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Anti-Hemojuvelin Monoclonal Antibody Alleviated Anemia Induced by Ruxolitinib Treatment in Mice

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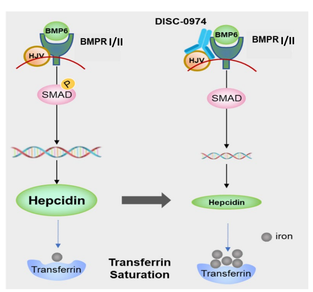
INTRODUCTION

Myelofibrosis (MF) is a hematologic malignancy characterized by excessive proliferation of myeloid cells and release of pro-inflammatory cytokines, leading to bone marrow dysfunction. Janus kinase (JAK) inhibitors, such as ruxolitinib, represent the first-line treatment in MF therapy. While ruxolitinib is effective at alleviating symptoms, the anemia associated with ruxolitinib is a limitation for the treatment.[1] Since anemia is already common in patients with newly diagnosed MF, there is an urgent need to minimize treatment-related anemia in patients with MF.

DISC-0974 is a humanized anti-hemojuvelin (HJV) monoclonal antibody. It was designed to disrupt the interaction between HJV and the bone morphogenetic protein (BMP) receptor complex, leading to decreased hepcidin expression and increased iron availability for enhanced erythropoiesis.



DISC-0974 is currently in clinical studies to treat anemia in patients with MF (NCT05320198) and chronic kidney disease (NCT05745883). In the MF trial, 10 participants were treated with JAK inhibitors; durable response (mean hemoglobin ≥1.5 g/dL above baseline for ≥12 weeks) was achieved in 4 of 8 non-transfusion-dependent participants, and 1 of 2 transfusion-dependent participants achieved transfusion independence (≥12 consecutive weeks without transfusion).[2]

AIM

The aim of this study was to evaluate whether DBIO-100, a murine analog of DISC-0974, could alleviate ruxolitinib-induced anemia *in vivo*.

METHODS

8-10-week-old C57BL/6J male mice were randomized to receive vehicle (Group 1), ruxolitinib at 90 mg/kg once daily (Group 2)/twice daily (Group 3), DBIO-100 at 20 mg/kg weekly (Group 4), ruxolitinib once daily in combination with DBIO-100 (Group 5), or ruxolitinib twice daily in combination with DBIO-100 (Group 6) for 28 days. At the end of the study, all mice were euthanized for further analysis.

RESULTS

DBIO-100 lowered serum hepcidin

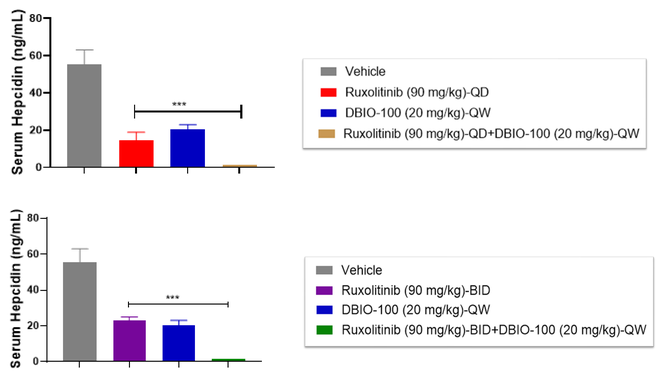


Figure 1. Ruxolitinib treatment lowered serum hepcidin level in wild-type mice. Adding DBIO-100 to ruxolitinib caused further decrease in serum hepcidin. *** $p <$ 0.001 by Student's *t* test. Values represent mean ± SEM.

DBIO-100 increased serum iron and TSAT

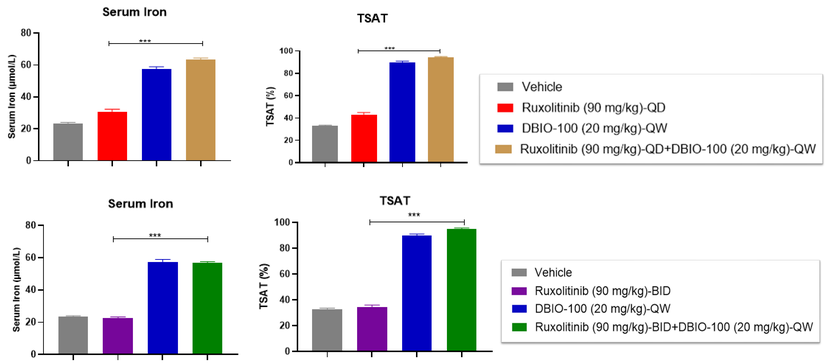


Figure 2. Mice with DBIO-100 treatment demonstrated significant increases in serum iron and transferrin saturation (TSAT). *** $p <$ 0.001 by Student's *t* test. Values represent mean ± SEM.

DBIO-100 alleviated anemia induced by ruxolitinib

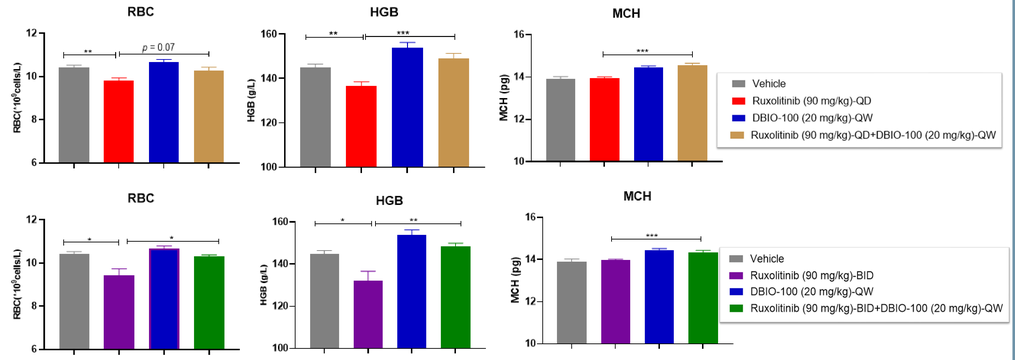


Figure 3. Ruxolitinib reduced hemoglobin in wild-type mice, regardless of the dosing regimen. Addition of DBIO-100 ameliorated anemia caused by ruxolitinib treatment. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ by Student's *t* test. Values represent mean ± SEM. RBC=red blood cell; HGB=hemoglobin; MCH=mean corpuscular hemoglobin.

CONCLUSIONS

This study demonstrated that ruxolitinib treatment reduced hemoglobin in wild-type mice. Adding DBIO-100, a mouse anti-HJV monoclonal antibody, can significantly increase iron availability and alleviate ruxolitinib-induced anemia. Taken together, these results underscore the potential of anti-HJV monoclonal antibodies as a therapeutic option for treating anemia in conditions like MF, where disease-directed therapies such as ruxolitinib, can significantly contribute to the development of anemia.

REFERENCES

1. Quintás-Cardama A, et al. Janus kinase inhibitors for the treatment of myeloproliferative neoplasias and beyond. Nat Rev Drug Discov. 2011;10(2):127-140.
2. Gangat N, et al. A Phase 1b trial of DISC-0974, an anti-hemojuvelin antibody, in patients with myelofibrosis and anemia. EHA Library. 2024;419146:P1059.

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