RKER-050, A NOVEL ACTIVIN RECEPTOR TYPE II LIGAND TRAP, RESCUED ANEMIA AND REDUCED BONE LOSS IN A MOUSE MODEL OF MYELODYSPLASTIC SYNDROMES

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INTRODUCTION

Myelodysplastic syndromes (MDS) are a group of hematopoietic stem cell diseases characterized by ineffective hematopoiesis, peripheral blood cytopenias and dysplasias resulting from molecular defects and dysregulated signaling that governs the regulation of hematopoietic stem and progenitor cells (HSPCs). Crosstalk between cells in the osteo-hematopoietic (O-H) niche is necessary for the maintenance and self-renewal of HSPCs[1]. Alterations in the interaction between bone precursors and HSPCs within the bone marrow (BM) microenvironment have been linked to the pathophysiology of MDS. By way of example, MDS patients may also present with increased risk of osteopenia/osteoporosis compared to patients without MDS (similar age and gender)[2], demonstrating the critical interplay between the O-H cells in the BM. Transforming growth factor-beta (TGF-β) superfamily signaling is instrumental in regulating both normal hematopoiesis and bone homeostasis[3]. KER-050 is a modified investigational activin receptor type II ligand trap designed to bind and inhibit select TGF-β superfamily ligands, including activin A, activin B, GDF8 and GDF11, to promote hematopoiesis and bone growth. These ligands are negative regulators of bone remodeling, suppressing bone growth and enhancing bone resorption and have been implicated in bone disorders including osteoporosis[4]. Preclinical studies have demonstrated that treatment with a research form of KER-050 (RKER-050) increased bone mass and promoted multi-lineage hematopoiesis in healthy mice.

AIM

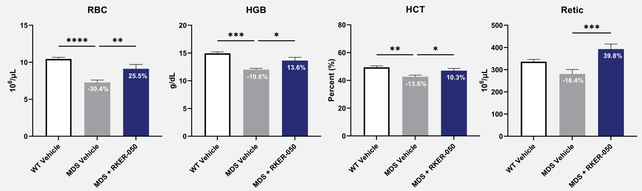
To investigate the effect of RKER-050 on hematopoiesis and skeletal mass in a murine model of MDS.

METHODS

- 5-month-old male MDS (NUP98/HOXD13) mice were treated IP with vehicle (MDS+VEH, n=10) or RKER-050 (7.5 mg/kg, MDS+RKER-050, n=9) once weekly for 6 weeks. Additionally, a wildtype control group was treated IP with vehicle (WT, n=7) once weekly for 6 weeks.
- CBCs were measured from peripheral blood; erythroid progenitors were assessed via antibody staining using the CytoFlex flow cytometer from cells isolated from the bone marrow and spleen.
- Femurs were scanned using GX2 µCT; trabecular bone at the distal femur was evaluated using Analyze 14.0 Bone Micro-architecture Analysis software (AnalyzeDirect).
- One-way ANOVA with Sidak multiple comparison was used for statistical analysis. Data is shown as mean ± SEM. *p ≤0.05, **p ≤0.01, ***p ≤0.005, ****p ≤0.001.

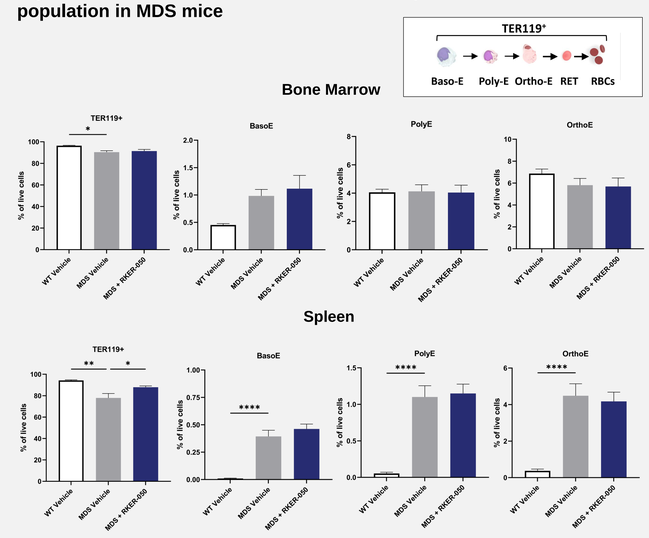
RESULTS

Figure 1. RKER-050 increased red blood cell parameters in MDS mice with established anemia



