INTRODUCTION

- Cognitive impairment (CI) persists in ~30-50% of chronically HIV-infected individuals despite access to antiretroviral therapy (ART). *There are no clinically approved therapies for CI.*
- Activated, HIV-infected monocytes are thought to contribute to CI by trafficking into the central nervous system (CNS), where viral seeding, inflammation and neuronal injury occur. Monocyte chemoattractant protein (MCP)-1, a potent monocyte chemoattractant ligand for C-C chemokine receptor 2 (CCR2), has been implicated in CI pathology.1,9
- Maraviroc (MVC), a CCR5 antagonist licensed as an ART drug, has shown promising efficacy against CI.10-13 MVC has also been shown to reduce monocyte cell associated HIV DNA levels and soluble sCD163 levels (marker of monocyte/macrophage activation)14, providing a platform for targeting chemokine receptors (CRs) to enhance therapeutic outcomes against CI.
- Given the involvement of both CCR2 and CCR5 in CI, targeting both CRs may be more effective than inhibiting a single CR.
- Cenicriviroc (CVC), an oral dual CCR2 and CCR5 antagonist14-24, has a long half-life of approximately 30-40 hours in humans and has been dosed once-daily in clinical studies. CVC is undergoing Phase 2b development for non-alcoholic steatohepatitis and liver fibrosis (CENTAUR study NCT0221747515) where it has demonstrated anti-fibrotic benefits.15 CVC, having completed Phase 2b development in HIV (NCT01338833),16 has been shown to decrease viremia and sCD14 levels (marker of monocyte/macrophage activation) in ART naïve HIV-infected individuals.17 CVC also has demonstrated anti-fibrotic and anti-inflammatory activity in animal models of liver disease, associated with decreased monocyte-derived macrophage infiltration in the liver following acute or chronic hepatocytic injury.18-20
- We hypothesize that CCR2 and CCR5 blockade will improve cognitive function by decreasing monocyte activation and migration into the CNS.

METHODOLOGY

Study Design

Chronically HIV-infected aviremic (HIV RNA <50 copies/ml) individuals on ART were enrolled in a single-arm open label, 24 week cenicriviroc intensification pilot study. Participants with low level of cognitive performance were defined as having < -0.5 in Neuropsychological (NP) Z Global score or < -0.5 in one of the 7 subdomains. Exclusion criteria included depression (BDI-II > 18).

CVC dosage

CVC was administered once-daily and dose was dependent on ART regimen.

Neuropsychological (NP) Testing

Neuropsychological performance included measures of psychomotor speed, executive function, learning and memory, working memory, visuospatial, attention, and gross motor. Domain-specific standardized scores (NPZ) were determined and a global NPZ was defined by aggregating the domain scores.

1. Learning and Memory: California Verbal Learning Test (CVLT) Total and Delay; Brief Visuospatial Memory Test (BVMT) Total and Delay
2. Psychomotor Speed: Digit Symbol; Trail A; Grooved Pegboard (GP) Dominant Hand (DOM); GP Non-DOM
3. Executive Function: Verbal Fluency Test (FAST); Stroop; Trail B; Action
4. Working Memory: Digit Span Backward; CVLT II List Letter Sequencing
5. Attention: CaCap Choice and Sequential; Digit Span Total
6. Gross Motor: Timed Gait; Tapping DOM and Non-DOM
7. Visuospatial: Rey Copy; Block Design

Note: NPZ subdomains were updated post abstract submission to more accurately reflect subdomains of interest. With updated domains, all individuals were considered to have low cognitive performance. New and old analyses were not measurably different.

Plasma Soluble Biomarkers by ELISA

Plasma sCD163, sCD14 and neopterin were quantified by single analyte ELISA array (Triilum Diagnostics, R&D Systems and Thermofischer Scientific, respectively).

Statistical Analyses

Wilcoxon signed rank test was used to compare entry and week 24 correlations. Analyses were evaluated by Spearman correlation coefficients. Statistical analyses were done using SAS software. A two-tailed p-value <0.05 was regarded as statistically significant.

CONCLUSIONS

A 24 week cenicriviroc intensification regimen in virally suppressed individuals with chronic HIV was well tolerated by participants.

After 24 weeks, CVC improved cognitive performance with increases in NPZ scores for global and subdomains of working memory and language domains. CVC also decreased monocyte/macrophage activation as evidenced by decreases in plasma sCD163, sCD14 and neopterin.

These data potentially link changes in monocyte/macrophage activation induced by CVC to the changes in cognitive performance in chronically HIV-infected participants.

Given the lack of pharmacological interventions to treat cognitive impairment in HIV-infected individuals, further study of CVC in a randomized controlled trial is warranted.

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