Pharmacological Evaluation of a First-in-Class Hemoglobin Elevating Agent (HbEA) AND017 in Townes SCD Mouse Model

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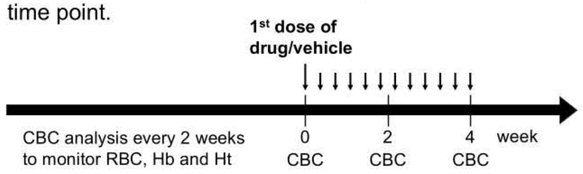
INTRODUCTION

Sickle cell disease (SCD) is a life-threatening genetic condition arising from a point mutation in β-globin gene that causes hemoglobin polymerization, vaso-occlusive sickling of RBCs, and hemolytic anemia. Hereditary persistence, pharmacologic or gene-based therapeutic induction of gamma-globin (HBG1 or HBG2) expression of fetal hemoglobin (HbF) that biophysically oppose hemoglobin polymerization and hemolysis. The current standard-of-care, a once daily oral hydroxyurea (HU), could increases expression of HbF and the magnitude of response (9-24% HbF) correlates with a reduction in anemia, pain crises and other complications in patients. However, the use of HU is limited by variable response, myelosuppression, gastrointestinal side effects and carcinogenicity risk.

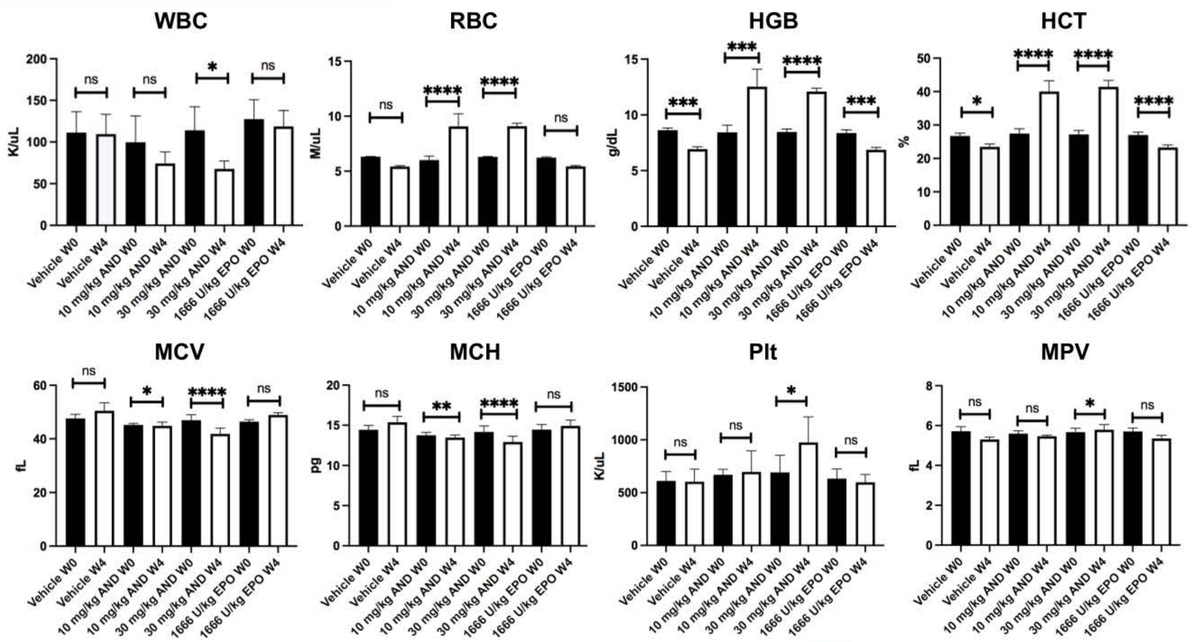
AND017 is a first-in-class hemoglobin elevating agent (HbEA), which has excellent efficacy in a wild-type rat model, rat 5/6 nephrectomy chronic kidney disease (CKD) model, MDS mouse model, and the Hbbd3th β-thalassemia mouse model, as well as has superb safety and efficacy in >300 patients in phases 1/2 clinical trials for CKD anemia. In this study, we evaluated AND017 in Townes SCD model.

