A Monoclonal Antibody Targeting ALK2 as a Potential Therapeutic Agent for Anemia of Inflammation

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Introduction

Hepcidin is a key mediator of iron metabolism[1]

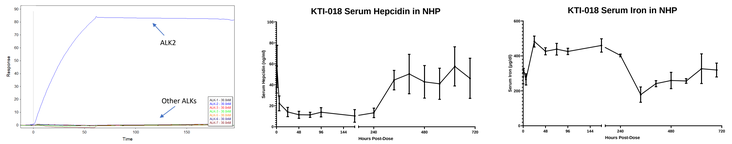
- Activates the degradation of the transmembrane iron exporter ferroportin
- Downregulates dietary iron uptake and release of iron from cells
- Activin receptor-like kinase 2 signaling in the liver controls hepcidin expression
  - ALK2 signaling requires bone morphogenic protein (BMP) ligand and co-receptor hemojuvelin

Preclinical and clinical data demonstrate ALK2 regulation of hepcidin

- Keros investigational small molecule ALK2 kinase inhibitors demonstrate proof-of-biology:
  - **KTI-2338** reduced hepcidin and improved anemia in a mouse model of chronic kidney disease
  - **KER-047** reduced hepcidin and increased iron in a Phase 1 healthy volunteer trial

Keros is developing KTI-018, an investigational fully human neutralizing antibody against ALK2

- Designed to bind ALK2 selectively; failed to bind other ALKS by Surface Plasmon Resonance (SPR)
- In monkeys, treatment resulted in reduction in serum hepcidin and increase in serum iron following a single dose

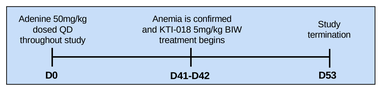


Anemia of inflammation[2, 3]

- Mediated in part by interleukin 6 (IL-6), a pro-inflammatory cytokine
- IL-6 upregulates hepcidin expression and reduces serum iron bioavailability, resulting in diminished incorporation of hemoglobin into reticulocytes and red blood cell formation
- This effect likely requires BMP signaling, so ALK2 inhibition may be a treatment approach

Our goal was to determine the potential of KTI-018, a neutralizing ALK2 antibody, in the treatment of anemia of inflammation

Methods



Animals: Six-week-old male C57Bl/6 mice

Induction of anemia: Mice were treated with once daily oral administration of adenine, a compound which causes chronic kidney disease and leads to anemia. Vehicle mice were treated with TBS.

- Anemia was confirmed at Day 42
- Daily TBS/adenine administration was maintained until study termination

Treatment: Once disease was confirmed, the CKD cohort was divided into two groups:

- Twice weekly intraperitoneal TBS
- Twice weekly intraperitoneal KTI-018

Study termination: Day 53

Statistics: Data were analyzed with Prism 9 (GraphPad Software, San Diego, CA, USA) using Grubbs' outlier test and one-way ANOVA. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. Error bars=SEM.

Results

Adenine treatment induced CKD and anemia

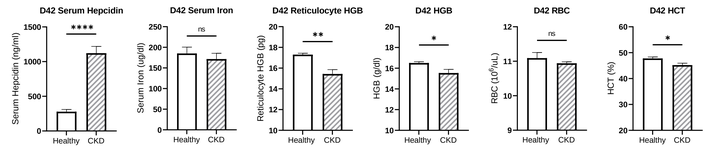


Figure 1. *After 42 days of adenine administration, the CKD cohort exhibited changes associated with anemia of inflammation: increased serum hepcidin, decreased serum iron (ns), and decreased hematologic parameters (reticulocyte hemoglobin content, hemoglobin, red blood cells (ns) and hematocrit).*

KTI-018 administration decreased serum hepcidin and increased iron

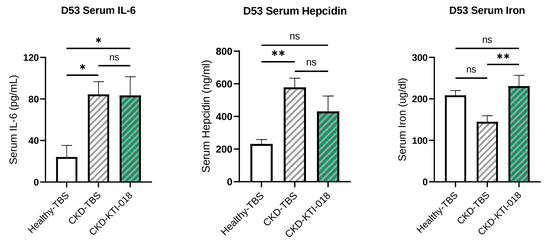


Figure 2. *After 11 days of twice weekly IP dosing with either TBS or KTI-018, CKD-TBS mice had increased serum IL-6 and serum hepcidin levels, and reduced serum iron (ns), as compared to Healthy-TBS mice. Administration of KTI-018 resulted in decreased serum hepcidin (ns) and increased serum iron in CKD mice.*

KTI-018 administration ameliorated anemia of inflammation

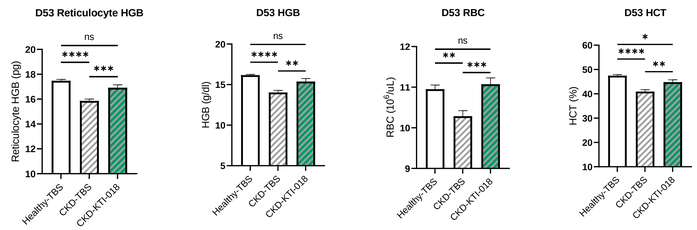


Figure 3. *CKD-TBS mice had decreased reticulocyte hemoglobin content, hemoglobin, red blood cells and hematocrit, as compared to Healthy-TBS mice. KTI-018 improved these hematologic parameters to Healthy-TBS levels.*

Conclusions

KTI-018 is a investigational novel neutralizing monoclonal antibody designed to inhibit ALK2 signaling

In a mouse model of chronic kidney disease with anemia of inflammation, inhibition of ALK2 with KTI-018:

→ Decreased serum hepcidin
→ Increased the bioavailability of iron for erythropoiesis
→ Restored hematologic parameters to healthy levels
→ Ameliorated anemia of inflammation

These data demonstrate that:

- ALK2 signaling plays a role in anemia of inflammation and in hepcidin-mediated iron mobilization
- Inhibition of ALK2 may be a treatment approach for anemia of inflammation

References

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