Preliminary Results of a Phase 1/2 Clinical Study of Zinc Finger Nuclease-Mediated Editing of BCL11A in Autologous Hematopoietic Stem Cells for Transfusion-Dependent Beta Thalassemia

Journal: Blood
Publication Year: 2019
Authors: Angela Smith, Gary Schiller, Gregory Vercellotti, Janet Kwiatkowski, Krishnamurti Lakshmanan, Erica Esrick, David William, Weston Miller, Adrian Woolfson, Mark Walters

Funding Grants: A Phase 1/2 Study to Assess the Safety, Tolerability, and Efficacy of ST-400 Autologous HSPC Transplant in Transfusion-dependent β-Thalassemia

Public Summary:
Methods: The Thales trial (NCT03432364) is a Phase I/II study of the safety, tolerability and efficacy of ST-400 in adult patients with TDT, defined as undergoing ≥8 annual packed red blood cell transfusion episodes for at least 2 consecutive years before enrollment. After routine leukapheresis following mobilization with G-CSF and plerixafor, autologous collections are enriched for CD34+ cells and transfected with mRNA encoding ZFNs with binding sites flanking the GATA-binding region of BCL11A ESE. ST-400 product is infused following myeloablative busulfan conditioning. The trial will enroll 6 patients who are monitored for safety and efficacy for 3 years post-infusion.

Results: Three patients have completed ST-400 manufacturing, and two have been infused. Patient 1 (β0/β0 genotype) received an ST-400 dose of 6.1 x 10^6 cells/kg. The patient experienced a serious adverse event (SAE) of hypersensitivity during ST-400 infusion considered to be related to the product cryoprotectant, DMSO, that resolved by the end of infusion. The patient had prompt hematopoietic reconstitution (ANC recovery day +14; platelet recovery day +24), with increasing HbF fraction that contributed to stable total hemoglobin. After being free from PRBC transfusions for 6 weeks, the patient has since required intermittent PRBC transfusions. Patient 2 (homozygous for the severe β+ IVS-I-5 G>C mutation) received an ST-400 dose of 4.5 x 10^6 cells/kg. There was prompt hematopoietic reconstitution (ANC recovery day +15; platelet recovery day +29) with on-target indels detected in PBMCs at last follow-up, and rising HbF levels observed through 90 days post-infusion. Longer follow-up will be required to assess the clinical significance of these early results. Patient 3 (β0/β+ genotype including the severe IVS-II-654 C>T mutation) has completed ST-400 manufacturing. Besides the SAE reported for Patient 1, no other SAEs related to ST-400 have been reported and other AEs have been consistent with myeloablation. No clonal hematopoiesis has been observed.

Conclusions: ST-400 is an ex vivo, ZFN-edited autologous HSC product for increased erythroid HbF expression in TDT. Two infused patients had rapid hematopoietic reconstitution following myeloablative busulfan conditioning, and both have elevated HbF levels following HSCGT. These data are preliminary, and additional patients and longer follow-up will be required to understand the safety and efficacy of this therapy.

Scientific Abstract:
Introduction: Persistently high fetal hemoglobin (HbF) expression can ameliorate severe transfusion-dependent beta thalassemia (TDT). BCL11A, a master regulator of the fetal-to-adult hemoglobin switch, is a rational gene-editing target in beta globinopathies. In pre-clinical studies with human hematopoietic stem cells (HSC), zinc finger nuclease (ZFN)-mediated disruption of the GATA-binding region of the intronic erythroid-specific enhancer (BCL11A ESE) increased endogenous HbF production in erythroid cells while allowing healthy, multi-lineage hematopoiesis. Though allogeneic hematopoietic stem cell transplantation (HSCT) can be curative in TDT, its application is partly limited by donor availability. Autologous transplantation using ex vivo gene-modified HSCs (HSCGT) can circumvent this, and lentiviral vector-mediated beta globin gene addition studies have shown efficacy in TDT. However, the long-term safety of random lentiviral genomic integration in HSCs is uncertain. ST-400 is an investigational cell therapy comprised of autologous CD34+ cells that have undergone high-precision, ZFN-mediated ex vivo editing at BCL11A ESE. The aim of this study is to induce HbF expression in edited erythroid cells. We hypothesized that HSCGT with ST-400 is safe and effective in TDT.
mediated