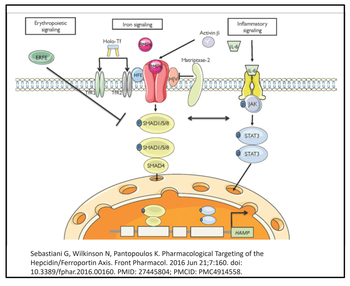
Targeted ALK2 inhibition as a therapeutic approach to reducing hepcidin and elevating serum iron

Thomas A. Backus, Natalia M. Medeiros, Evan M. Lema, ffolliott M. Fisher, Jasbir S. Seehra, Jennifer L. Lachey

Keros Therapeutics, Lexington MA

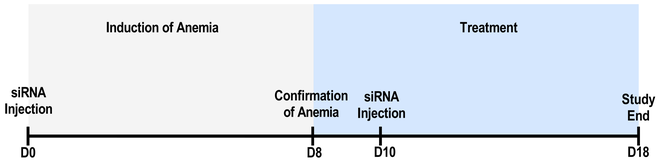


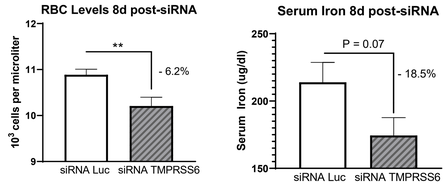
BACKGROUND

Hepcidin is an endocrine regulator of iron metabolism that, when elevated, can decrease levels of iron available for erythropoiesis resulting in decreased red blood cell production. Signaling though activin-like kinase-2 (ALK2), a TGF-β type 1 receptor, has been implicated in regulation of hepcidin-mediated iron regulation and mobilization; however, to date, ALK2's specific degree of involvement has not been convincingly elucidated, mainly due to the redundant effects of the type 1 receptors ALK3 and ALK5. Activation of type 1 receptors including ALK2, ALK3, and ALK5 via ligand BMPs and co-receptor hemojuvelin (m-HJV), results in downstream SMAD phosphorylation, increased hepcidin, and decreased serum iron while suppression of the receptor signaling would have the opposite effects. To assess the specific effect of ALK2 inhibition on hepcidin and iron mobilization, we utilized multiple modalities of inhibition and tested inhibitors in both naive and diseased animals in both models of iron refractory iron deficiency anemia (IRIDA) and anemia of chronic inflammation (AI) via induced chronic kidney disease (CKD). Both forms of anemia are characterized by elevated hepcidin and suppressed serum iron levels.

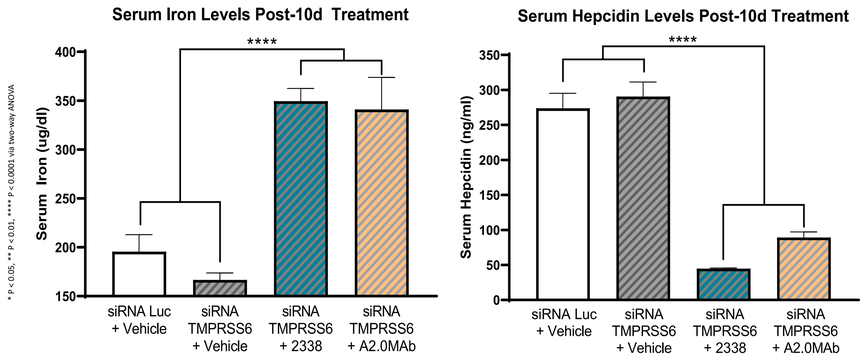
METHODS

IRIDA: C57BL/6 mice were dosed intravenously with lipid encapsulated siRNA targeted against either Luciferase (control) or TMPRSS6 (0.75 mg/kg), confirmed anemic at 8 days post-administration and began treatment with KTI-2338, KTI-A2.0MAb, or vehicle. Mice were taken down following 10 days of therapeutic administration. At takedown we collected hematology data, serum iron, and serum hepcidin levels.

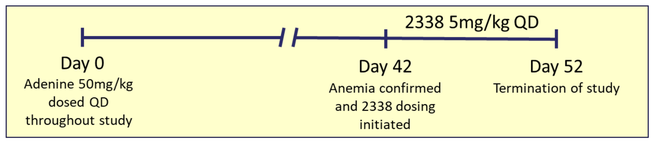


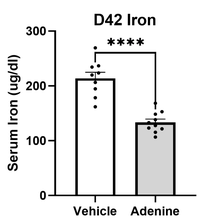


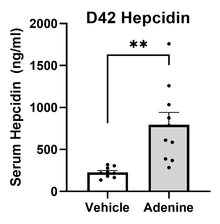
IRIDA: 10 days of therapeutic dosing following confirmation of disease at Day 8 with KTI-2338 or KTI-A2.0MAb resulted in rescue of the disease phenotype. At study termination, mice receiving TMPRSS6 siRNA in combination with KTI-2338 or KTI-A2.0MAb had improved serum iron, 109.8% and 104.8% higher than the vehicle-treated mice receiving TMPRSS6 siRNA, respectively. Additionally, serum hepcidin was decreased by 84.6% and 69.3%, respectively.



