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Total Raltegravir Concentrations in Cerebrospinal Fluid Exceed the 50-Percent Inhibitory Concentration for Wild-Type HIV-1

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HIV-associated neurocognitive disorders continue to be common. Antiretrovirals that achieve higher concentrations in cerebrospinal fluid (CSF) are associated with better control of HIV and improved cognition. The objective of this study was to measure total raltegravir (RAL) concentrations in CSF and to compare them with matched concentrations in plasma and in vitro inhibitory concentrations. Eighteen subjects with HIV-1 infection were enrolled based on the use of RAL-containing regimens and the availability of CSF and matched plasma samples. RAL was measured in 21 CSF and plasma pairs by liquid chromatography–tandem mass spectrometry, and HIV RNA was detected by reverse transcription-PCR (RT-PCR). RAL concentrations were compared to the 50% inhibitory concentration (IC50) for wild-type HIV-1 (3.2 ng/ml). Volunteers were predominantly middle-aged white men with AIDS and without hepatitis C virus (HCV) coinfection. The median concurrent CD4+ cell count was 276/μl, and 28% of CD4+ cell counts were below 200/μl. HIV RNA was detectable in 38% of plasma specimens and 4% of CSF specimens. RAL was present in all CSF specimens, with a median total concentration of 14.5 ng/ml. The median concentration in plasma was 260.9 ng/ml, with a median CSF-to-plasma ratio of 0.058. Concentrations in CSF correlated with those in plasma (r2, 0.24; P, 0.02) but not with the postdose sampling time (P, >0.50). RAL concentrations in CSF exceeded the IC50 for wild-type HIV in all specimens by a median of 4.5-fold. RAL is present in CSF and reaches sufficiently high concentrations to inhibit wild-type HIV in all individuals. As a component of effective antiretroviral regimens or as the main antiretroviral, RAL likely contributes to the control of HIV replication in the nervous system.

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and either the level of HIV RNA in CSF or neuropsychological performance: the higher the penetration estimates, the lower the HIV RNA levels in CSF (15, 16) and the better the neuropsychological performance (5, 14, 21, 23), although not all studies are consistent (16).

Raltegravir (RAL) is the first drug in the new class of integrase inhibitors that prevent the covalent insertion of unintegrated linear HIV DNA into the host cell genome, ultimately limiting the formation of HIV provirus. RAL has shown exceptional potency in suppressing HIV replication, with a mean plasma viral load change of $-2.2 \log_{10}$ copies/ml after 10 days of monotherapy (20). The objectives of this analysis were to measure RAL concentrations in CSF and to estimate whether they are in the therapeutic range.

MATERIALS AND METHODS

Eighteen subjects enrolled in the project at the HIV Neurobehavioral Research Center (HNRC) at the University of California—San Diego (UCSD) between April 2007 and February 2009. Five subjects were coenrolled in clinical trials of the antiviral effectiveness of RAL sponsored by the manufacturer, and the remaining participants were coenrolled in observational cohort studies, including the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) project. This study and all linking studies were approved by the UCSD Human Research Protections Program. Eligible subjects had HIV-1 infection, were ART naïve or experienced, were receiving RAL from either a clinical trial or their medical provider, were able to give informed consent, and were willing to undergo lumbar punctures. Subjects with contraindications to lumbar puncture, psychiatric disease potentially interfering with study participation, opportunistic infections within 30 days, or moderate to severe cognitive impairment were excluded. Blood and CSF samples were obtained after informed consent was provided. CSF was obtained by lumbar punctures performed with aseptic techniques by experienced operators using 22-gauge pencil-point needles. Blood was obtained within 1 h of CSF collection by routine phlebotomy. All specimens were stored at $-80^\circ$C until analysis. The study was designed to distribute the sampling times evenly after RAL dosing. Twenty-two CSF-plasma pairs were obtained. One was obtained more than 24 h after the reported dose and was excluded from analyses. The remaining 21 specimen pairs were obtained from 17 subjects, of whom 14 provided a single pair each, 2 provided 2 pairs each, and 1 provided 3 pairs. The interval between multiple samplings varied from 2.5 weeks to 5 months, with a median of 4 weeks.

RAL concentrations were measured at Merck Research Laboratories based on a previously described method (19). In brief, RAL and the internal standard ($^{13}$C$_6$-labeled RAL) were measured in plasma and CSF by reverse-phase high-performance liquid chromatography with tandem mass spectrometry detection employing an atmospheric-pressure chemical-ionization interface in the positive ionization mode. Sample preparation consisted of 96-well liquid-liquid extraction of 200 µl of plasma or 250 µl of CSF. The multiple-reaction-monitoring transitions were $m/z$ 445 to 109 for the drug and $m/z$ 451 to 367 for the internal standard. The lower limit of quantitation (LLOQ) was 2 ng/ml for plasma, with a linear calibration range from 2 to 1,000 ng/ml, and 0.25 ng/ml for CSF, with a linear calibration range from 0.25 to 100 ng/ml. Plasma study samples were analyzed over 2 days. The interday accuracy of the plasma quality control samples was 104.6 to 108.0%, and the interday precision was 1.3 to 5.3%. CSF study samples were analyzed in one analytical run. The intraday accuracy of the CSF quality control samples was 98.7 to 101.2%, and the intraday precision was 1.9 to 3.0%.