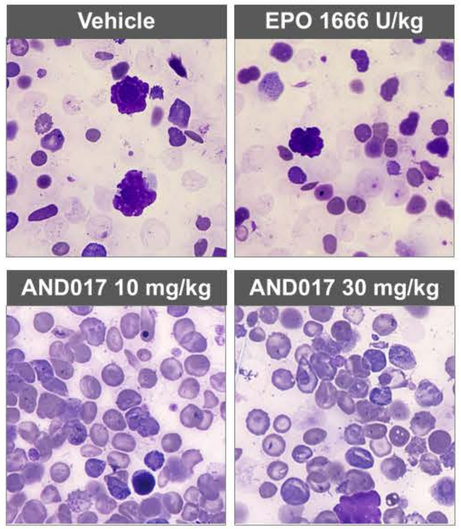
METHOD

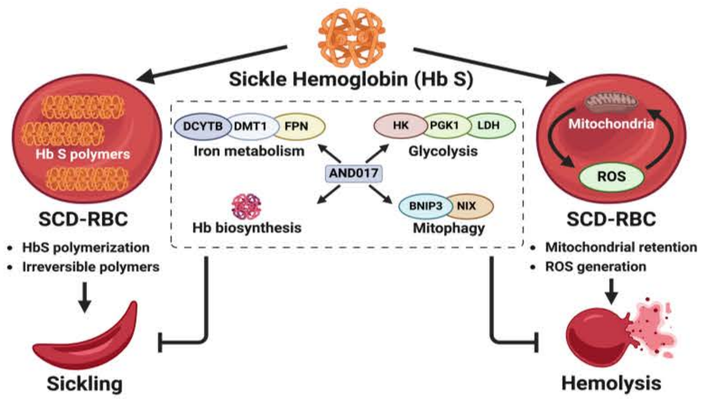
Forty Townes SCD mice (female/F: 20; male/M: 20; 6 weeks) were randomly divided into 4 groups: G1, G2, G3, and G4 (5F + 5M in each group). Mice in G1, G2, G3 and G4 were orally dosed three times per week with vehicle, 10 mg/kg AND017, 30 mg/kg AND017 and 1666 U/kg erythropoietin (EPO) respectively for 28 days. WBC, RBC, HGB, HCT, MCV, MCH, Plt and MPV were measured and calculated by a hematology system on days 0 and 28, respectively. The level of statistical significance was set at 5% or P < 0.05; the data were compared to G1 at the same time point.



RESULTS







Mechanistically, AND017 promoted glycolysis, enucleation, mitophagy and terminal differentiation of MEL leukemic cells. We confirmed in SCD mice that AND017 promoted terminal differentiation of erythrocytes and significantly reduced mitochondria retention in reticulocytes and mature red blood cells, which subsequently prolonged the life of red blood cells.

AND017 was well tolerated in both 10- and 30-mg/kg treatment groups. The WBC levels (K/μL) for G1 to G4 were 111.5, 99.72, 104.8 and 127.7 respectively on day 0; and were 109.6, 74.28, 67.75* and 118.7 on day 28. The RBC numbers (×10^6cells/μL) for G1 to G4 were 6.31, 6.01, 6.31 and 6.23 respectively on day 0; and were 5.42, 9.06****, 9.09**** and 5.43 on day 28. HGB levels (g/dL) for G1 to G4 were 8.63, 8.43, 8.47 and 8.37 respectively on day 0; and were 6.93, 12.5***, 12.1**** and 6.87 on day 28. The HCT (%) for G1 to G4 were 26.72, 27.43, 27.20 and 27.00 respectively on day 0; and were 23.47, 40.03****, 41.45**** and 23.25 on day 28. The MCV levels (fL) for G1 to G4 were 47.62, 45.20, 46.97 and 46.45 respectively on day 0; and were 50.48, 44.90*, 41.88**** and 48.94 on day 28. The MCH levels (pg) for G1 to G4 were 14.44, 13.75, 14.17 and 14.45 respectively on day 0; and were 15.38, 13.47**, 12.92**** and 14.94 on day 28. The Plt levels (K/μL) for G1 to G4 were 611.5, 669.3, 692.1 and 633.5 respectively on day 0; and were 603.8, 697.3, 976.0* and 597.4 on day 28. The MPV levels (fL) for G1 to G4 were 5.72, 5.60, 5.67 and 5.70 respectively on day 0; and were 5.30, 5.47, 5.79** and 5.35 on day 28. (*, **, ***, and ****: for p < 0.05, 0.01, 0.001, and 0.0001 respectively).

CONCLUSIONS

AND017 through unique mechanisms elevated several important parameters related to anemia, including Hb, RBC, and HCT, significantly and dose-dependently. AND017 also reduced the WBC, MCV and MCH and increased platelets in Townes SCD mice. These results indicate that AND017 has the potential to be a safe, efficacious and convenient oral drug for SCD patients.

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