The HDAC Inhibitor Romidepsin is Safe and Effectively Reverses HIV-1 latency in vivo as Measured by Standard Clinical Assays

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Background: In a recently published ex vivo study, the latency reversing agent (LRA) romidepsin induced HIV expression in resting CD4+ T cells isolated from patients undergoing combination antiretroviral treatment (cART). In light of this exciting finding, we evaluated the effects of romidepsin on measures of viral transcription and plasma viremia in vivo.

Methods: In a phase I/II clinical trial, six aviremic HIV-infected adults received intravenous romidepsin (5 mg/m²) once weekly for 3 weeks while maintaining cART. We used flow cytometry to determine H3 histone acetylation levels in lymphocytes as a cellular measure of the pharmacodynamic response to romidepsin. Changes in intracellular viral transcription were quantitated by cell-associated unspliced HIV-1-RNA (CA-US HIV-1-RNA) using digital droplet PCR in unfractionated CD4+ T cells. Plasma HIV-1-RNA was analyzed by a standard clinical viral load assay (Cobas Taqman) and a transcription-mediated amplification (TMA) assay (Procleix Ultro Plus). Safety was evaluated at each study visit. Baseline values were compared with post-infusion values using Wilcoxon signed-rank tests. Binary outcomes were analyzed using two-sided binomial exact tests.

Results: All 6 patients (5 males, 1 female) completed three romidepsin infusions. H3 histone acetylation increased rapidly (max 17.7 fold relative to baseline) within the first hours following each romidepsin administration and then decreased between day 3 and 7 day post-infusion. Concurrently, CA-US HIV-1-RNA levels increased significantly from baseline during treatment (2.1-3.9 fold after 2nd infusion; p=0.03). Importantly, viral load increased from “undetectable” at baseline to readily quantifiable levels at multiple post-infusion timepoints in 5 of 6 patients (range 46-103 copies/mL after 2nd infusion, p=0.007). Plasma HIV-1-RNA was also detected by TMA more frequently at post-infusion timepoints vs. baseline (p=0.03 after 2nd infusion). Furthermore, the emergence of quantifiable plasma HIV-1-RNA corresponded directly with the cyclic romidepsin infusions. Adverse events (all grade 1-2) were consistent with the known side effects of romidepsin and HDAC inhibitors in general.

Conclusions: Romidepsin safely induced HIV-1 transcription resulting in plasma viremia that was readily quantified with standard commercial assays. Our data show that potent in vivo latency reversal is possible with a single LRA. A trial combining romidepsin and therapeutic vaccination is ongoing.