Using Quantitative Systems Pharmacology Modeling to Understand the Pathophysiology of Idiopathic Pulmonary Fibrosis

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ABSTRACT

Patients with idiopathic pulmonary fibrosis (IPF) have a poor survival prognosis and limited treatment options. Underlying its clinical presentation is a complex pathophysiology. Mechanistic, mathematical modeling approaches such as quantitative systems pharmacology (QSP) can identify the links between pathophysiologic mechanisms and clinical sequela, aid in interpreting drug treatment results, and predict potential efficacy for novel treatments. One such QSP model, IPFsym, has recently been developed and has been applied to better understand IPF patient pathophysiology.

A simulated population (SimPops) of IPF patients was generated using the QSP model, IPFsym. Inter-patient variability in inflammation, epithelial cell health, fibroblasts, and collagen synthesis was introduced in accordance with published data. The resultant clinical presentation was also compared with published clinical data to ensure validity of SimPops. The response to simulated administration of nintedanib or pirfenidone was also predicted.

More than 700 simulated patients were generated within an IPF patient SimPops. The SimPops had appropriate ranges of alveolar epithelial cells (type I and II), macrophages, and myofibroblasts, in accordance with published data from IPF patients. The levels of extracellular matrix components were also consistent with clinical data, as were the fibroblastic foci and honeycombed lung volumes. Taken together, this pathophysiology generated a range of effects on respiration. Figure 1 shows the FVC (forced vital capacity) and DLCO (diffusing capacity of lung for carbon monoxide) across the SimPops and highlights how each can decrease as the disease progresses in untreated simulated IPF patients. Simulated administration of nintedanib or pirfenidone was predicted to reduce the rates of progression in the SimPops to varying extents, similar to published clinical data.

The validated IPF patient SimPops within IPFsym accurately describes various pathophysiologic mechanisms to produce FVC and DLCO outputs that decline as the disease progresses in simulated patients. Decline in respiratory function is predicted to be linked to the extent of honeycomb and fibroblastic foci lung volume. Moreover, the IPFsym SimPops can be used to investigate how modifying disease mechanisms with potential treatments can efficaciously reduce the rates of progression.

INTRODUCTION

- IPFsym, a QSP model of IPF pathophysiology, was recently developed to help increase understanding of IPF pathophysiology.
- IPFsym was also designed to support the development of treatments for IPF patients, enabling the use of simulations to optimize clinical studies prior to initiating those studies.
- IPFsym includes an SimPops with interpatient variability in numerous mechanisms that contribute to IPF pathophysiology. The SimPops has been validated with multiple clinical data sets, including the response to pirfenidone and nintedanib treatment.

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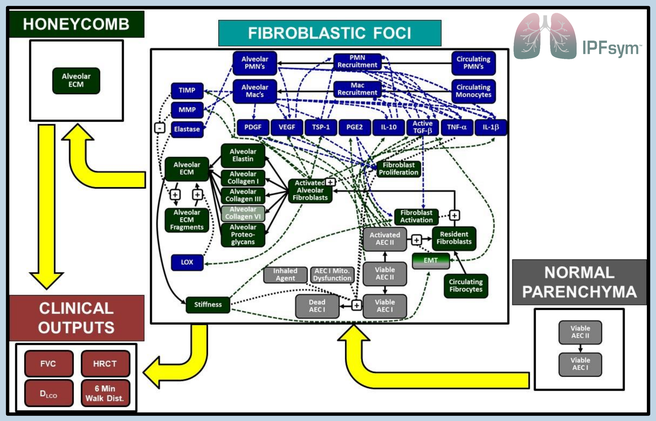
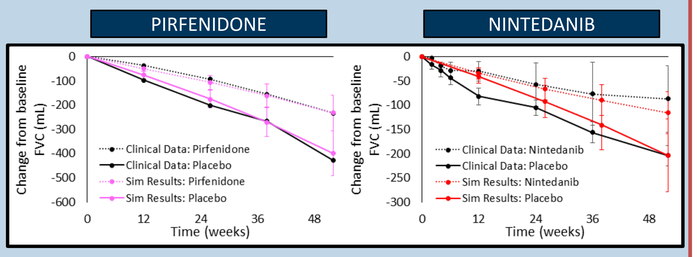
RESULTS

IPFsym Overview Diagram

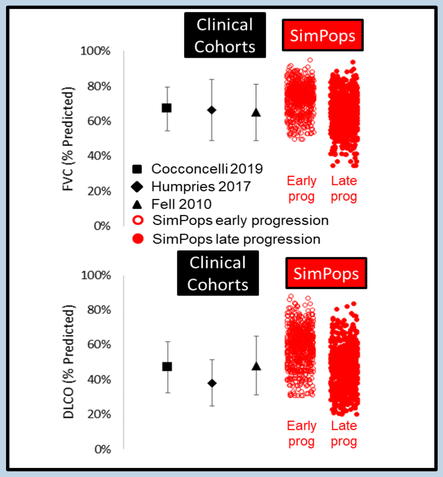


Predicted FVC with Pirfenidone or Nintedanib Treatment in IPFsym SimPops



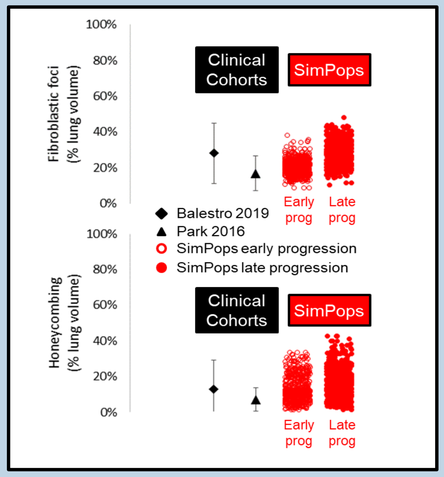
The combination of predicted compound exposure and effects on relevant pathophysiologic mechanisms within IPFsym are predicted to slow the rate of disease progression for both pirfenidone (801 mg TID) and nintedanib (150 mg BID) to the same extent as was observed in clinical studies [15-16].

