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SINGLE ROMIDEPSIN INFUSIONS DO NOT INCREASE HIV EXPRESSION IN PERSONS ON ART (A5315)
Basic Science: (D) HIV Reservoirs, Latency, and All Curative Strategies Including Therapeutic Vaccines and Gene Therapy
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Background: Romidepsin (RMD) is a potent histone deacetylase inhibitor reported to increase HIV RNA in plasma and cells after single or multiple infusions of 5 mg/m2. We sought to determine the safest, lowest effective dose of RMD for induction of HIV expression.
Methods: Three single-dose cohorts (0.5 mg/m2, 2 mg/m2, 5 mg/m2) of HIV-infected participants were sequentially enrolled in a double-blind, randomized, placebo-controlled (3:1 active/placebo per cohort) study, target 15/cohort. Enrollees were virally suppressed on EFV, RAL, or DTG-containing ART with plasma HIV RNA ≥0.4 but <50 cps/mL. Viremia was measured by single copy assay (SCA) before and after RMD/placebo 4 hr infusion at hrs 6, 12, 24, 48 and days 7, 14, 28. Cell-associated HIV DNA (CAD) and unspliced RNA (CAR) were measured by qPCR in resting CD4+ cells pre- and post-infusion (hr 24; day 14). Histone-3 acetylation (H3-Ac) was measured by flow in total CD3+ T-cells pre-infusion and at hrs 12, 24, 48 and days 7, 14, 28. RMD was measured pre- and post-infusion at hrs 4, 6, 12, 24. Pre-specified primary comparisons were between the pooled RMD and pooled placebo groups using the Wilcoxon test.
Results: 43 participants enrolled (36 RMD; 7 placebo); 40 male; 27 white, 14 black; median screening SCA 1.5 cps/mL; median CD4 667 cells/mm3. All completed the infusions; all but one completed 28-day follow-up. No Grade 3 events were deemed treatment-related. Median RMD levels at hr 4 were 12.0, 75.2, 89.0 ng/mL in the 0.5, 2.5 and 5 mg/m2 cohorts, respectively, and declined rapidly. The primary efficacy measure of SCA change from pre-infusion to the average of 24 and 48 hr post was similar between the pooled RMD and placebos (median: 0.12 vs. 0.12 log10 cps/mL, p=0.88, [95% CI on difference: -0.48, 0.33]). There was no significant difference in change in CAR from pre-infusion to 24 hr post (-0.09 vs. 0 log10 cps/106 resting CD4+ cells, p=0.37, [-0.54, 0.23]) or in CAD (-0.04 vs. 0.05 log10 cps/106 resting CD4+ cells, p=0.73, [-0.33, 0.32]). No significant increases in any virologic measure or in H3-Ac were observed in any of the RMD dose arms compared to pooled placebos or from pre-infusion to other timepoints (all p > 0.05).
Conclusion: In contrast to prior uncontrolled studies, in this placebo-controlled, dose-escalation study, single RMD doses that achieved a range (>5-fold) of systemic exposures were well-tolerated but did not increase HIV expression OR H3-Ac. Multiple or higher RMD doses may be needed to induce HIV expression.