DISC-0974, AN ANTI-HEMOJUVELIN (HJV) MONOCLONAL ANTIBODY, REDUCED HEPCIDIN AND IMPROVED ANEMIA IN A RAT MODEL OF CHRONIC KIDNEY DISEASE

M WU[1], K WANG[1], B MACDONALD[1]
1. Disc Medicine Inc, Watertown, MA

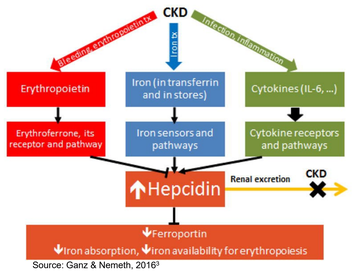
#3641

INTRODUCTION

DISC-0974 is a monoclonal antibody against hemojuvelin (HJV) and is currently in Phase I clinical studies[1]. HJV is a pathway-specific coreceptor for bone morphogenetic protein (BMP) signaling that regulates the expression of HAMP, the gene encoding hepcidin[2]. Loss-of-function mutations in HJV in juvenile hemochromatosis patients cause profound reductions in hepcidin synthesis and elevated serum iron levels. Consequently, it is hypothesized that pharmacological reduction of HJV activity will lead to reduction of hepcidin synthesis and increased iron availability for improved erythropoiesis.

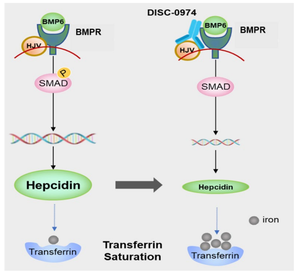
Anemia is a common complication in patients with CKD and has been associated with multiple adverse outcomes in this population[3]. Increased hepcidin is believed to be a central contributor to the development of anemia in CKD by reducing the availability of iron from systemic iron stores and by reducing dietary iron absorption. We hypothesize that by downregulating hepcidin, DISC-0974 will have beneficial effects in treating anemia in the CKD patients because it will make iron available for increased hemoglobin synthesis.

The Pathogenesis of Hepcidin Dysregulation in CKD



Source: Ganz & Nemeth, 2016[3]

Proposed Mechanism of Action of DISC-0974

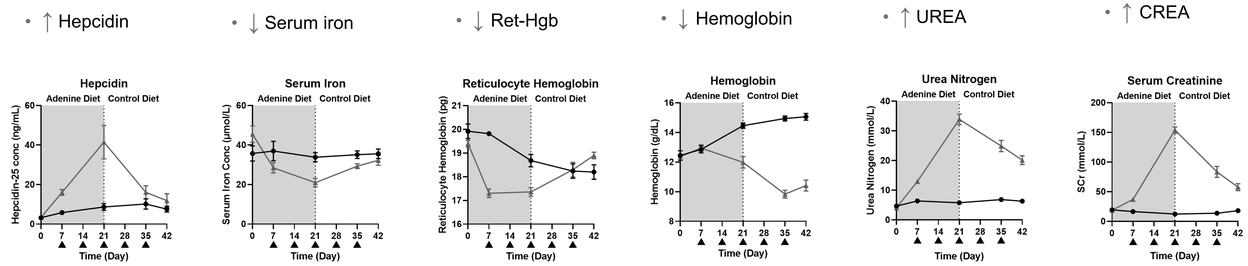


RESULTS

Effect of Adenine in Rats (CKD Rats)
(Group 1 vs. Group 2)

- control diet + vehicle
- 0.75% adenine diet + vehicle
- Administration with DISC-0974

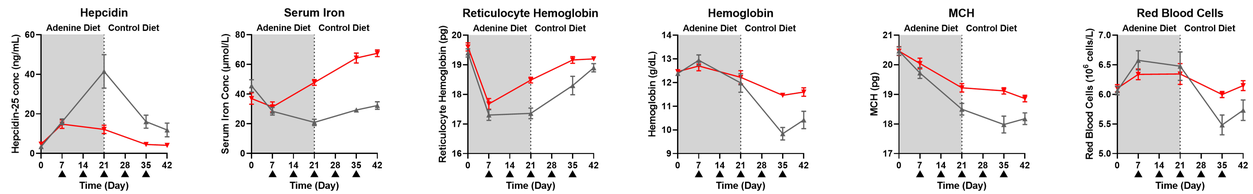
- ↑ Hepcidin
- ↓ Serum iron
- ↓ Ret-Hgb
- ↓ Hemoglobin
- ↑ UREA
- ↑ CREA



Effect of DISC-0974 in CKD Rats
(Group 2 vs. Group 3)

- 0.75% Adenine Diet + Vehicle
- 0.75% Adenine Diet + DISC-0974
- Administration with DISC-0974

- ↓ Hepcidin
- ↑ Serum iron
- ↑ Ret-Hgb
- ↑ Hemoglobin
- ↑ RBC counts
- ↑ MCH



OBJECTIVES AND STUDY DESIGN

Study Design

Adapted from Sun et al, 2013[4]

Group 1: control diet + Vehicle
Group 2: 0.75% adenine diet + Vehicle
Group 3: 0.75% adenine diet + DISC-0974 @ 20 mg/kg

- **Goal: evaluate the effect of DISC-0974 in adenine-induced rat CKD model**
- **Study design:**
  - Male Wistar rats were fed a 0.75% adenine diet for 3 weeks to induce kidney injury, followed by normal diet for another 3 weeks
  - DISC-0974 @ 20 mg/kg or vehicle was administered IV once per week from day 7 to day 35 (n=5/group)
  - Specimens collected on day 0, 7, 21,35 and 42 for samples analysis

CONCLUSIONS

- 0.75% adenine diet induced kidney dysfunction, as evidenced by the marked increase in UREA and CREA, along with increased hepcidin and anemia
- Treatment with DISC-0974 in CKD rats reduced serum hepcidin levels, increased iron availability, and substantially prevented the reduction in hemoglobin that is seen in animals with renal impairment induced by adenine.
- This study provides preclinical proof of concept for the development of DISC-0974 for the treatment of patients with CKD anemia (See DISC-0974 Ph1 healthy volunteer trial results in ASH poster #2339).

REFERENCES

1. Kovac S, Böser P, Cui Y, et al. Anti-hemojuvelin antibody corrects anemia caused by inappropriately high hepcidin levels. Haematologica. 2016 May;101(5): e173-6.
2. Xia Y, Babitt JL, Sidis Y, et al. Hemojuvelin regulates hepcidin expression via a selective subset of BMP ligands and receptors independently of neogenin. Blood. 2008 May 15;111(10):5195-5204.
3. Ganz T, Nemeth E. Iron Balance and the Role of Hepcidin in Chronic Kidney Disease. Semin Nephrol. 2016 Mar;36(2):87-93.
4. Sun CC, Vaja V, Chen S et al. A hepcidin lowering agent mobilizes iron for incorporation into red blood cells in an adenine-induced kidney disease model of anemia in rats. Nephrol Dial Transplant. 2013 Jul;28(7):1733-43.

ACKNOWLEDGEMENTS

Thank you to the DISC Nonclinical and CMC Teams

CONTACT INFORMATION

Min Wu, PhD, Vice President of Biology, Disc Medicine
mwu@discmedicine.com