Abstract Number 25

DELAYED VIRAL REBOUND DURING ATI AFTER INFUSION OF CCR5 ZFN-TREATED CD4 T CELLS

Pablo Tebas1, Julie Jadlowsky1, Pamela Shaw1, Gary Lee2, Dale Ando2, Sukyung Kim1, SoeYu Naing1, Simon Lacey1, Bruce L. Levine1, Don L. Siegel1, Carl H. June1, James L. Riley1
1University of Pennsylvania, Philadelphia, PA, USA, 2Sangamo Therapeutics, Inc., Richmond, CA, USA

Background:
Autologous CD4 T cells modified using CCR5 specific Zinc Finger Nucleases (ZFN) have a survival advantage in the presence of HIV, but the levels of modification are insufficient to control viremia (NCT00842634). The main goals of this study were to evaluate: 1) if delivery of ZFN using RNA-based transfection provides similar level of CCR5 disruption as the Ad5/35 vector 2) the safety and tolerability of a single dose of this product in HIV+ subjects 3) if a single dose of cyclophosphamide (CTX) increases engraftment 4) the persistence of the disrupted cells and their impact on viral rebound during an ATI and 5) if Δ32 CCR5 heterozygotes preferentially benefit from infusion of CCR5 ZFN treated T cells.

Methods:
We conducted a 3-arm open-label pilot study of the safety and antiviral activity of a single infusion of autologous CD4 T cells modified at the CCR5 gene by RNA encoding ZFN SB-728 with or without the prior administration of two different doses of CTX in well-controlled HIV+ individuals in which some were CCR5 Δ32 heterozygotes. We compared the AUC of the modified cells during the 16-week ATI between groups and time to viral rebound with ACTG historical controls.

Results:
We enrolled 14 participants; 93% male, 57% AA, 7% Hispanic, median age 44. Median baseline CD4 count was 831 c/mm3 (IQR 630-1030). SB-728mR-T was safe and well tolerated. No related grade 3 or higher adverse events were observed. CCR5 disruption in the product (MiSeq) was 24% vs 23% with Ad5 vector. The median CCR5-modified T cells was 7.4% at 1 week post infusion. The engraftment of the modified cells varied between groups during the 16-week ATI (KW p=0.04) with trend to greater early engraftment in the CTX groups (p=0.08) that was significant for the Δ32 group compared to the control (p=0.04). The rebound of HIV viremia (HIV RNA > 200 copies/ml) (Fig 1) was delayed when compared to ACTG historical controls (p=0.03). A subset of Δ32 CCR5 heterozygotes had low viral load in the absence of ART for up to 40 weeks.

Conclusion:
Introduction of CCR5 ZFNs via RNA transfection led to similar levels of disruption as Ad5/35 vectors. CTX led to an increase in engraftment and the administration of the product led to a modest, significant delay in viral rebound during the ATI and maintenance of low level viremia for up to 40 w in some, suggesting that a more efficient CCR5 modification could potentially benefit more individuals from this cure strategy.