ePDS: 348

Oral plasma kallikrein inhibitor KV998052 improves arterial blood oxygenation in a murine model of acute respiratory distress syndrome (ARDS)

Nivetha Murugesan, Allen C. Clermont and Edward P. Feener
KalVista Pharmaceuticals, Inc., Cambridge, MA, USA

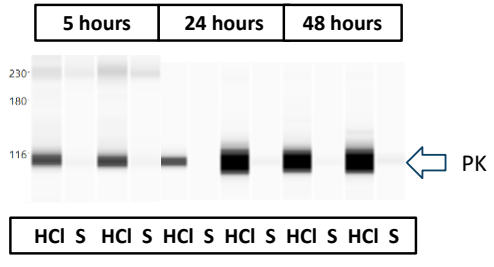
Background/Objective

- 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 with 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 mouse model of ARDS

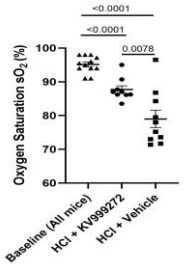
Methods

- 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, sO_2,%) was measured using a paw pulse oximeter (Kent Scientific)
- Contact system activation was triggered with dextran sulphate (DXS, Sigma, 6.25 μg/ml) in undiluted citrated mouse plasma in the absence or presence of PKa inhibitor KV998052

Results

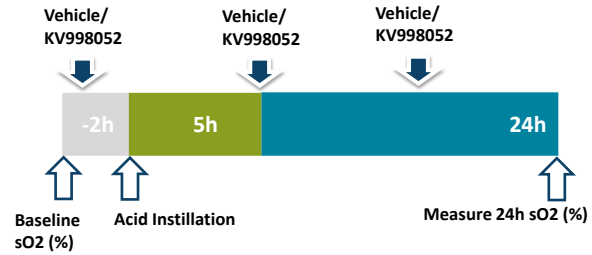


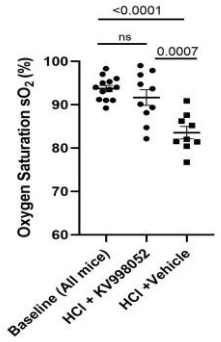
Acid instillation in mice increased PK levels in BALF at 5,24,48 hours.



Systemic administration of KV999272 improves oxygen saturation in acid instilled mice compared with vehicle controls.

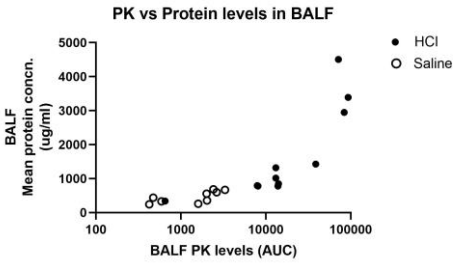
Results



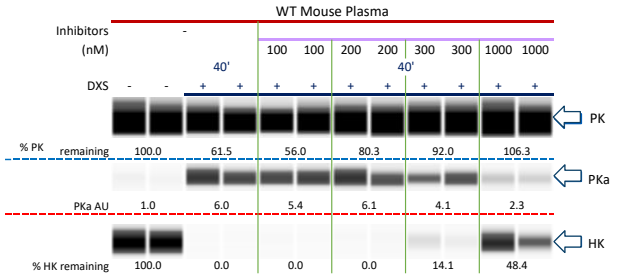


Pretreatment with orally administered KV998052 was associated with significantly improved blood oxygenation.

Results

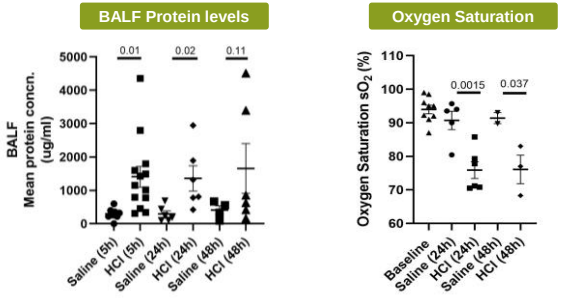


PK levels correlates with protein concentrations in BALF in acid instilled ARDS mice.



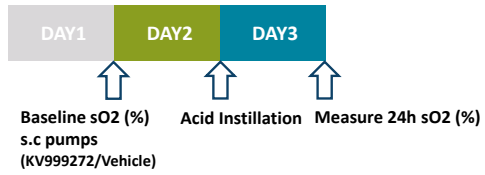
KV998052 protects against DXS stimulated PKa generation and HK cleavage in mouse plasma, in vitro.

Results



Acid-instillation increased BALF protein concentration and impaired blood oxygenation in mice.

Results



Experimental design for subcutaneous administration of KV999272 in acid instilled ARDS mice.

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 sO_2 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 sO_2 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
1. de Maat S et al., Semin. Thromb. Hemost. 2020;46(7):835-7 2. van de Veerdonk et al., JAMA Network Open. 2020;3(8):e2017708; 3. Lipsey et al., Front. Immunol., 2021; 4. Mansour et al., Viruses, 2021;13(2):309.

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