

NEUROTOXICITY WITH HIGH DOSE DISULFIRAM AND VORINOSTAT USED FOR LATENCY REVERSAL

Authors:

McMahon JH¹, Evans V², Lau JSY¹, Solomon A², Tennakoon S², Dantanarayana A², Hagenauer M¹, Lee S³, Palmer P⁴, Fisher K⁴, Bumpus N⁵, Burger D⁶, Howell B⁷, Rasmussen TA², Lewin SR^{1,3}

¹Department of Infectious Diseases, Alfred Hospital and Monash University, Melbourne, Australia; ²The Peter Doherty Institute for Infection and Immunity, The University of Melbourne and Royal Melbourne Hospital, Melbourne, Australia;

³University of California San Francisco, San Francisco, California, United States;

⁴The Westmead Institute for Medical Research,, University of Sydney, Westmead, Australia, ⁵Johns Hopkins University, Baltimore, Maryland, United States;

⁶Department of Pharmacy, Radboud University Medical Center, the Netherlands; ⁷ Department of Infectious Disease Merck & Co. Inc., Kenilworth, New Jersey, USA

Background:The histone deacetylase inhibitor, vorinostat (VOR), and disulfiram (DSF), a drug used to treat alcohol dependence, reverse HIV latency by different pathways. Both have been safely administered to people with HIV including three days of 2000mg DSF. This study aimed to determine if the combination: reversed HIV latency more potently than a single agent, and is safe.

Methods:HIV-infected adults on antiretroviral therapy (ART) were enrolled in a single-arm study of DSF 2000mg daily for 28 days and VOR 400mg daily on days 8-10 and 22-24. The primary endpoint was plasma HIV RNA on day 11 relative to baseline. We quantified cell associated (CA) unspliced (US) and multiply spliced (MS) RNA and HIV DNA in CD4+ T-cells from blood; single copy HIV RNA; p24 expression by; histone acetylation and plasma concentrations of ART, VOR and DSF.

Results:The first two participants (P1 and P2) experienced grade 3 neurotoxicity (altered mental status related to DSF), leading to trial suspension. On study day 24 P1 (67 year-old male on ABC/3TC/DTG) presented with confusion, lethargy, and ataxia having stopped DSF and all ART from day 17-24. Neuroimaging revealed sagittal sinus thrombosis and chronic vertebral artery occlusion. He was admitted to hospital, anticoagulated and symptoms resolved by day 29. P2 (61 year-old male on TAF/FTC+RAL) presented on day 11 with paranoid ideation, emotional lability, lethargy and ataxia. He was admitted to hospital; brain CT scan was normal and symptoms resolved by day 23. Both participants had increased CA-US RNA, which persisted for weeks after drug cessation. P2 had plasma viremia from day 8-37 (peak 81 copies/mL) with therapeutic ART drug levels. Histone acetylation and low but detectable levels of VOR, DSF were also seen.

Conclusion:The study drug combination was not safe with significant but reversible neurotoxicity, likely related to prolonged high-dose DSF. There was evidence of latency reversal in both participants. Prolonged high-dose DSF, with or without VOR, should not be further pursued.

Disclosure of Interest Statement:

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