Darunavir Concentrations in Central Nervous System

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Darunavir concentrations in cerebrospinal fluid (CSF) exceeded the median inhibitory concentration (IC50) for wild-type (nonmutant) virus in all 18 people studied by investigators at the University of California, San Diego [1]. Scott Letendre and colleagues believe their findings suggest "darunavir should contribute to control of HIV replication in the nervous system as a component of effective ART."

Cognitive impairment can persist in people with good control of HIV in plasma, perhaps partly because the antiretrovirals they are taking do not penetrate the central nervous system well (from Jules: and because HIV can damage the brain and CNS penetration by HAART may improve cognition but not necessarily resolve impairment). To determine how well darunavir breaches the central nervous system, Letendre and coworkers measured levels of the protease inhibitor in 29 stored CSF and matching plasma samples from 18 people taking a darunavir-containing regimen. Lower limits of darunavir quantitation were 5 ng/mL in CSF, 5 ng/mL for unbound darunavir in plasma, and 90 ng/mL for total darunavir in plasma. Earlier work by another group found a 34.2 ng/mL median darunavir concentration in CSF [2].

The study group had a median age of 48 years, 62% were white, 88% were men, all had AIDS, and 19% had hepatitis C virus coinfection. Patients had taken darunavir for a median of 7.5 months (interquartile range [IQR] 3.6 to 14.6). Median CD4 count stood at 197, and half of these people had a count below 200. HIV RNA lay below 50 copies in 18 of 29 plasma samples (62%) and 26 of 29 CSF samples (90%). HIV RNA levels did not correlate with darunavir concentrations in blood or CSF.

Darunavir could be detected in all CSF samples at a median concentration of 56.9 ng/mL (IQR 39.6 to 81.4), higher than the earlier study [2]. For total darunavir, median plasma concentration measured 4094 ng/mL (IQR 2933 to 6410), and the median CSF-to-plasma ratio was 1.4% (IQR 0.9% to 1.8%). Median unbound darunavir concentration in plasma was 542 ng/mL (IQR 376 to 971), and the median CSF-to-unbound ratio was 9.4% (IQR 6.8% to 14.2%).

Darunavir levels in CSF exceeded the IC50 for wild-type (nonmutant) virus (2.75 ng/mL) in all samples by a median 20.7-fold (IQR 14.4 to 29.6). CSF concentrations of darunavir did not correlate with time since dosing.

CSF concentrations of darunavir correlated with plasma concentrations. But because darunavir CSF levels did not correlate significantly better with unbound darunavir in plasma than with total darunavir in plasma, the investigators propose that "factors in addition to plasma protein binding probably determine distribution of darunavir across the blood-brain barrier."

Because darunavir concentrations in CSF did correlate with blood levels, Letendre suggests that

blood concentrations "may provide indirect guidance for therapeutic drug monitoring of antiretroviral effectiveness in the nervous system."

References

1. Letendre S, Rossi S, Best B, et al. Darunavir concentrations in CSF exceed the median inhibitory concentration. 49th ICAAC (Interscience Conference on Antimicrobial Agents and Chemotherapy). September 12-15, 2009. San Francisco. Abstract A-1312.
2. Yilmaz A, Izadkhashti A, Price RW, et al. Darunavir concentrations in cerebrospinal fluid and blood in HIV-1-infected individuals. AIDS Res Hum Retroviruses. 2009;25:457-461.