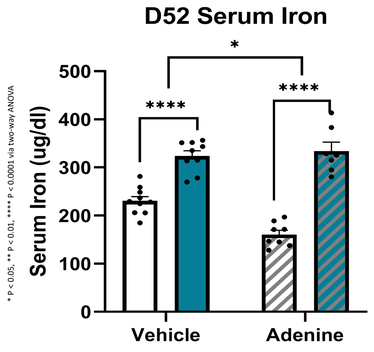
AI: C57BL/6 mice were dosed daily via PO administration with 50mg/kg of adenine or vehicle. After 6 weeks of adenine administration, anemia was confirmed in subset of mice. Concomitantly, the remainder of mice began dosing with either vehicle or KTI-2338 5 mg/kg PO daily whilst still receiving daily adenine or vehicle for 10 days. The study was terminated at 52 days and hematology, serum hepcidin, and serum iron levels were assessed.

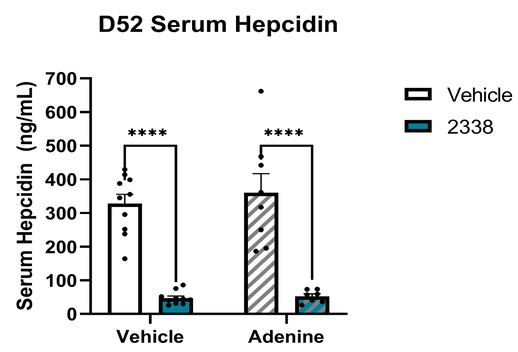


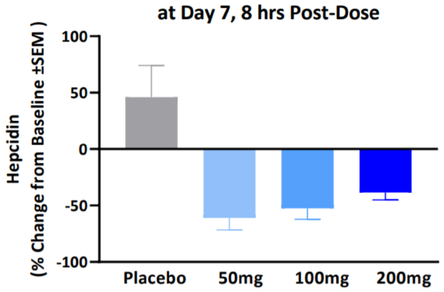


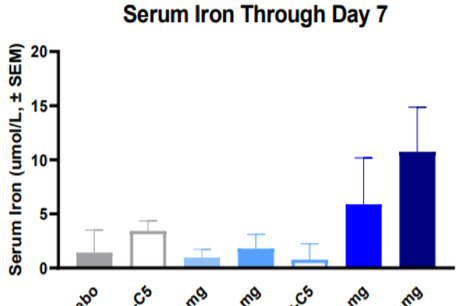


AI: 10 days of therapeutic dosing following confirmation of anemia at Day 42 with KTI-2338 resulted in elevation of serum iron and suppression of serum hepcidin beyond baseline levels in both anemic and control mice. At study termination, mice receiving adenine in combination KTI-2338 had serum iron values 108.2% higher than the vehicle-treated mice receiving adenine and vehicle. Additionally, serum hepcidin was decreased by 85.4% over vehicle treated mice.









RESULTS

DISCUSSION

Herein, we have evaluated the utility of ALK2 inhibition in multiple models of anemia arising from high hepcidin including TMPRSS6 inactivation and chronic inflammation. We have characterized that inhibition of ALK2 signaling in either model contributed to a decrease in serum hepcidin and increase in serum iron levels. Though the use of a selective ALK2 targeted biologic does not completely preclude involvement of other BMP receptors such as ALK3, these data support our assertion that ALK2 signaling is an integral part of hepcidin-mediated iron mobilization and the potential of therapeutic targeting of ALK2 inhibition (with a small molecule inhibitor or a neutralizing monoclonal antibody) in anemia of high hepcidin including IRIDA and AI.

Finally, KER-047, an investigational compound structurally related to KTI-2338, was observed to increase serum iron levels and decrease serum hepcidin levels in a Phase I clinical trial of healthy volunteers. Taken together, these data substantiate the role of ALK2 signaling in anemia arising from high hepcidin and illustrate the potential therapeutic benefit of specific ALK2 inhibition in these diseases.

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