Background/Objective

- Acute respiratory distress syndrome (ARDS) is the acute onset of noncardiogenic pulmonary edema, hypoxemia and widespread inflammation in the lungs.
- ARDS is a serious complication associated with the infection SARS-CoV-2 virus that causes COVID-19.
- Recent reports have implicated the kallikrein-kinin system in ARDS caused by SARS-CoV-2.1,4
- Pharmacological inhibition of plasma kallikrein (PKa) may provide a therapeutic target for treating ARDS symptoms.
- The aim of this study is to evaluate effects of two plasma kallikrein inhibitors, subcutaneously implanted KV999272 (14.4 mg/kg/day) and oral KV998052 (45 mg/kg bid) on an acid-aspiration lung injury model of ARDS.

Methods

- Tracheostomy was performed on anesthetized C57BL/6 mice and 0.1N HCl (pH 1.25) instilled to induce ARDS; control animals received saline (S).
- Bronchoalveolar lavage fluid (BALF) was collected via a blunt cannula inserted into the trachea.
- Protein concentrations in the BALF were measured using a BCA protein assay.
- Plasma prekallikrein (PKa) and high molecular weight kininogen (HK) were measured by immunoassay using the WES system (ProteinSimple).
- Arterial blood oxygenation (oxygen saturation, S\textsubscript{O2}, %) was measured using a paw pulse oximeter (Kent Scientific).
- Contact system activation was triggered with dextran sulphate (OXS, Sigma, 62.5 μg/ml) in undiluted citrated mouse plasma in the absence or presence of PKa inhibitor KV998052.

Results

- Acid instillation in mice increased PK levels in BALF at 5, 24, 48 hours.
- PK levels correlate with protein concentrations in BALF in acid instilled ARDS mice.
- KV998052 protects against DXS stimulated PKa generation and HK cleavage in mouse plasma, in vitro.
- Treatment with orally administered KV998052 was associated with significantly improved blood oxygenation.

Summary and Conclusion

- ARDS in mice was associated with high levels of BALF protein concentration at 5h and 24h post surgery. This correlated with a significant reduction in S\textsubscript{O2} levels in acid instilled ARDS mice at both 24h and 48h.
- PK levels were increased in the BALF fluid at 5h, 24h and 48h in HCl-instilled ARDS mice compared to saline-instilled controls.
- Increase in PK correlated with increased BALF protein concentration.
- Systemic administration of a PKa inhibitor, KV999272, was associated with higher S\textsubscript{O2} in HCl instilled mice compared with vehicle treated mice.
- KV998052, an orally available PKa inhibitor, protected against DXS stimulated HK cleavage in mouse plasma, in vitro.
- Pretreatment of mice with orally administered KV998052 was associated with significantly improved blood oxygenation in mice with HCl induced ARDS compared with mice receiving vehicle.
- Pharmacological inhibition of PKa may provide a therapeutic opportunity for the treatment of ARDS.

References

2. van de Wetering et al., JAMA Netw. Open. 2020;3(6):e2017038
4. Moreau et al., Viruses, 2021;13(2):348

Conflicts: Authors are or were employees of KalVista Pharmaceuticals during the execution of this work.