


Neutrophil elastase inhibitor (sivelestat) may be a promising therapeutic option for management of acute lung injury/acute respiratory distress syndrome or disseminated intravascular coagulation in COVID-19

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Abstract

What is known and objective: This article summarizes the effects of sivelestat on acute lung injury/acute respiratory distress syndrome (ALI/ARDS) or ARDS with coagulopathy, both of which are frequently seen in patients with COVID-19.

Comment: COVID-19 patients are more susceptible to thromboembolic events, including disseminated intravascular coagulation (DIC). Various studies have emphasized the role of neutrophil elastase (NE) in the development of DIC in patients with ARDS and sepsis. It has been shown that NE inhibition by sivelestat mitigates ALI through amelioration of injuries in alveolar epithelium and vascular endothelium, as well as reversing the neutrophil-mediated increased vascular permeability.

What is new and conclusions: Sivelestat, a selective NE inhibitor, has not been evaluated for its possible therapeutic effects against SARS-CoV-2 infection. Based on its promising beneficial effects in underlying complications of COVID-19, sivelestat

could be considered as a promising modality for better management of COVID-19-induced ALI/ARDS or coagulopathy.

KEYWORDS

acute lung injury/acute respiratory distress syndrome, coagulopathy, COVID-19, neutrophil elastase inhibitor, sivelestat

1 | WHAT IS KNOWN AND OBJECTIVE

The little-known respiratory infection by a novel coronavirus 2019-nCoV in December 2019 has now become a global pandemic. The virus and the disease it causes are officially designated as SARS-CoV-2 and COVID-19, respectively.¹ At the time of preparing this manuscript, WHO reported over ten million confirmed positive cases of COVID-19 and the number of global deaths now exceeds 499 913 (https://covid19.who.int/?gclid=CjwKCAjwxev3BRBBEiwAiB_PWDVmEMC7Tn5vgLxqlWMIo-sKDYOMlfZ0Z-u7CEdDsriOCxOop6cf2hoCOHoQAvD_BwE). The death rate of COVID-19 is estimated to be 2%,² which is less than SARS and the Middle East respiratory syndrome (MERS), but SARS-CoV-2 has proven to be more contagious.³

Although the symptoms of COVID-19 vary depending on age and underlying conditions,⁴ most patients exhibit symptoms such as fever, dry cough, myalgia, tiredness, and diarrhoea. Patients with COVID-19 are also more susceptible to thromboembolic events because of immobility, inflammation, hypoxia and disseminated intravascular coagulation (DIC). In one study, the incidence of thrombotic complications in patients admitted to the intensive care unit (ICU) with COVID-19 was reported to reach 31%.⁵ In this regard, hyperfibrinolysis related to increased levels of D-dimer was observed in 97% of patients with COVID-19 at the time of hospital admission and it continued to rise in all patients before death. Fibrin degradation products also significantly increased during the course of the disease. In severe cases of COVID-19 or in dying patients, a significant drop in platelet levels was observed.⁶ Numerous reports outlined that a severe form of the disease in COVID-19 patients develops during a few days, which is often manifested as an acute lung injury/acute respiratory distress syndrome (ALI/ARDS), respiratory failure, heart failure or sepsis.⁴ The animal models of SARS-CoV and MERS-CoV showed that the significant levels of inflammatory and immune responses cause 'cytokine storm' and apoptosis of epithelial and endothelial cells. This is followed by an increase in vascular permeability and leakage, abnormal T-cell and macrophage responses, and ALI/ARDS that could eventually lead to death.⁷

In patients with COVID-19, the inflammatory cytokine storm is closely associated with the development and progression of ARDS.⁸ In these patients, the high-level cytokine expression of interleukin (IL)-1 β , interferon (IFN)- γ -induced protein (IP-10) and monocyte chemoattractant protein 1 (MCP-1) could result in activated T-helper-1 (Th1) response. When compared to hospitalized

COVID-19 patients on general wards, those in the ICU appear to show a higher level of granulocyte colony-stimulating factor, IP-10, MCP-1, macrophage inflammatory protein-1A, and tumour necrosis factor-alpha (TNF- α). Several studies emphasized this direct correlation between cytokine storm and the severity of COVID-19.⁹ Furthermore, an elevated level of IL-6 was shown to be a predictor of poor outcome in severe COVID-19 with pneumonia and ARDS.¹⁰ Hence, the inflammatory cytokine storm plays a key role both for the development of ARDS and extra-pulmonary organ failure.⁸

