Sphingosine 1 phosphate agonists (SPI); a potential agent to prevent acute lung injury in COVID-19

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Abstract
SARS-CoV-2 is a worldwide pandemic, that has led to the morbidity and mortality of millions of people. This virus rapidly proliferates and destroys lung epithelial cells directly, which is worsened by a subsequent cytokine storm. This cytokine storm diffusely damages the alveolar barriers and leads to fibrin and fluid exudation, hyaline membrane formation, and infiltration of inflammatory cells into the lung causing acute respiratory distress syndrome (ARDS). To date, there exists no medication to treat SARS-CoV-2 infection and novel new therapeutics are still being explored to prevent or limit the damage to the lung. Sphingosine 1-phosphate (S1P) is an effective bioactive lipid mediator and its related signaling pathways are vital for endothelial cell integrity. Stabilizing the pulmonary endothelial barrier and decreasing the inflammatory infiltrate by S1P analogs such as Fingolimod (FTY720-P) would be a new therapeutic approach for the hindrance of pulmonary exudation and subsequent ARDS.

Introduction
Severe acute respiratory syndrome coronavirus virus 2 (SARS-CoV-2) targets the respiratory epithelial cells, which leads to a severe respiratory presentation in 15% to 20% of patients. This virus rapidly proliferates, destroys the epithelial cells, and triggers the immune system causing a cytokine storm. This cytokine storm diffusely damages the alveolar barriers and leads to fibrin and fluid exudation, hyaline membrane formation, and infiltration of inflammatory cells into the lung causing acute respiratory distress syndrome (ARDS). Morbidity and mortality of SARS-CoV-2 infection are directly related to this dysregulated immune response (1). Researchers identified Sphingosine 1-phosphate (S1P), a membrane sphingolipid metabolite, as a biologically active lipid-signaling mediator in the 1990s (2). S1P and its receptors have a pivotal role in the preservation of vascular endothelial cell barrier integrity and the regulation of immune cells’ diapedesis. S1P binds to a five-membrane related G-protein coupled receptors (GPCRs) including S1PR 1, -2, and -3 which are present in the cardiovascular system, while the S1PR1 is the dominant receptor in the lung. S1P binds to S1PR1 on the endothelial cell to improve the integrity of endothelial barrier and restrict the effector lymphocytes migration toward the inflamed area and infiltration to the alveolar space (3). The activation of S1PR1 additionally displays a cytokine blunting activity and attenuates IL-6 secretion (4). In the following paragraphs, we will concisely discuss the existing science on S1P signaling in the lung.

Key point
Stabilizing the endothelial barrier and decreasing the inflammatory infiltrate by a sphingosine 1-phosphate analog (Fingolimod, FTY720) would be a new therapeutic strategy towards hindering pulmonary exudation.

Pathology of the SARS-CoV-2
SARS-CoV-2 was a novel and sudden disease outbreak, therefore there are very few lung histopathology reports. In the lung histopathology studies of two asymptomatic patients, who underwent pulmonary surgery because of another reason, but were later
Role of S1P in endothelial barrier regulation

Over the past decade, several studies have validated that S1PR1 signaling is imperative for the enhancement of lung endothelial barrier function (7-9). Enhancing the effects of S1P on endothelial barrier are ascribed after the activation of S1PR1, which subsequently activates downstream signaling through Rho GTPases and then stabilizes the endothelial actin cytoskeleton (10). S1P mediated localization of beta-catenin and VE-cadherin at the sites of endothelial cells’ adherent junctions maintains vascular integrity (11).

The intracellular myosin light chain phosphorylation and the rearrangement of adherent junction proteins in the lung endothelium cells have been proposed as possible S1P-induced barrier function improvement (12-15). In an in vivo model of ventilator-associated lung damage, S1P analog stabilizes endothelial cytoskeleton, cell-matrix adherence and tightens the inter-cellular junction to prevent alveolar exudation (16-18).

