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The CXCR4 Antagonist POL3026 is a Potent Inhibitor of Human Immunodeficiency Virus

Gemma Moncunill [1,*], Imma Clotet-Codina [1], Anuska LLano [1], Mercedes Armand-Ugón [1], Bonaventura Clotet [1], Jan Willem Vrijbloed [2], José A. Esté [1]

[1] Retrovirology Laboratory IrsiCaixa and AIDS Unit, Hospital Germans Trias i Pujol, 08916 Badalona, Spain; [2] Polyphor Ltd., Basel, Switzerland

The HIV-1 coreceptors are an important target for the design of new antiviral compounds for the multidrug therapy of the HIV infection. Here, we show the potent anti-HIV activity of novel specific b-hairpin mimetic CXCR4 antagonist POL3026 and its mechanism of action. POL3026 consistently blocked the replication of X4 and dualtropic HIV strains in different stable cell lines, peripheral blood lymphocytes, macrophages and ex vivo lymphoid tissue. Our results show that POL3026 was active with 50% effective concentrations (EC_{50}) at the nanomolar range (25–0.1 ng/ml) against laboratory adapted and clinical isolates of HIV-1 including virus strains that are resistant to current antiretroviral agents (nucleoside and non-nucleoside reverse transcriptase inhibitors, protease inhibitors and the fusion inhibitor enfuvirtide). However, AMD3100-resistant and SDF-1 resistant HIV-1 strains presented cross-resistance to POL3026, suggesting a similar mode of anti-HIV activity. POL3026 specifically blocked the binding of anti-CXCR4 monoclonal antibody 12G5 (IC_{50}: 0.0005 mg/ml) and the intracellular Ca^{2+} signal induced by CXCL12 but did not inhibit anti-CCR5, -CD4 or -CD45 monoclonal binding or signaling induced by CCR5 ligands, suggesting its specificity for CXCR4. In a cell culture model of the evolution of HIV-1 coreceptor use, POL3026 prevented the emergence of the X4 variants from a R5 HIV-1 strain. POL3026 and analogues, have shown excellent plasma stability, high selectivity for CXCR4 and favorable pharmacokinetics. These agents have the potential to become a therapeutic option for application in the treatment of HIV infections.

doi:10.1016/j.antiviral.2007.01.011

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Mutations in the RNaseH Region Observed in the HIV-1 of Antiretroviral Treatment (ART) Experienced Patients

J. Waters [1,*], W. O'Neal [1], K. White [2], E. Lansdon [2], M. Miller [2], J. Harris [1], K. Borroto-Esoda [1]

[1] Gilead Sciences, Durham, NC, USA; [2] Gilead Sciences, Foster City, CA, USA

Background: ART that targets the HIV-1 protease and reverse transcriptase (RT) has been effective in the management of HIV-1 disease. As new drugs are being developed to target RNaseH activity, it is imperative to evaluate if previous ART, specifically RT inhibitors, may induce mutations in RNaseH that could lessen the efficacy of novel RNaseH inhibitors.

Methods: Genotypic analysis was performed on HIV polymerase from 100 ART-naive and 110 ART-experienced patients with subtype B HIV-1. Sequences were divided into four regions: RT (amino acid (AA) 1–240), RT C-terminus (AA 241–318), RT connection domain (AA 319–426) and RNaseH (AA 427–560). Patient sequences were compared to a reference and the percent conserved at each AA position was calculated for each group separately and then compared to the other using a Fisher's exact test. Changes between the two groups within the RT region were used as a control to establish significance. An unadjusted cutoff for significance was defined as a p-value ≤ 0.01 at conserved AA positions ($\geq$95% homology in naive or 100% conserved in either group).

Results: Within the RT domain, there were 21 positions at known resistance sites with significant AA changes between the groups. Within the RNaseH domain, there were two AA positions, 451 and 463, with significant changes between the groups. The consensus K451 was replaced by arginine in 7.3% of experienced patients but remained 100% conserved among naive patients. This position appears to interact with the phosphate backbone of the primer in HIV-1 polymerase models. By contrast, the consensus R463 was 100% conserved in experienced patients while 8% of naive patients had lysine at this position. Differences between the two groups were also observed at position 284 ($p = 0.007$) in the RT C-terminus and at position 348 ($p < 0.001$) in the RT connection domain. At each of these positions there was only one AA change.

Conclusions: Significant AA differences between ART-naive and experienced patients were observed at positions outside of HIV-RT that appear to be the result of ART with RT inhibitors. These changes may impact the development of new compounds that target other functions of the HIV polymerase such as RNaseH.

doi:10.1016/j.antiviral.2007.01.012

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Involvement of New Mutational Pattern in HIV-1 gp41 in T-20 Treatment

Stefano Aquaro [1,2,*], Valentina Svicher [2], Roberta D'Arrigo [3], Mario Santoro [2], Giovanni Di Perri [4], Sergio Lo Caputo [5], Ubaldo Visco-Comandini [3], Pasquale Narciso [3], Andrea Antinori [3], Carlo Federico Perno [3]

[1] University of Calabria, Rende (CS), Italy; [2] University "Tor Vergata", Rome, Italy; [3] "L Spallanzani" Institute, Rome, Italy; [4] University of Turin, Italy; [5] "SM Annunziata" Hospital, Florence, Italy

Recently, V38A and Q40H + L45M have been correlated with a gain and with a loss of CD4 count, respectively, in HIV-infected patients (pts) receiving T-20. The aim of this study is to investigate the long-term association of such mutations with the viro-immunological parameters, and