ANTIRETROVIRAL TREATMENT OF HIV-1 IN THE CENTRAL NERVOUS SYSTEM

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs Universitet kommer att offentligen försvaras i föreläsningssalen, Infektionskliniken, Sahlgrenska Universitetssjukhuset/Östra
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Avhandlingen baseras på följande arbeten:

I. Yilmaz A, Ståhle L, Hagberg L, Svennerholm B, Fuchs D, Gisslén M. **Cerebrospinal fluid and plasma HIV-1 RNA levels and lopinavir concentrations following lopinavir/ritonavir regimen**. *Scand J Infect Dis* 2004, 36: 823-828.

II. Yilmaz A, Fuchs D, Hagberg L, Nillroth U, Ståhle L, Svensson JO, Gisslén M. **Cerebrospinal fluid HIV-1 RNA, intrathecal immunoactivation, and drug concentrations after treatment with a combination of saquinavir, nelfinavir, and two nucleoside analogues: the M61022 study**. *BMC Infectious Diseases* 2006, 6: 63.

III. Yilmaz A, Svennerholm B, Hagberg L, Gisslén M. **Cerebrospinal fluid viral loads reach less than 2 copies/mL in HIV-1-infected patients with effective antiretroviral therapy**. *Antiviral Therapy* 2006, 11:833-837.

IV. Yilmaz A, Price RW, Spudich S, Fuchs D, Hagberg L, Gisslén M. **Persistent intrathecal immune activation in HIV-1-infected individuals on antiretroviral therapy**. *Submitted.*

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Abstract

HIV-1 invades the central nervous system (CNS) early in the infectious course. It establishes a chronic progressive infection, and triggers an intrathecal immune response. If left untreated, a majority of patients will develop neurological complications, caused by opportunistic pathogens or HIV-1 itself. The most devastating manifestation of HIV-1 in the CNS is AIDS dementia complex (ADC), a subcortical dementia, occuring in about 20% of untreated patients. The incidence of neurological complications has decreased dramatically since the introduction of antiretroviral drugs. In order for these drugs to act in the CNS, they must penetrate the blood-brain barrier (BBB) into the cerebrospional fluid (CSF). It is, therefore, important to determine which agents have this capacity, and what impact they have on HIV-1 CNS infection.

We analysed CSF concentrations of three protease inhibitors (PIs): lopinavir co-formulated with a low dose of ritonavir, and saquinavir in combination with nelfinavir. Lopinavir was detectable in 15/15 samples. The concentrations achieved were probably high enough for antiviral activity in the CSF, generally exceeding severalfold the concentration needed to inhibit viral replication by 50% (IC_{50}). The concentrations of saquinavir were very low, and only detectable in 7/15 CSF samples. Nelfinavir was detectable in 9/15 CSF samples, with concentrations in the range of the IC_{50}. Antiretroviral treatment (ART) containing lopinavir/ritonavir or saquinavir/nelfinavir significantly reduced plasma and CSF viral loads, as well as intrathecal cell-mediated immunoactivation, measured as decreasing levels of CSF neopterin and β2-microglobulin.

HIV-1 has the capacity of establishing viral latency in resting memory CD4+ T-cells, making the virus impossible to eradicate with ART alone. Even in patients on effective ART, a low-level viral replication in plasma can be detected. This probably originates from latently infected cells. To determine whether there is a similar low-level viral replication in CSF, we used an HIV-1 RNA quantification assay with a detection limit of 2 copies/mL in 13 neurologically asymptomatic individuals on effective ART. All patients had CSF viral loads < 2 copies/mL. In plasma, 5/13 patients had levels ranging from 2.3 to 8.2 copies/mL. This makes it unlikely that the CSF in neurologically asymptomatic individuals acts as a viral reservoir in which HIV-1 can replicate independently from the periphery.

CSF neopterin levels remain abnormal in many patients, despite a long period on successful ART. We retrospectively evaluated what influence various levels of CSF HIV-1 RNA, different antiretroviral regimens, and different levels of plasma viral load have on CSF neopterin levels in patients on effective ART. We found that patients with the lowest CSF viral loads (< 2.5 copies/mL) also had the lowest CSF neopterin concentrations. Subjects treated with PI- or non-nucleoside analogue-based regimens had CSF neopterin in the same range. Plasma HIV-1 RNA levels did not affect CSF neopterin levels. These findings indicate that the low-grade persistent intrathecal immunoactivation observed in treated patients is mainly driven by residual viral replication within the CNS. The more the antiretroviral regimen suppresses viral replication in the CNS, the less the intrathecal immunoactivation.

Key words: HIV-1, cerebrospinal fluid, antiretroviral treatment, lopinavir, saquinavir, nelfinavir, neopterin, beta-2-microglobulin, HIV-1 RNA, IgG index, blood-brain barrier, albumin ratio, ultra-ultra sensitive PCR

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