MoA) to modulate SSc-ILD pathophysiology and predict efficacy. Treatment MoA were defined based on available data. For MMF and NIN, treatment responses were optimized to SSc-ILD forced vital capacity (FVC) clinical data[3,5]. TCZ response was optimized to C-reactive protein (CRP) data (downstream of MoA) from rheumatoid arthritis patients[6]; treatment response in SSc-ILD was subsequently validated against clinical FVC data[7]. Simulated patients were selected (i.e., SimCohorts™ generation) to match the baseline FVC and progression rates of placebo groups for clinical trials with NIN, MMF, and TCZ.

ILDSYM OVERVIEW DIAGRAM



QSP model of ILD associated with SSc, incorporating inflammation, fibrosis, alveolar epithelial cells, endothelial cells, mediators, biomarkers, and clinical outputs. Over 700 simulated patients[4]; can be trial-matched via sub-selection

MECHANISTIC SIMULATION OF DRUG EFFICACY



- Simulations combine compound exposure (PBPK models developed in GastroPlus®), MoA, and underlying pathophysiology captured by the QSP model to predict drug efficacy outcomes in a simulated patient population
- MoA for each drug, based on literature, incorporated into QSP model to modulate pathophysiology
  - MoA explicitly incorporated (e.g., inhibiting fibroblast proliferation and collagen synthesis); PD not explicitly modeled (e.g., inhibition of tyrosine kinase)

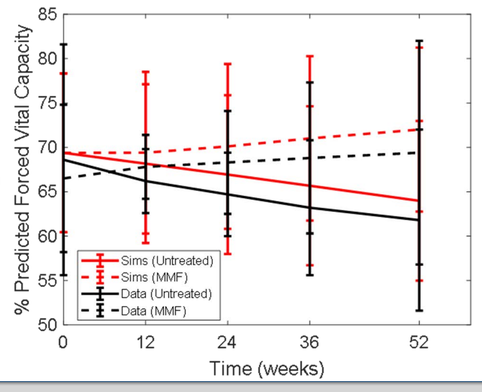
Mechanism of Action	NIN	MMF	TCZ
Inhibition of fibroblast proliferation	✓[8]	✓[9]	-
Inhibition of fibroblast collagen synthesis	✓[8]	-	-
Inhibition of T cell proliferation	-	✓[9]	-
Inhibition of EC proliferation	-	✓[9]	-
Inhibition of macrophage proliferation	-	✓[9]	-
Inhibition of autoantibody production	-	✓[10]	-
Inhibition of systemic DAMPs	-	✓[11]	-
Inhibition of IL-6 signaling	-	-	✓[12]

RESULTS

ILDSYM MODEL CALIBRATION TREATMENTS

MYCOPHENOLATE MOFETIL

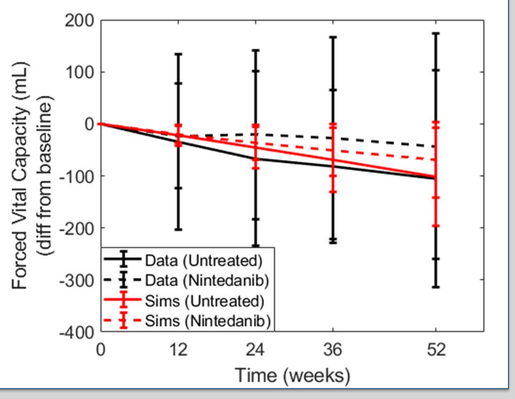
- MMF is a prodrug of mycophenolic acid (MPA) which preferentially inhibits de novo guanine synthesis in activated T and B cells, reducing DNA synthesis and proliferation
  - Additional anti-proliferative and anti-inflammatory effects identified
- Utilized off-label for SSc-ILD treatment[2]
- Simulated change in FVC with MMF treatment was comparable to clinical data[3]
  - Clinical untreated (n=79) and MMF (n=69) SSc-ILD groups
  - ILDsym SimCohorts (n=71), matched to inclusion/exclusion criteria of clinical SSc-ILD patients, and clinical ILD patients were treated with 1500 mg BID MMF for 52 weeks



NINTEDANIB

- NIN is a small molecule receptor tyrosine kinase inhibitor targeting growth factor receptors (PDGFR, FGFR, and VEGFR*), with anti-fibrotic effects
- FDA approved NIN for SSc-ILD treatment in 2019[2]
- Simulated change in FVC with NIN treatment was comparable to clinical data[5]
  - Clinical untreated and NIN groups each composed of n=288 SSc-ILD patients
  - ILDsym SimCohorts (n=444), matched to inclusion/exclusion criteria of clinical SSc-ILD patients, and clinical ILD patients were treated with 150 mg BID NIN for 52 weeks

