Title

Quantitative systems pharmacology modelling for evaluating the impact of interleukin 6 on the development and progression of sepsis induced acute respiratory distress syndrome

Authors

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Objectives

Sepsis is the life-threatening multiple organ dysfunction caused by the dysregulated host defense reactions to infections (1). The severe inflammatory responses in the lung induced by sepsis can lead to development of acute respiratory distress syndrome (ARDS), which is one of the most severe organ dysfunctions. A critical process for development and progression of ARDS is the increasing permeability of the vasculature wall induced by inflammatory mediators including interleukin 6 (IL-6) through the degradation of glycocalyx, which provides an extracellular matrix-type barrier to the vasculature endothelium (2). To evaluate the impact of IL-6 on the clinical output of sepsis-induced ARDS and make a biomarker evaluation plan for a clinical trial, we developed the systemic mechanism-based model.

Methods

The model describes the process of sepsis exacerbation to ARDS development including the inflammation in lung and blood vessels caused by immune cells and inflammatory mediators (e.g., IL-6 and tumor necrosis factor alpha (TNFα)), resulting in fibrosis of lung tissue, and vasculature damage with glycocalyx degradation (3, 4). The constructed model was calibrated using clinical

and in vitro/vivo data reported in the literature. To assess which parameters were the strongest contributors to outcomes of interest, sensitivity analysis (SA) was performed.

Results

The calibrated model reflects the previously reported clinical time course of sepsis-induced ARDS, including the early peak of glycocalyx damage (5). The result of SA suggested that vasculature damage was sensitive to changes in glycocalyx, and parameters related to IL-6, TNFα, and other pro-inflammatory factors. Simulations in the model showed that sepsis-induced glycocalyx damage is an early event that would be difficult to prevent clinically, but inhibition of pro-inflammatory factors can speed recovery. In particular, simulations suggested that inhibition of IL-6 signaling helps promote recovery of glycocalyx and reverse vascular damage, with improvements seen within two weeks.

Conclusion

The developed model provided valuable information for discussion and proposal of a biomarker evaluation plan for a clinical trial with sepsis patients. We also expect the model will contribute to considering the treatment strategy of sepsis in clinical practice.

Citations

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