GBT1118, a drug that increases oxygen affinity of hemoglobin, improved survival during murine hypoxic acute lung injury

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Background

Acute Respiratory Distress Syndrome (ARDS) causes hypoxemia due to impaired gas exchange. GBT1118 is a new pharmacologic agent that shifts the oxy-hemoglobin dissociation curve, increasing hemoglobin affinity for oxygen.

Hypothesis

Oral administration of GBT1118 will improve arterial oxygen saturation, oxygen delivery, and outcomes of mice in an animal model of acute respiratory distress syndrome (ARDS) with superimposed hypoxemia.

Objectives

1. To test the effect of GBT1118 on survival in a two hit LPS+hypoxia model of acute lung injury
2. To test the effect of GBT1118 on arterial oxygen saturation
3. To test the effect of GBT1118 on the oxyhemoglobin dissociation curve
4. To test the effect of GBT1118 on lung permeability and inflammation

Methods

- To induce acute lung injury, C57Bl/6 mice were treated with intratracheal injection of 100ug LPS (Sigma, St. Louis, MO). After 24 hours, mice were given GBT1118 or vehicle (50%alcohol) by oral gavage 2 hours prior to placement in a hypoxia chamber. Mice were exposed to either 5% or 10% O2 for 4 hours.
- Arterial oxygen saturation (SpO2) was measured with a pulse oximeter (STARR Life Sciences, Oakland, PA) at baseline and hourly during exposure to hypoxia.
- Severity of illness scores were determined before and after hypoxia exposure. Clinical severity markers were used to determine the composite sickness score: mobility, enopchealpacy, and appearance.
- During hypoxia exposure, mice were monitored continuously. Time to death was assessed by tym to moribund status.
- Pharmacokinetics (PK) measurements performed to detect presence of GBT1118 and pharmacodynamics (PD) to measure efficacy of GBT1118 on whole blood by Global Blood Therapeutics.
- BAL inflammatory cell counts and differentials were determined manually after staining cytospins with DiffQuik. BAL protein was measured using a BioAssay System ELISA (R&D Systems, Minneapolis, MN).
- Groups were compared by Mann Whitney U test. Survival was compared by log rank.

Results

Oral administration of GBT1118 increased the SpO2 of mice during exposure to hypoxia. GBT1118 may be a novel therapy to treat hypoxia associated with ARDS.

Panel B: GBT1118 does not significantly change lung permeability or inflammation.

Figure 1: Experimental timeline.

Panel A: GBT1118 improved cumulative survival with LPS+Hypoxia.

Summary

1. Oral administration of a single dose of GBT1118 in mice effectively shifts the Hb dissociation curve to the left.
2. GBT1118 increased the SpO2 of mice during exposure to hypoxia.
3. Administration of GBT1118 improved cumulative survival with LPS+hypoxia.
4. GBT1118 does not significantly change lung permeability or inflammation.

Conclusions

1. A single oral dose of GBT1118 achieved therapeutic plasma levels at 4 hours as indicated by a significant shift in the oxyhemoglobin saturation curve.
2. The improved outcomes of mice treated with GBT1118 were not due to the attenuation of lung inflammation and permeability.
3. GBT1118 may be a novel therapy to treat hypoxia associated with ARDS.

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