Rivastigmine for the Treatment of HIV-associated Neurocognitive Disorders: a Randomized, Double-blind, Placebo-controlled, Crossover Pilot Study

S. Simioni1, M. Cavassini1, M. Micheli1, J.-M. Annoni1,2, K. Iglesias1, A. Calmy2, E. Giacobini3, B. Hirschel2, R. A. Du Pasquier1, and the Swiss HIV Cohort Study

1Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland, 2Geneva University Hospital, Geneva, Switzerland; *Authors contributed equally to this work

Introduction

• HIV-associated neurocognitive disorders (HAND) remain common in the era of highly active antiretroviral therapy (HAART) (Heaton et al., 2011).
• While HAART may help improve cognitive functioning (Winston et al., 2010), it seems insufficient to completely prevent HAND. Indeed, the prevalence of HAND has been reported to range from 15% to more than 50% according to studies conducted in the HAART era (McArthur, 2004; Heaton et al., 2010), even in the context of long-lasting viral load suppression (Simioni et al., 2010).
• Neuroprotective agents may be important adjunctive treatments in HIV+ patients with HAND.
• In SIV-infected Rhesus Monkeys, Choline Acetyltransferase (ChAT), a major source of acetylcholine in the brain and a marker of cognitive function, is severely and rapidly decreased in putamen and hippocampus. This drop of ChAT has been suggested to be an early marker of dementia (Koutsiel et al., 2000).

Methods

Population

17 HAART-treated HIV+ patients (12 men, 54.7 ± 9.6 years old, 660 ± 218.2 CD4+ T cells) with HAND (according to Frascati criteria), and undetectable viremia in both plasma (<20 copies/ml) and CSF at study entry. Exclusion criteria (according to Frascati criteria), and undetectable viremia in both plasma (<20 copies/ml) and CSF at study entry, (4) active drug use, (5) major depression or psychiatric condition interfering with the conduct of the study, (6) brain MRI showing mass effect, or indicating ongoing tumor, abscess, etc., (7) use of cholinergic/anticholinergic agents ≤2 weeks prior to screening.

Study design

Randomized, double-blind, placebo-controlled, crossover study (Fig. 1). Rivastigmine dosage was progressively increased to reach 12mg/day.

Assessments (4 study visits)

• Psychiatric (Hospital Anxiety and Depression scale, HAD) and functional (MOS-IMO) assessment (Visit 1-4).
• Brain MRI (Visit 1 and 2).
• Blood analyses + Therapy Drug Monitoring (TDM) for HAART (Visit 1, 2 and 4).
• Lumbar puncture (Visit 1, 2 and 4, if patients agreed).

Outcomes/measure

Effectiveness Improvement in ADAS-Cog and other NP measures (primary endpoint), change in perceived quality of life (secondary endpoint).

Safety: Frequency/magnitude of adverse events, abnormalities on laboratory tests and TDM.

Statistical analyses

Difference between start/end values during each 5 month study period used as a combined outcome for each subject. On this outcome, ANOVA with repeated measures (treatment as a within effect, arm as a between factor) were computed to look for treatment effects.