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POSTER ABSTRACTS

102.IRON HOMEOSTASIS AND BIOLOGY

Rker-216 Reversed Microcytic Anemia in a Mouse Model of Iron Refractory Iron Deficiency Anemia

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Background
Iron refractory iron deficiency anemia (IRIDA) is an inherited disease caused by *TMPRSS6* mutations that increase serum hepcidin and result in microcytic anemia from iron malabsorption. As hepcidin promotes ferroportin (Fpn) degradation to limit iron absorption, its production in anemia should be decreased to make up body iron deficits. In contrast to typical iron deficiency anemia that can be improved by oral iron supplementation or intravenous (IV) iron infusion, IRIDA patients tend to have no response to iron supplements and only transiently respond to iron infusion, resulting in lifelong anemia. Hepcidin is mainly regulated by the bone morphogenetic protein (BMP) pathway, in which BMP ligands activate transcription factors SMAD1/5/9 by binding to the BMP receptors, including ALK2. We previously showed that RKER-216 (m216), a research ALK2 neutralizing antibody, improved iron availability in mice with anemia of inflammation resulting from high hepcidin. Here, we explored m216 pharmacology in an IRIDA mouse model.
Aim
To examine 1) mechanism of action (MOA), 2) efficacy of IV iron infusion and m216-mediated iron absorption, and 3) dose response of m216 in resolving microcytic anemia in *Tmprss6* knockout (KO) mice.
Methods
TMPRSS6 KO mice at 8-11 weeks (wk) were subcutaneously dosed with isotype control or m216 at 1 or 3 mg/kg in all studies. Mice were given a single dose for 6, 24 or 96 h in MOA and twice weekly for 9 or 21 d for efficacy studies. For IV iron, KO mice were given a single dose of iron dextran at 100 mg/kg and evaluated on day 9.
Results
TMPRSS6 KO mice at 8 wk had high serum hepcidin, low transferrin saturation (TSAT), and microcytic anemia as indicated by low mean corpuscular volume (MCV) and hemoglobin (Hb), key features in IRIDA. Liver SMAD1/5/9 phosphorylation, hepcidin (*Hamp*) mRNA, and serum hepcidin levels were decreased similarly in KO mice dosed with 1 or 3 mg/kg of m216 for 6 h, compared to isotype controls. KO mice given both dose levels for 24 h decreased serum hepcidin by 88% and increased TSAT by 4-fold, compared to isotype mice, but only mice receiving 3 mg/kg had sustained effects by 96 h. These data suggest that m216 inhibited SMAD signaling to lower serum hepcidin, allowing more iron absorption to increase TSAT.
To explore the relevance of m216 to current therapy, we compared the result of IV iron or 1 mg/kg of m216 in KO mice for 9 d. Compared to controls, liver iron, serum hepcidin, and TSAT were increased in mice given IV iron whereas mice receiving m216 exhibited reduced hepcidin with increased duodenal Fpn and TSAT, confirming target engagement. Although TSAT was higher in mice dosed with m216 compared to IV iron, anemia improved similarly (1-2 g/dl in Hb; 2 fl in MCV) in these two groups. These data suggest that despite high hepcidin, IV iron improved anemia via increased TSAT; however, the relationship between TSAT and anemia recovery is not always linear. We next examined KO mice dosed with m216 at 1 or 3 mg/kg for 3 wk. Hb and MCV improved from 9.2 g/dl and 26.2 fl in isotype controls to 11.5 g/dl and 33.7 fl in 1 mg/kg-m216 mice and further improved to 14.1 g/dl and 39.8 fl in the 3 mg/kg-m216 cohort, respectively, showing a dose proportional mitigation in improving microcytic anemia compared to isotype controls. In fact, Hb and MCV of the 3 mg/kg-m216 cohort were restored to the levels of WT mice, indicating that microcytic anemia was fully resolved in this group.
Conclusion
These data suggest that m216 inhibited the BMP pathway to increase iron absorption via hepcidin suppression and was able to provide similar effects as iron infusion in reversing microcytic anemia in a mouse model of IRIDA.

Disclosures Wang: *Keros Therapeutics:* Current Employment. **Melgar-Bermudez:** *Keros Therapeutics:* Current Employment. **Welch:** *Keros Therapeutics:* Current Employment. **Cadena:** *Keros Therapeutics:* Current Employment. **Lerner:** *Keros Thera-*

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