Acute respiratory distress syndrome is a severe type of acute lung injury and is characterized by massive infiltration of neutrophils, monocytes and lymphocytes. The diffuse bilateral oedema followed by reduced lung compliance, alveolar damage and bronchoalveolar lumen hyaline deposition result in hypoxic respiratory failure. Degranulating neutrophils have a key role in the development of capillary injury and leakage and hyaline deposition. These events may progress to ARDS or a more fatally diffuse alveolar damage.¹¹ The key role of neutrophils in the pathogenesis of ALI/ARDS has also been shown in animal and clinical studies. Histological assay on autopsy samples of ARDS patients has illustrated a significant accumulation of polymorphonuclear cells (PMN) including neutrophils in the damaged alveoli and the interstitial tissues.¹²

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) is a basic transcription factor that is essential for the expression of inflammation-related genes such as inducible nitric oxide synthase (iNOS) and inflammatory cytokines.¹³ In patients with ARDS, the activation of NF- κ B leads to increased expression of immunoregulatory and pro-inflammatory cytokines.¹⁴

Viral infection has also the potential to induce the production of oxidized products or oxidative stress that aggravates the inflammation-mediated COVID-19 pathology. For example, oxidized low-density lipoprotein under SARS-induced ALI activates the innate immune response. This leads to the overproduction of IL-6 in alveolar macrophages via the Toll-like receptor 4 (TLR4)/NF- κ B signalling pathway.¹⁵ Furthermore, with an active viral infection, the retinoic acid-inducible gene I (RIG-I) senses viral RNA and triggers signalling cascades, adaptor proteins (MAVS and TRAF) and different transcription factors (NF- κ B and IRF3/IRF7) at host pattern recognition receptors (PRRs). This accounts for the initiation of antiviral type I interferon transcription and pro-inflammatory cytokines.¹⁶

As major components of inflammatory responses to endothelial injury, neutrophils have proteolytic and pro-apoptotic properties

through the action of several enzymes.¹⁷ Among them is the serine protease, neutrophil elastase (NE), which has antimicrobial properties due to its ability to degrade phagocytosed pathogens.¹⁸ It also contributes to inflammation by increasing vascular permeability¹⁹ and induction of pro-inflammatory cytokines release, such as IL-6 and IL-8.²⁰ In this regard, NE is needed for neutrophil function during sepsis. Under normal physiological conditions, the function of NE is rigorously regulated by endogenous protease inhibitors.²⁰ However, under exaggerated inflammatory conditions, NE is enabled to attack the endothelial barrier and infiltrate to bronchoalveolar space. This is due to the inactivation of protease inhibitors by neutrophil oxidants.²¹ Thus, excessive activity of NE may lead to tissue damage and remodelling in several pulmonary diseases such as community-acquired pneumonia, ventilator-associated pneumonia, exacerbated COPD, cystic fibrosis, bronchiectasis and ALI/ARDS.²² Furthermore, in those patients with ALI/ARDS, the plasma levels of NE are significantly higher in comparison with healthy subjects.²³ Significantly higher level of proteolytic activity of NE was also observed in the bronchoalveolar lavage (BAL) of ARDS patients.²⁴

Sivelestat, also known in the scientific literature as ONO-5046, is a selective, reversible and competitive neutrophil elastase inhibitor. Hence, it does not affect the function of other proteases in the body.²⁵ Its protective effects in attenuating ALI/ARDS have been described in several models of lung injury. In different pre-clinical and animal models of lung injury, sivelestat mitigated the lung vascular permeability, elevated pulmonary artery pressure (PAP), lung tissue wet to dry weight ratio, and neutrophil count.²⁶⁻²⁸ Furthermore, sivelestat improved pathogen clearance, the decrease in PaO₂, and prevented digestion of surfactant protein D.^{29,30}

2 | COMMENT

The following databases were searched to identify relevant literature concerning empirical evidence: The Cochrane Library, PubMed, MEDLINE and EMBASE from 1980 through March 2020.

It has been shown that NE inhibition by sivelestat mitigates ALI through amelioration of injuries in alveolar epithelium and vascular endothelium, as well as reversing neutrophil-mediated increased vascular permeability.²⁶ In a clinical study on patients with ARDS and systemic inflammatory response syndrome, continuous infusion of sivelestat has been shown to significantly improve pulmonary function, as indicated by an increase in PaO₂/FIO₂ ratio, shortened duration of mechanical ventilation time and length of ICU care. However, the mortality rate did not differ in comparison with the control group.³¹ In another phase III clinical double-blinded trial with 230 ALI patients, sivelestat was shown to increase recovery rates of the pulmonary functional parameters, reduce the duration of the mechanical ventilator and better weaning rates, and shortened ICU length of stay by almost half. However, this selective NE inhibitor was not able to reduce the 30-day survival rate. In this study, only

around 20% of death occurred due to respiratory failure. This may explain why the survival rate between the two arms of the study did not reach a significant value.³²