Role of S1P activation in viral-induced lung injuries

H1N1 viral infection causes a cytokine storm, whose major target is endothelial cells. Based on experimental findings in a mouse model of H1N1 infection, intensified endothelial S1PR1 signaling blunts the cytokine-induced inflammatory cell infiltration (19). A S1PR1 agonist preserves the lung tissue by diminishing the endothelial cells response to a high cytokine state. In H1N1 influenza murine models (2009), S1PR1 agonists showed a decrease of more than 80% of deaths compared to 50% protection by oseltamivir, an antiviral neuraminidase inhibitor. The combination therapy of these drugs had optimal protection up to 96% (20). The immune-modulatory strategies using S1P analog had a promising outcome in influenza infection (21). In another study, the combined usage of S1PR1 agonist; oseltamivir and CYM-5442 had the greatest protection against the influenza-induced lung injury (22).

FTY720

FTY720 (Fingolimod) is a sphingosine analog and agonist of S1P receptors. Sphingosine kinase (SphK) phosphorylates FTY720 to its active form FTY720-P. In 2010, the Food and Drug Administration of United States (FDA), approved FTY720 as a treatment of multiple sclerosis (23). Several murine and canine studies have showed meaningful reduction in pulmonary damage after treatment with FTY720 or Sph 1-P (16,24). Additionally, another study showed FTY720 inhibits lymphocyte-mediated airway inflammation (25) and ameliorates central nervous system-induced inflammatory cell recruitment in experimental autoimmune encephalomyelitis (26). Protective impacts of S1P analogous and FTY720 has been described in vascular endothelial growth factor (VEGF)-mediated models of vascular leakage (27,28). Recent findings also support the role of FTY720 on the endothelial barrier enhancement and subsequent suppression of trans-endothelial migration of inflammatory cells (29-31).

Proposed hypothesis

The clinical accessibility of S1P agonist, FTY720, makes it a striking therapeutic option. The 0.5 mg daily oral administration of FTY720 for three consecutive days within the first 72 hours of acute ischemic stroke is associated with a noteworthy reduction of ischemic lesion expansion and its administration protects the brain from the intense lymphocytes infiltration that happens after stroke-induced cytokine storm (32); we can make an analogy between those findings and maybe the same course of FTY720 (Fingolimod protocol) could be a useful scheme in high-risk individuals with COVID-19 infection. The early start of S1P agonist may prevent the pulmonary infiltration and functional deterioration.

Conclusion

S1P is an effective bioactive lipid mediator and its related signaling pathways might be a crucial area for new therapeutics for SARS-CoV-2. Stabilizing pulmonary endothelial barrier and decreasing the inflammatory infiltrate by S1P analog/FTY720 is a novel therapeutic approach towards hindering pulmonary exudation, a major cause of morbidity and mortality in SARS-CoV-2 patients (Figure 1).

Authors’ contribution

SZV and MRA developed the idea and revised the manuscript. ShG and SMHK contributed in preparing original draft. MMS and RT revised the manuscript. BP revised and edited the manuscript.

Conflicts of interest

No conflict of interest.

Ethical considerations

Ethical issues (including data fabrication, double publication, and plagiarism) have been detected by the authors.

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References

Figure 1. Sphingosine 1 phosphate agonist is a promising plan against SARS-CoV-2-induced pulmonary damage.

ACE2 is identified as the functional receptor for SARS-CoV-2. ACE2 is highly present on human alveolar epithelial cells (33), its high expression is identified in type II alveolar cells facilitating the replication of coronavirus in the lung (34, 35). The injured cells promote an innate inflammation in the lungs mediated by pro-inflammatory macrophages (6). S1P is an effective bioactive lipid mediator and its related signaling pathways are crucial for endothelial integrity. As a S1P analogs, FTY720-P (Fingolimod) binding to S1PR1 on the endothelial cell enhances the endothelial barrier integrity and limits the migration of effector lymphocytes toward the inflamed area. It can also decrease the fluid extravasation and cytokine storm in the alveolar space (3). ACE2: angiotensin-converting enzyme 2, S1P: Sphingosine 1-phosphate, Sph: sphingosine, MQ: macrophage.


