Preclinical development of EDIT-301, an autologous cell therapy comprising AsCas12a-RNP-modified mobilized peripheral blood CD34+ cells for the potential treatment of transfusion-dependent beta thalassemia

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DISCLOSURES

EDIT-301 is a cell therapy product consisting of autologous CD34+ hematopoietic stem and progenitor cells edited at the γ-globin gene promoter distal CCAAT box region where multiple naturally occurring fetal hemoglobin-inducing mutations reside, using a highly specific and engineered AsCas12α enzyme. Editing at the γ-globin promoter distal CCAAT box region mimics these natural mutations and induces robust γ-globin production. EDIT-301 is currently being evaluated in the Phase 1/2 RUBY clinical trial for the treatment of severe sickle cell disease.

OBJECTIVE

Based on ex vivo assay analysis, confirm that EDIT-301, an autologous cell therapy comprising hematopoietic stem and progenitor cells edited at the HBG1 and HBG2 promoters using a highly specific and efficient engineered AsCas12α enzyme, could be an efficacious therapy for patients with transfusion-dependent beta thalassemia.

INTRODUCTION

Beta thalassemia is one of the most common recessive hematologic disorders in the world, characterized by limited or complete absence of β-globin production. Insufficient β-globin production leads to the formation of toxic α-globin aggregates, which cause maturation blockage and premature death of erythroid precursors and hemolysis of red blood cells, leading to severe anemia. Patients with transfusion-dependent beta thalassemia (TDT), the most severe form of beta thalassemia, are burdened with lifelong blood transfusions and iron chelation therapy. EDIT-301 is a cell therapy product consisting of autologous CD34+ hematopoietic stem and progenitor cells edited at the γ-globin gene promoter distal CCAAT box region which multiple naturally occurring fetal hemoglobin-inducing mutations reside, using a highly specific and engineered AsCas12α enzyme.

RESULTS

EDIT-301 mechanism of action

Three batches of EDIT-301 were generated by electroporating mobilized peripheral blood CD34+ cells from three TDT donors with an engineered AsCas12α ribonucleoprotein. EDIT-301 was placed in erythroid differentiation conditions and underwent erythroid differentiation at a similar rate to unedited controls. EDIT-301 erythroid cells exhibited significantly improved erythroid maturation and decreased erythroid death compared with unedited controls.

CONCLUSIONS

EDITOR-301 erythroid cells exhibited significantly improved erythroid maturation and decreased erythroid death, therefore reversing the maturation blockage associated with TDT mutations. These preclinical data suggest that EDIT-301, edited at the γ-globin promoters where multiple naturally occurring fetal hemoglobin-inducing mutations reside, may be an efficacious treatment option to correct the ineffective erythropoiesis and severe anemia that characterize TDT, and support the start of clinical investigation.

REFERENCES

3. Clinicaltrials.gov. NCT04853576

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Methods

Three batches of EDIT-301 were generated by electroporating mobilized peripheral blood CD34+ cells from three TDT donors with an engineered AsCas12α ribonucleoprotein. EDIT-301 was placed in erythroid differentiation conditions and underwent erythroid differentiation at a similar rate to unedited controls. EDIT-301 erythroid cells exhibited significantly improved erythroid maturation and decreased erythroid death compared with unedited controls.

Figure 1. Engineered AsCas12α efficiently edited TDT-derived CD34+ cells while maintaining high viability

Figure 2. EDIT-301 cells successfully underwent erythroid differentiation at a similar rate to unedited controls

Figure 3. EDIT-301 erythroid cells had significantly improved erythroid maturation and decreased erythroid death compared with unedited controls

Figure 4. EDIT-301 erythroid cells had significantly increased γ-globin and total hemoglobin levels compared with unedited controls at both the mRNA and protein levels

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