Several studies have indicated that sivelestat increases ventilator-free days and survival in patients with ALI/ARDS through inhibition of the overstretch-induced signalling pathway and neutrophil chemotaxis.³³⁻³⁵ During mechanical ventilation (MV), the risk of ALI is increased due to over-activation of neutrophil elastase and myeloperoxidase. Furthermore, phosphorylation of c-Jun NH₂-terminal kinase (JNK) is increased in alveolar type 2 epithelial cells.³⁶ There is a direct relationship between the inhibition of JNK and the prevention of over-ventilation lung injury. JNK is also critical in the induction of apoptosis during stress responses.³⁷ The protective effects of sivelestat against MV were evaluated in an animal model of mice where sivelestat (100 mg/kg, intraperitoneally) or saline was administered 30 minute before ventilation. Under 4 hours of MV with a high tidal volume of 20 mL/kg, sivelestat prevented histopathological MV-induced lung damage, decreased lung tissue wet to dry weight ratio, and suppressed the serum and bronchoalveolar lavage fluid levels of macrophage-inflammatory protein 2 (MIP-2), IL-6 and TNF- α . Through inhibition of neutrophil chemotaxis, sivelestat also normalized the phosphorylation of JNK and attenuated apoptotic changes in pneumocytes after the MV-induced ALI.³⁸

In a retrospective study of sivelestat in 110 patients with ALI and sepsis, sivelestat significantly increased the number of ventilator-free days and PaO₂/FIO₂, especially in those patients with baseline procalcitonin levels of ≥ 0.5 ng/mL.³⁵ In another multicenter, prospective study using 164 mechanically ventilated ARDS patients with high wet to dry lung weight ratio, the efficacy of sivelestat was compared to the control group. In this study, sivelestat increased ventilator-free days with no significant effect on 28-day mortality.³⁴

In a phase IV open-label, non-randomized, multi-centre clinical trial for the treatment of ALI associated with SIRS on 581 patients, sivelestat was continuously administered intravenously at a dose of 0.2 mg/kg/h for 2 weeks. The results of this study showed a significantly higher ventilator-free day, ICU discharge rate and early weaning from the mechanical ventilator with sivelestat compared to the control group. Furthermore, those patients received sivelestat had a substantially higher 180-day survival than control patients. The results of this clinical trial emphasized on the clinical efficacy of this NE inhibitor in this group of patients.³⁹

During ARDS and cytokine storm, the host's inflammatory responses, including serum levels of TNF- α , IL-6, high mobility group box 1 (HMGB1) protein and NO synthesis from iNOS, rise significantly.⁴⁰⁻⁴² As indicated above, the NF- κ B signalling pathway regulates the expression of these inflammatory factors.^{43,44} Furthermore, NE-mediated chemotaxis to the lung potently induces epithelial cells and macrophages to produce inflammatory cytokines.⁴⁵ It has been demonstrated that sivelestat downregulates the NF- κ B pathway and inhibits the secretion of HMGB1 from macrophages through inhibition of I κ B kinase phosphorylation.⁴⁶ Moreover, following the administration of sivelestat, the serum levels of TNF- α , IL-6, HMGB1 and NO were shown to

decrease significantly. This selective NE inhibitor could also substantially reduce the level of MCP-1 mRNA in macrophages during ischemia-reperfusion injury.⁴⁷

As outlined above, COVID-19 patients are more susceptible to thromboembolic events. In this regard, various studies have emphasized on the role of NE in the development of disseminated intravascular coagulation (DIC) in patients with ARDS and sepsis. In a study on 167 septic patients with ARDS and DIC, sivelestat was administered upon admission to ICU and continued for 5 days. The results showed that sivelestat improved lung injury score, PaO₂/FIO₂ ratio, DIC score, and ICU length of stay and survival rate when compared to the control group.⁴⁸

In another study on 142 ARDS patients with DIC, the efficacy of sivelestat alone, recombinant human soluble thrombomodulin (rhTM) alone, combination therapy of sivelestat and rhTM or untreated control were evaluated and compared to each other. The results were very promising, indicating that combination therapy with sivelestat and rhTM significantly increased the 60-day patient survival, mechanical ventilator-free days, better PIO₂/FIO₂ ratio and DIC score.⁴⁹ Recently, neutrophil elastase inhibitors were proposed as a potential prophylactic treatment option for COVID-19 patients.⁵⁰

3 | WHAT IS NEW AND CONCLUSIONS

An overview of the effects of sivelestat on ALI/ARDS or ARDS with coagulopathy was presented, both of which are frequently seen in patients with COVID-19. Sivelestat has not been evaluated for its possible therapeutic effects against COVID-19. Nevertheless, based on its promising beneficial effects in underlying complications of COVID-19, this selective NE inhibitor could be considered as a promising treatment for better management of ALI/ARDS or coagulopathy in patients with COVID-19. We believe that testing the possible efficacy of this therapeutic modality in this group of patients could help in developing new strategies for combating COVID-19.

CONFLICT OF INTEREST

None declared.

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