

AMD-3100, a CXCR4 Antagonist, Reduced HIV Viral Load and X4 Virus Levels in Humans

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Background: The antiviral efficacy of the CXCR4 antagonist AMD-3100 was evaluated in an open-label, non-comparative, dose-escalating phase Iia trial in HIV-positive patients, where AMD-3100 was given 10-day continuous infusion. A retrospective longitudinal analysis was performed on patient plasma samples using a new PhenoSense HIV entry assay that measures co-receptor tropism and susceptibility to entry inhibitors.

Methods: 40 patients with plasma HIV RNA >5000 copies/mL on stable ART/no ART received doses of AMD-3100 ranging from 2.5 mcg/kg/h to 160 mcg/kg/h and were evaluated for safety, PK, and antiviral effects. All day 0 and day 11 samples were tested for SI/NSI phenotype and for co-receptor use and viral tropism (CXCR4 or CCR5) using the PhenoSense assay. In this assay, virus stocks are produced by transfecting HEK 293 cells with a vector that expresses patient-derived HIV envelope sequences plus an HIV genomic vector containing a luciferase indicator gene. Co-receptor tropism is defined by assessing the ability of a virus to infect CD4. CCR5 cells and/or CD4. CXCR4 cells, and whether or not infection is inhibited by specific entry inhibitors. Viral tropism was independently confirmed by testing the ability of patient virus stocks derived from PBMC co-cultures to replicate in transfected cell lines.

Results: 1 patient receiving AMD-3100 at 160 mcg/kg/h (a steady-state plasma concentration of 3.6 mcg/mL, no concomitant antiviral medications) exhibited a 0.8-0.9 log₁₀ decrease in plasma HIV RNA by day 11 of treatment. Viruses from this patient on day 1 and day 11 were SI and exclusively used CXCR4, based on the PhenoSense assay and by replication of the virus stock in transfected cell lines. The virus stock was sensitive to AMD-3100 in PBMC, with an IC₅₀ (day 1 and day 11) of 16 and 18 ng/mL, respectively. Notably in 8 of 19 patients with dual (X4/R5) or mixed (X4+R5) virus at baseline, we observed a complete loss of X4 virus by day 11 of treatment. This was seen at 80 and 160 mcg/kg/h in 1 patient each and at 40 mcg/kg/h in 3/4. A loss of X4 virus was detected with a dose as low as 5 mcg/kg/h.

Conclusions: 1 patient with pure X4 virus, receiving AMD-3100, exhibited a viral load reduction that was virologically and phenotypically consistent with an antiviral effect. Also in 8 patients with dual or mixed virus at baseline, X4 viruses were no longer detected at day 11 at a dose as low as 5 mcg/kg/h. The PhenoSense assay accurately determined the co-receptor tropism of HIV from patient samples and may be used to predict drug susceptibility and virologic response.