

HIV reactivation by the histone deacetylase inhibitor panobinostat: Effects on CNS

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Background

Histone deacetylase inhibitors (HDACi) are currently being evaluated in experimental clinical trials for their ability to reactivate HIV-1 expression in latently infected cells with the overall aim of eradicating the latent HIV-1 reservoir. Panobinostat has previously been shown to reactivate HIV-1 expression in latently infected cells in vitro. However, caution has been raised that reactivation of latent HIV-1 could potentially have harmful consequences on the brain. The proposed adverse effects on the central nervous system (CNS) include neuronal injury caused by activated T cells or by early viral proteins induced by HDACi, CNS immune reconstitution inflammatory syndrome and, finally, adverse effects on brain function due to elimination of latently infected microglia and/or astrocytes.

Methodology

In a clinical trial among HIV-infected adults on suppressive combination antiretroviral therapy (cART), patients were treated with the potent HDACi panobinostat (20 mg orally 3 times per week every other week over the course of 8 weeks). As described elsewhere (abstract #2881) panobinostat treatment led to significant increases in HIV transcription as measured by cell-associated unspliced HIV RNA in CD4+ T cells. To address whether viral reactivation induced by panobinostat was associated with adverse effects on CNS, we evaluated the following biomarkers of neurodegeneration and neuroinflammation in cerebrospinal fluid (CSF) obtained before panobinostat administration and during the final dosing week.

CSF biomarkers of neurodegeneration:

- Total tau (t-tau)
- Phosphorylated tau (p-tau)
- Soluble amyloid- β

CSF biomarkers of neuroinflammation:

- C-reactive protein (CRP)
- Soluble CD14 (sCD14)
- Soluble CD163 (sCD163)
- Neopterin
- Monocyte chemoattractant protein-1 (MCP-1)
- Interferon- γ induced protein-10 (IP-10)
- Macrophage inflammatory protein-1 β (MIP1- β)
- Matrix metalloproteinase-9 (MMP-9)

Biomarkers of neurodegeneration and neuroinflammation were determined by enzyme-linked immunosorbent assays. CRP was determined by a particle-enhanced immunoturbidimetric assay. The presence or absence of HIV RNA in CSF was assayed by a transcription-mediated amplification (TMA)-based assay with a detection limit of 3.8 copies/ml. Changes from baseline in biomarker levels were tested using Wilcoxon signed-rank test.

Results

Of 15 patients included in the clinical trial, 11 consented to repetitive lumbar punctures. All CSF samples were negative for HIV RNA, both at baseline and during panobinostat treatment. Paired levels of biomarkers of neurodegeneration and neuroinflammation are shown in figure 1 and 2. There was no significant change from baseline to the final panobinostat treatment week neither in biomarkers of neurodegeneration nor in biomarkers of neuroinflammation.

Conclusion

Repeated, cyclic treatment with the HDACi panobinostat was not associated with CNS adverse effects as measured by CSF biomarkers of inflammation and neurodegeneration in HIV patients on suppressive cART.

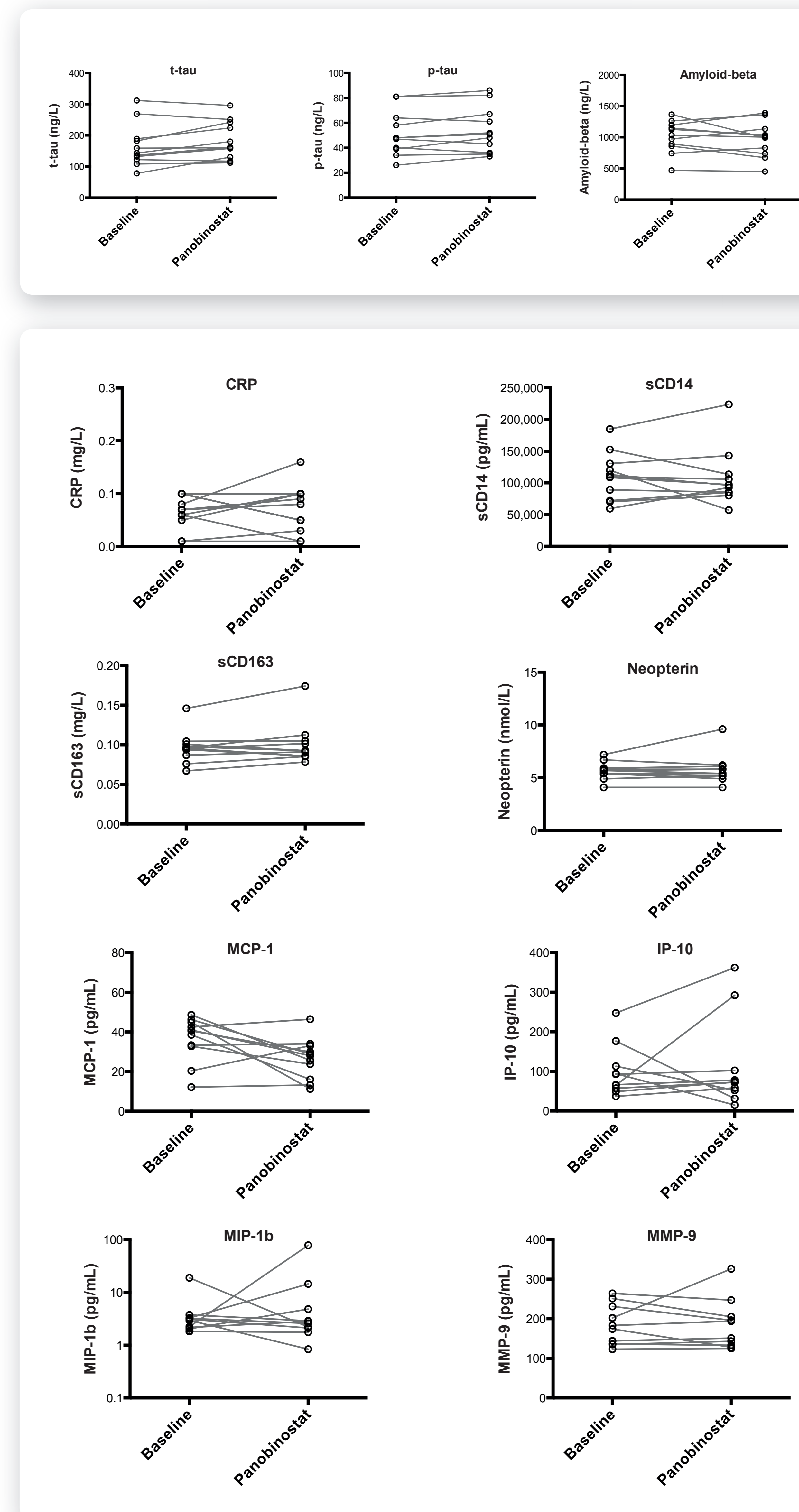


Figure 1. Levels of biomarkers of neurodegeneration at baseline and during the final panobinostat dosing week shown for each of the 11 patients who consented to lumbar punctures. All biomarkers were determined by enzyme-linked immunosorbent assays.

Figure 2. Levels of biomarkers of neuroinflammation at baseline and during the final panobinostat dosing week shown for each of the 11 patients who consented to lumbar punctures. All biomarkers except C-reactive protein (CRP) were determined by enzyme-linked immunosorbent assays. CRP was determined by a particle-enhanced immunoturbidimetric assay.