Predicted FVC and DLCO in IPFsym SimPops



Predicted FVC and DLCO in IPFsym SimPops early and later in disease progression. Red circles represent individual SimPops patients. Black symbols represent clinical data in published reports listed in legend [1-3].

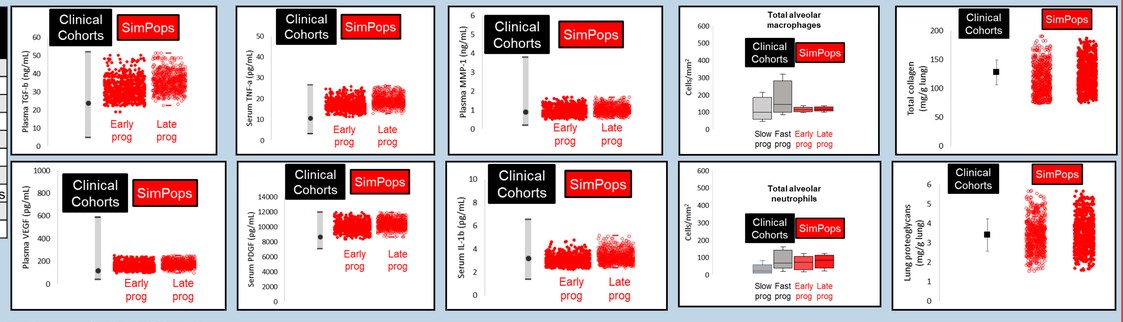
Predicted HRCT in IPFsym SimPops



Predicted HRCT fibroblastic foci and honeycombing lung volumes in IPFsym SimPops early and later in disease progression. Red circles represent individual SimPops patients. Black symbols represent clinical data in published reports listed in legend [4-5].

IPF SimPops Pathophysiology

Variables Used to Construct the IPFsym v1A SimPops
Height
Age
AEC apoptosis rates
Immune cell recruitment and activation
Inflammatory mediator production
Fibroblast activation and proliferation
ECM synthesis and degradation
Collagen cross linking and ECM stiffness
EMT (exploratory)
Progression rates



Construction and validation of IPF SimPops

- Simulated IPF patients (n=716) include combinations of parameter ranges based on reported responses from literature [6-14].
- Simulated patients within SimPops have pathophysiologic and clinical characteristics consistent with what has been reported in literature [6-14].

REFERENCES

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METHODS

Overview IPFsym is a mechanistic, mathematical, QSP model that was utilized for all simulations. IPFsym includes a representation of the contributions to IPF clinical responses from honeycombed tissue, normal parenchymal tissue, and fibroblastic foci within the lungs. Mechanistic contributions from alveolar epithelial cells, inflammation, myofibroblasts, and the extracellular matrix are also included.

Simulated patients A simulated population of patients with the pathophysiological aspects of IPF are included in IPFsym. This SimPops (n=716) includes a number of characteristics that are consistent with the observed heterogeneity of pathophysiologic and clinical features of IPF. Key IPF clinical outputs like FVC, DLCO, and HRCT (high resolution computed tomography) (i.e., honeycombing and fibroblastic foci volumes) are outputs of IPFsym [1-5]. The SimPops has been further validated by demonstrating consistency with clinical data for all simulated patients when comparing predicted levels of key immune mediators, cells, and levels of extracellular matrix components [6-15].

Simulated Protocols Specific SimCohorts were treated with pirfenidone or nintedanib for 52 weeks.

Pirfenidone: 801 mg of pirfenidone was dosed TID, and a PBPK model developed with GastroPlus was used to predict compound exposures within the lungs. This was combined with the reported effects on fibroblast activation and collagen expression [17-18] to affect IPF pathophysiology. FVC was used as a primary output of these simulations. The SimCohorts for these simulations included 62 simulated patients selected to have comparable untreated FVC progression rates as clinical cohort.

Nintedanib: 150 mg of nintedanib BID was administered to the SimCohorts. Predicted lung concentrations of nintedanib were generated using a PBPK model developed in GastroPlus. The effects of nintedanib on the inhibition of myofibroblast proliferation as well as collagen synthesis [19-20] were combined with the predicted lung concentrations to simulate the FVC change over time in IPF patients. The SimCohorts for these simulations included 322 simulated patients selected to have comparable untreated FVC progression rates as clinical cohort.

Placebo: The IPF SimPops patients were simulated for 1-4 years without treatment and compared with clinical data to ensure validity [1-16].

RESULTS

- Pirfenidone was predicted to slow the rate of FVC decline in IPF patients, consistent with what has been demonstrated in clinical studies [15].
- IPFsym accurately predicted the clinical effects of nintedanib to slow disease progression (i.e., FVC reductions), as has been reported in the literature [16].
- Untreated IPFsym SimPops were predicted to have clinical markers, inflammatory cells and mediators, fibrotic mediator levels, and extracellular matrix levels consistent with what was reported in the clinical literature. Moveover, the influence of disease progression on these outputs was properly recapitulated.

CONCLUSIONS

- IPFsym recapitulates the pathophysiology and clinical aspects of IPF, including disease progression
- IPFsym can be used to predict the clinical response to treatments, as evidenced by the appropriate predictions of pirfenidone and nintedanib to reduce disease progression rates
- The QSP modeling approaches embedded within IPFsym can be used to support the development of novel IPF treatment approaches, using simulations to support decision making and optimizing clinical study protocols.