Sphingosine 1-Phosphate Receptor Modulators as a Potential Treatment Option in COVID-19 Induced Acute Respiratory Distress Syndrome: Mechanistic Insights and Benefit-Risk Assessment

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a viral infection caused by a newly emergent coronavirus, SARS-CoV-2, primarily affecting the respiratory tract. Maladjusted immune responses, e.g. cytokine release syndrome, may result in immunopathology and acute respiratory distress syndrome (ARDS). Sphingosine-1-phosphate (S1P), a bioactive lipid mediator, is crucial in maintaining endothelial cell chemotaxis and barrier integrity (**Table 1**). An industry-independent clinical study is currently underway in China investigating the efficacy of oral fingolimod 0.5 mg (a non selective S1P receptor modulator) taken once-daily, for three consecutive days in patients with COVID-19.

METHODS

Here we review the potential mechanisms by which fingolimod may regulate the inflammatory response to SARS-CoV-2 and assess the potential benefit-risk of short-term treatment with fingolimod in patients with COVID-19 experiencing ARDS.

RESULTS

The key hypotheses through which beneficial effects manifest are (1) attenuation of cytokine release via activation of serine/threonine protein phosphatase 2A (PP2A); (2) inhibition of Th17-mediated pathway; and (3) enhancement of the pulmonary endothelial barrier via c-Abl tyrosine kinase pathway (**Table 2**).

The short-term intervention with fingolimod might rapidly attenuate maladjusted immune responses while sparing memory immune responses and thus has relatively low risk of infections. Any potential effects on heart rate and cardiac rhythm could be managed under the

intensive care treatment setting. Furthermore, simulations from a PKPD model of lymphocyte count data with short-term fingolimod treatment will be presented.

CONCLUSIONS

S1P receptor modulators, such as fingolimod, may represent a potential treatment option to ameliorate immune responses against SARS-CoV-2 and merit further investigation following careful benefit-risk evaluation in this setting.

TABLES/FIGURES

Table 1. Role of sphingolipids in hyperinflammatory sequence of events in ARDS

Mediator	Neutrophil chemotaxis	Endothelial permeability	Neutrophil Apoptosis	Epithelial permeability
NSMase*	⬆		⬇	
ASMase*		⬆		⬇
S1P	⬇		⬇	
S1P1R		⬇		⬇
S1P2R				⬆
S1P3R				⬆
S1P4R	Unknown			

*catalyses the breakdown of sphingomyelin to ceramide and phosphorylcholine
ARDS, acute respiratory distress syndrome; ASMase, acid sphingomyelinase; NSMase, neutral sphingomyelinase; S1P, sphingosine-1-phosphate; S1P1-4R, type 1-4 S1P receptors

Table 2. Potential mechanisms of S1P receptor modulators

	Chemotaxis/immune response	Endothelial permeability
S1P receptor- modulated effects		
Reduction in Th-17 cell	Reduced tissue infiltration and release of IL-17 and downstream proinflammatory cytokines and chemokines	
Enrichment of T_{regs} and B_{regs} (*via* sparing of this subpopulation)	Shift towards anti-inflammatory response	
Innate immune cells	Reduced pro-inflammatory cytokines	
S1P1-mediated modulation of the endothelial barriers		Barrier enhancement
Non S1P receptor- modulated effects		

Increased PP2A	Suppresses IL-6 and IL-8 cytokine secretion in human alveolar epithelial cell lines	
	Decreases downstream CXCL1 and CXCL2 release	
Inhibition of c-Abl tyrosine kinase		Barrier enhancement by increased transendothelial electrical resistance

IL, interleukin; PP2A, protein phosphatase 2A

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