

Anti-HIV activity profile of AMD070, an orally bioavailable CXCR4 antagonist

D. Schols^{1*}, S. Claes¹, S. Hatse¹, K. Princen¹, K. Vermeire¹, E. De Clercq¹, R. Skerlj², G. Bridger², G. Calandra².

¹Rega Institute, Leuven, Belgium, ²AnorMED Inc., Langley, BC, Canada.

Background: The antiviral efficacy of the CXCR4 antagonist AMD3100 was recently shown in a phase IIa clinical study, where the compound was given as a 10-day continuous infusion. This study demonstrated that CXCR4 is a viable target for antiretroviral therapy. Here, we evaluated the in vitro anti-HIV activity profile of AMD070, a novel orally bioavailable CXCR4 antagonist.

Methods: AMD070 was examined for its activity against a wide variety of HIV-1 and HIV-2 laboratory strains (R5, X4, R5/X4), primary clinical isolates and drug-resistant viruses in different T-cell lines, CXCR4-transfected cell lines and PBMCs. Chemokine binding, chemokine-induced Ca²⁺ signaling and chemotaxis assays were performed to demonstrate the specific interaction of AMD070 with CXCR4.

Results: AMD070 was found to act as a potent CXCR4 antagonist which strongly inhibited virus infectivity at a 50% effective concentration (EC₅₀) of 1-10 nM. The compound inhibited X4 HIV replication in 5 different CD4⁺ T cell lines, CXCR4-transfected cell lines and PBMCs. AMD070 had no activity against R5 HIV-1 variants. However, R5X4 and R3R5X4 HIV strains, which were able to use CCR3 and/or CCR5, in addition to CXCR4, for entering transfected cells, were prevented from infecting PBMCs in the presence of AMD070. AMD070 was additive or synergistic when evaluated in combination with other known HIV inhibitors such as fusion inhibitors (T-20), RT inhibitors (zidovudine, tenofovir) and protease inhibitors (amprenavir). The compound was equally active against NRTI-, NNRTI-, and PI-resistant viruses that use CXCR4 for entry. Its anti-HIV potency correlated closely with its potency in inhibiting SDF-1 binding, Ca²⁺ signaling and chemotaxis. AMD070 does not interact with any other chemokine receptor (other than CXCR4) examined to date.

Conclusions: AMD070 holds great promise as a candidate anti-HIV drug and a clinical phase I trial with the compound is planned for the first half of 2003.