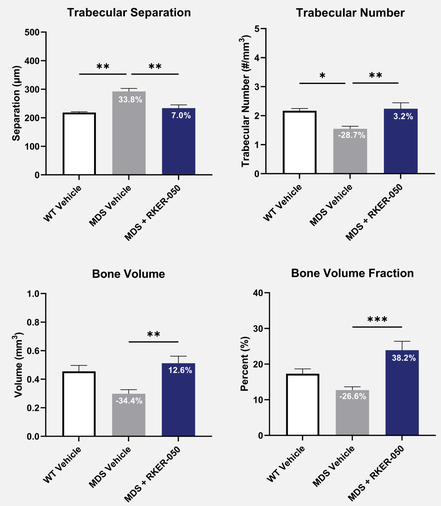
MDS+VEH mice showed a reduction in red blood cells (RBC; 30%), hemoglobin (HGB; 19%), hematocrit (HCT; 13%) and reticulocytes (Retic; 16%) compared to WT; all hallmarks of human MDS. Relative to MDS+VEH, MDS+050 showed increased RBC, HGB, HCT and Retic by 25%, 13%, 10% and 39%, respectively, demonstrating RKER-050's ability to mitigate anemic blood parameters in an MDS model.

Figure 2. RKER-050 treatment recovered the splenic TER119⁺ population in MDS mice



The TER119⁺ cell population was slightly reduced in BM and spleen of MDS+VEH mice compared to WT. The BM TER119⁺ cells were unchanged in the MDS+050 cohort relative to MDS+VEH; however, the spleen TER119⁺ cells were increased similar to the levels in WT mice. Specific erythroid precursor populations were altered in BM and spleen of MDS+VEH mice vs WT, consistent with the ineffective erythropoiesis in this model. Erythroid precursor populations were similar between MDS+VEH and MDS+050, yet MDS+050 exhibited recovered reticulocyte and RBC production (Fig.1), suggesting an increase in maturation of erythroid precursors with RKER-050 treatment.

Figure 3. RKER-050 ameliorated trabecular bone loss in MDS mice



MDS+VEH mice had significant increases in trabecular separation (33%) and significant decreases in trabecular number (28%) as well as trending decreases in bone volume (34%) and bone volume fraction (26%) compared to WT, changes that are consistent with reduced bone strength. MDS+050 treated mice had a significant increase in bone volume (12%), higher bone volume fraction (38%), increased trabecular number (3%) and decreased trabecular spacing (7%) compared to MDS+VEH, demonstrating RKER-050's potential to promote bone health in the context of a dysregulated O-H niche.

Figure 4. RKER-050 treatment remodeled bone microarchitecture in MDS mice

Representative three-dimensional images of the femur where trabecular architecture is reduced in MDS+VEH compared to WT and MDS+050. The apparent bone loss in MDS mice was improved with RKER-050 treatment. Transverse and sagittal cross sections of the distal femur depicting trabecular (red) and cortical (opaque) bone.

CONCLUSIONS

In an MDS mouse model, RKER-050 treatment increased RBC parameters, recovered the splenic TER119⁺ population and alleviated trabecular bone loss apparent in MDS mice.

These results suggest that RKER-050 can mitigate anemia and bone loss in an MDS mouse model, potentially by rebalancing hematopoiesis and bone turnover. In particular, the ability of RKER-050 to improve bone microarchitecture within the trabecular region, where the O-H niche predominantly resides, could be an important step in reestablishing healthy blood cell production. While changes to precursor cells in the BM compartment were not observed in this study, the observed increase in splenic TER119⁺ cells demonstrates that RKER-050 has the potential to improve erythropoiesis. An alternative treatment time course may be needed to better show changes to BM precursors.

Exploratory pharmacodynamic data from an ongoing phase 2 clinical trial (NCT04419649) in MDS patients demonstrate improved blood parameters with KER-050 treatment, including platelets and RBC[5]. KER-050, thus, represents a potentially promising approach for patients with MDS and other hematological diseases, including myelofibrosis, where a toxic BM microenvironment contributes to ineffective hematopoiesis and bone loss.

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