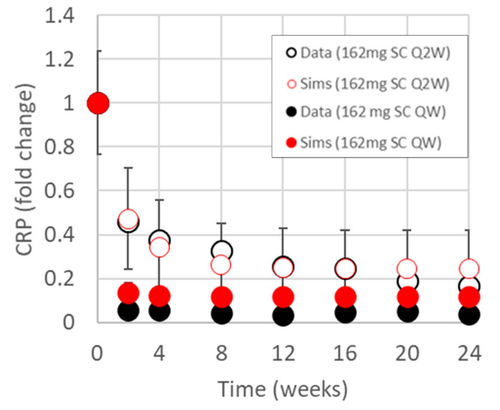
**PDGFR: platelet-derived growth factor receptor, FGFR: fibroblast growth factor receptor, VEGFR: vascular endothelial growth factor receptor*

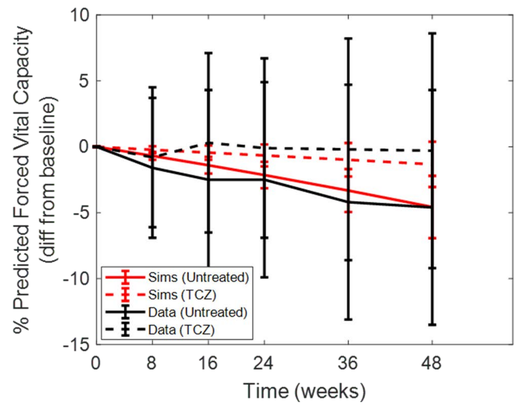


ILDSYM MODEL VALIDATION TREATMENT

TOCILIZUMAB

- TCZ is a biologic therapy that recognizes the IL-6 binding site of the human IL-6 receptor (IL-6R), inhibiting IL-6 signaling through competitive blockade of IL-6 binding
- FDA approved TCZ for SSc-ILD treatment in 2021[2]
- TCZ simulations used as ILDsym model validation
  - No further calibration of MoA in SSc-ILD to reproduce FVC in ILD patients
- Obtained reasonable simulated fit to relative CRP response data, optimizing IC_{50} for TCZ IL-6 effects with QW and Q2W dosing paradigms
  - CRP response simulations performed in N=12 simulated ILD patients, with CRP levels similar to those of RA patients in the study[6]
- Calibration simulations reproduced observed dose-response, providing increased confidence in parameterization of TCZ-mediated inhibition of IL-6 signaling
  - Increases confidence in TCZ role as validation compound in ILDsym
- Validation simulated change in FVC with TCZ treatment was comparable to clinical data[7]
  - Clinical intent-to-treat data composed of placebo group (n=106) and TCZ group (n=104)
  - ILDsym SimCohorts (n=114), matched to inclusion/exclusion criteria of clinical SSc-ILD patients, and clinical ILD patients were treated with 162 mg SC QW for 48 weeks





CONCLUSION

ILDsym is well-positioned to support SSc-ILD drug development by providing a dynamic representation of variable SSc-ILD pathophysiology and disease progression with demonstrated success in representing treatment responses. The flexible framework of ILDsym enables its use in exploring novel targets, optimizing protocols, exploring mechanistic hypotheses, and evaluating monotherapies and combination therapies.

REFERENCES

1. Asano. J Clin Med. 2020; 9(9): 2687-2714.
2. Khanna. Arth Rheum. 2022; 74(1): 13-27.
3. Volkmann. Arth Rheum. 2017; 69(7): 1451-60.
4. Kenz. AAPS PharmSci 360. 2022.
5. Distler. NEJM. 2019; 380(26): 2518-28.
6. Abdallah. J Clin Pharm. 2017; 57(4): 459–468.
7. Khanna. Lancet Respir Med. 2020; 8(10): 963-74.
8. Atanelishvili. Clin Exp Rheum. 2019; 37: S115-24.
9. Eugui. Scan J Immun. 1991; 33(2): 161-73.
10. Tashkin. Lancet Respir Med. 2016; 4(9): 709-19.
11. Yoshizaki. J Clin Immun. 2009; 29(2): 180-9.
12. Nishimoto. Blood. 2008; 112(10): 3959-64.

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