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MULTIDOSE IV ROMIDEPSIN: NO INCREASED HIV-1 EXPRESSION IN PERSONS ON ART, ACTG A5315

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Background:

Romidepsin (RMD) is a histone deacetylase inhibitor that has been reported to increase HIV-1 RNA expression in plasma and cells after single or multiple infusions of 5 mg/m². We sought to determine if administering multiple doses of RMD would be safe and induce HIV-1 expression.

Methods:

HIV-1-infected participants were enrolled in a double-blind, randomized, placebo-controlled (3:1 RMD/placebo) cohort to receive RMD 5 mg/m² x 4 doses (at days 0, 14, 28, 42). Enrollees were receiving RAL- or DTG-containing ART with plasma HIV-1 RNA <50 cps/mL. Viremia was measured by integrase single copy assay (iSCA) before and 24hr after each RMD/placebo infusion and 72hr after the 2nd infusion. Cell-associated HIV-1 DNA (CAD) and cellular unspliced RNA (CAR) were measured by qPCR in PBMC at the same time points, as well as changes in CD4%, histone-3/4 acetylation and methylation (H3-Ac/Me), P-TEFb, and NFκB by flow. Other measures included changes in T cell activation and apoptosis from baseline to 24 hrs post 1st and 4th infusion. RMD levels were measured at hr 4 post-infusions 3 and 4. Comparisons between arms used Wilcoxon tests.

Results:

16 participants enrolled (13 RMD; 3 placebo); 11 male; median CD4 699 cells/mm³. All but two completed 4 infusions. One Grade 3 event (transient neutropenia) was deemed possibly treatment-related. Median RMD levels were 69 and 134 ng/mL, at hr 4 post-infusions 3 and 4, respectively. No significant increases in iSCA, CAR, or CAD were observed from baseline to post-baseline time points or from pre- to post-infusion for each infusion compared to placebo (Figure; all p>0.05). Evidence of host pharmacodynamic effects was demonstrated as significant decreases in CD4% at 24hr after infusions 2, 3, and 4 (median -3.5% to -4.5% vs. 1.5% to 1% in placebos, all p≤0.022). Significant increases were observed in H3-Ac/Me (pNFκB+)% , (pS175+)% on CD4+ T cells 24 and 72 hrs after 2nd infusion of RMD compared to placebo (Figure; all p≤0.02). No differences were detected in T cell activation/apoptosis changes between arms.

Conclusion:

Multiple RMD doses were safe but did not induce HIV-1 expression in individuals on suppressive ART despite pharmacodynamic effects on host cells including reductions in % CD4+T-cells, increases in histone acetylation, and PTEFb activation. More effective strategies will be needed to reverse HIV-1 latency.