

In vitro Anti-HIV Activity Profile of AMD887, a Novel CCR5 Antagonist, in Combination with the CXCR4 Inhibitor AMD070

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Background: The antiviral efficacy of several CCR5 antagonists (e.g. SCH-C, UK427,857) (against R5 viruses) and a CXCR4 antagonist (e.g., AMD3100) (against X4 viruses) was demonstrated in clinical phase 2 studies. Here, we evaluated the in vitro anti-HIV activity of a novel CCR5 antagonist (AMD887) and AMD070, a recently described orally bioavailable CXCR4 antagonist.

Methods: AMD887 (alone and in combination with AMD070) was examined for its activity against a wide variety of HIV-1 laboratory strains (R5, X4, R5/X4), primary clinical isolates in different T-cell lines, cells expressing CD4 and CXCR4 or CCR5 and PBMCs. Chemokine (RANTES and SDF-1) binding and internalization, chemokine-induced Ca²⁺ signaling and chemotaxis assays were performed to demonstrate the specific interaction of the compounds with their respective chemokine receptors.

Results: AMD887 was found to act as a potent CCR5 antagonist that strongly inhibited virus infectivity at a 50% effective concentration (EC₅₀) of 1 to 10 nM. The compound inhibited different clades of R5 HIV replication in cells expressing CCR5 and PBMC. AMD887 (as also described for SCH-C and UK427,857) had no activity against X4 or R5/X4 HIV-1 isolates in PBMC. However, these X4 and R5/X4 HIV variants were prevented from infecting PBMCs in the presence of AMD070. When both compounds, AMD887 and AMD070 were combined, no viral replication was measured in PBMCs. Their anti-HIV potency correlated closely with their potency in inhibiting chemokine binding, chemokine-induced internalization, chemokine-induced Ca²⁺ signaling and chemotaxis. AMD887 and AMD070 did not interact with any other chemokine receptor (other than CCR5 and CXCR4) examined to date.

Conclusions: Both compounds (separate and in combination) hold great promise as candidate anti-HIV drugs.