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P1453 STABLE TRANSDUCTION OF FETAL HEMOGLOBIN IN PATIENTS WITH SICKLE CELL DISEASE IN THE PHASE 1/2 MOMENTUM STUDY OF ARU-1801 GENE THERAPY AND REDUCED INTENSITY CONDITIONING

Topic: 25. Gene therapy, cellular immunotherapy and vaccination - Clinical

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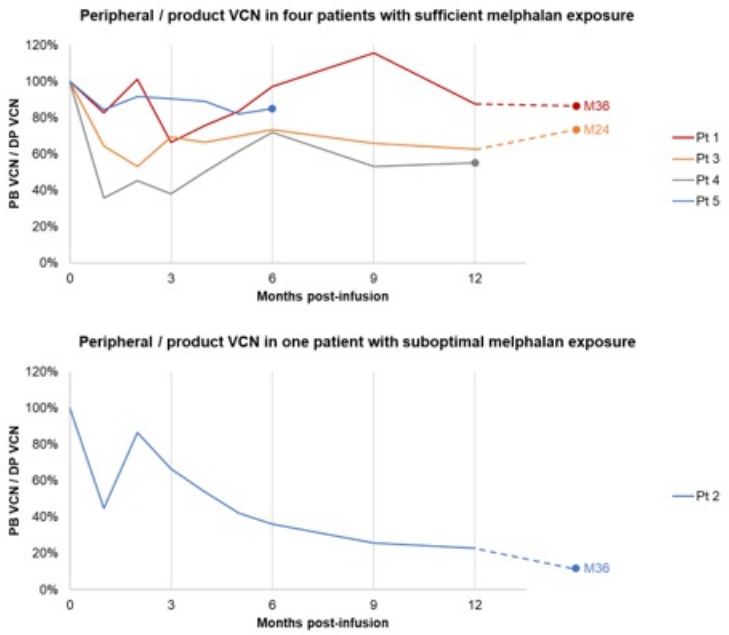
Background: Sickle cell disease (SCD) is a genetic red blood cell disorder that causes chronic hemolytic anemia, progressive organ damage, and painful vaso-occlusive crises. ARU-1801 is a gene therapy for SCD, designed to produce HbF^{G16D} expression in autologous CD34+ hematopoietic stem cells (HSCs). The ongoing Phase 1/2 MOMENTUM study (NCT02186418) is evaluating the safety and efficacy of ARU-1801, which is administered following reduced-intensity conditioning (RIC) and has demonstrated clinically meaningful improvements with drug product vector copy number (DP VCN) at and below 1.

Aims: Here, we demonstrate stable, high levels of HSC engraftment in patients treated with ARU-1801 gene therapy after RIC melphalan.

Methods: Adults (18-45 years old) with severe SCD (as defined by recurrent vaso-occlusive events [VOE] and acute chest syndrome) were screened for eligibility. Prior to infusion of ARU-1801, all patients received a single IV dose of RIC melphalan (140 mg/m^2). Endpoints included measures of melphalan pharmacokinetics, safety, engraftment, peripheral blood (PB) VCN, hemoglobin, and SCD-related outcomes.

Results: As of Feb 1, 2022, five patients (mean age [range], 26 [19-35] years old) have been treated with ARU-1801 gene therapy for SCD. Transient thrombocytopenia and neutropenia lasted a mean of 6 and 8 days, respectively. There have been no other serious adverse events related to chemotherapy or ARU-1801 to date. To quantify the proportion of genetically modified HSCs that engrafted in the setting of RIC, the ratio of PB VCN to DP VCN was measured over time (Figure 1). Four patients (Patients 1, 3, 4, and 5) had adequate RIC melphalan exposure (AUC = 6.8-10.1 mg.h/L) following a 140 mg/m^2 dose, maintaining a ratio of 72-97% at 6 months, which has remained stable. Anti-sickling globin expression has correlated with PB VCN and also remains stable (16-25% HbF^{G16D}, 22-39% total anti-sickling globin). One patient (Patient 2) had renal hyperfiltration (eGFR = 200 mL/min/1.73 m^2) resulting in sub-therapeutic melphalan exposure (AUC = 5.7 mg.h/L) and a decline in PB VCN which stabilized at ~10% of DP VCN. The protocol has since been amended to adjust the dose of melphalan for patients with renal hyperfiltration.

Image:



Summary/Conclusion: High engraftment in this trial compares favorably to other clinical trials of SCD gene therapy which have observed marked decreases in VCN shortly after infusion and is particularly significant in the setting of RIC, where a population of patients' unmodified HSCs remain and compete with the genetically modified HSCs. The ARU-1801 manufacturing process uses a proprietary methodology to prevent HSC differentiation in culture, which may favor transduction of long-term HSCs over short-term progenitor cells. Overall, preliminary data suggest ARU-1801 achieves stable, high engraftment of transduced HSCs even in the setting of RIC, resulting in robust long-term maintenance of therapeutic hemoglobin levels. We have previously shown (1) ARU-1801 can reach effective levels of anti-sickling hemoglobin at VCN ≤1, with 42% HbF^{G16D} expression per DP VCN and (2) HbF^{G16D} may have a more potent anti-sickling effect than endogenous HbF. Along with these effects, strong long-term HSC engraftment (as demonstrated by high, stable ratios of PB to DP VCN) requiring only RIC makes ARU-1801 a promising gene therapy alternative to treatments that require myeloablative conditioning, offering amelioration of SCD phenotype without the toxicities and resource utilization of full myeloablation.