HIV RNA was quantified by reverse transcription-PCR (RT-PCR) with a Roche TaqMan real-time assay (Roche Diagnostics) with an assay LLOQ of 50 copies/ml. Blood CD4+ T-cell counts were determined by flow cytometry, and hepatitis C virus (HCV) serostatus was determined by immunoassay. The lowest past CD4+ cell count (i.e., the nadir) was obtained by a combination of self-report and record review.

Descriptive and bivariate statistics were generated using standard methods. RAL concentrations were log transformed to improve their distribution. Concentrations of the drug in CSF were compared to concentrations of the drug in plasma and to the 50% inhibitory concentration (IC$_{50}$) for wild-type HIV (3.2 ng/ml) (6). Pearson's correlation method was used to assess the relationship between RAL concentrations in plasma and RAL concentrations in CSF. In addition, pharmacokinetic data were fit to a population semiphysiologic two-compartment model (ADVAN4, TRANSI) by the NONMEM VI program (ICON) using a model approach used previously with abacavir (3). RAL concentrations in plasma alone and combined plasma-plus-CSF RAL concentrations were modeled sequentially, with CSF penetration estimated using the FOCE (first-order conditional-estimation) subroutine, with interaction and separate residual-error terms for concentrations in plasma and CSF. The covariance estimation step was required to be successful for the model to be accepted. Different initial estimates were used to ensure the avoidance of convergence at a local minimum. The half-life from each compartment was calculated as 0.693 divided by the appropriate rate constant. Given the limited data, no covariate analysis model building was attempted.

RESULTS

Subjects were predominantly middle-aged (median age, 46 years; range, 32 to 70 years) white (89%) men (94%) who had AIDS (85%). Nearly all (16/18 [88%]) were HCV seronegative. The median CD4+ cell count at the time of sampling was 276/µl (range, 20 to 1,216/µl), with 28% of values falling below 200/µl. The median nadir CD4+ cell count was 51/µl (range, 0 to 323/µl). Disease severity was categorized as stage C for 55%, stage B for 17%, and stage A for 28% based on the CDC classification system. The median plasma HIV RNA concentration was 1.70 log$_{10}$ copies/ml (interquartile range [IQR], 1.70 to 2.25).

The median duration of RAL use was 4.2 months (IQR, 1.4 to 27.4 months). All subjects reported the use of 400 mg of RAL twice daily. Concurrent antiretrovirals included one to three nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) for all but 1 patient (94%), one non-NRTI for 6 patients (33%), one ritonavir-boosted protease inhibitor for 11 patients (61%), and one fusion inhibitor for 5 patients (28%). All subjects reported taking at least 95% of their antiretroviral doses in the 4 days preceding sampling, except for one. The last RAL dose was taken with food prior to sampling in 20 of 21 cases.

RAL concentrations in plasma and CSF are displayed in Fig. 1, and aggregate data are summarized in Table 1. RAL was present in all CSF specimens, with a median concentration of 14.5 ng/ml (IQR, 9.3 to 26.1 ng/ml). The median concentration in plasma was 260.9 ng/ml (IQR, 72.0 to 640.4 ng/ml). The median CSF-to-plasma ratio was 0.058 (IQR, 0.021 to 0.130).

![FIG. 1. Raltegravir concentrations in plasma (squares) and CSF (circles). Horizontal dashed line, IC$_{50}$ vertical dashed line, end of the typical dosing interval. Solid and dashed boldface lines, plasma and CSF population pharmacokinetic modeling.](http://aac.asm.org/)
The CSF-to-plasma ratio increased across the dosing interval, with higher ratios later in the dosing interval (r^2, 0.25; P, 0.02). Sampling was moderately well balanced across the dosing interval, with 3 pairs obtained between 1 and 2 h after the dose, 7 pairs between 2 and 4 h, 5 pairs between 5 and 8 h, 5 pairs between 8 and 12 h, and 1 pair at 15 h. RAL concentrations in CSF exceeded the IC_{50} for wild-type HIV in all specimens by a median of 4.5-fold (IQR, 2.7- to 7.7-fold). HIV RNA was undetectable in 20 of 21 (95%) CSF specimens and in 13 of 21 (62%) plasma specimens. There was a statistically significant correlation between RAL concentrations in CSF and those in plasma (r^2, 0.24; P, 0.02) (Fig. 2) but not between RAL concentrations and the postdose sampling time (P, >0.50). Higher RAL concentrations in plasma were not associated with undetectable HIV RNA levels in plasma (r, 0.37; P, >0.20). Too few CSF samples had detectable levels of HIV RNA to enable reliable statistical analyses comparing HIV RNA levels with RAL concentrations in CSF. The results were not substantially different when the analyses were performed with the inclusion of a single time point for each subject, using only the first time point for subjects with multiple CSF-plasma pairs. Population pharmacokinetic modeling estimated the typical CSF-to-plasma ratio at 0.078 and showed that the average RAL half-life for the population was longer in CSF than in plasma.

Possible interactions between RAL and other selected antiretrovirals, such as atazanavir (n, 3), efavirenz (n, 1), etravirine (n, 6), and ritonavir (n, 9), were explored despite the small sample size. RAL levels in plasma or CSF did not differ between those who reported use of these drugs and those who did not, with the exception of atazanavir. RAL concentrations in plasma (r, 3.0; P, 0.008) and in CSF (r, 2.3; P, 0.03) were higher for those reporting atazanavir use than for those who used other drugs.

**DISCUSSION**

RAL concentrations in plasma were highly variable, a finding consistent with prior reports (24). RAL concentrations in CSF were relatively less variable and exceeded the concentration required to inhibit wild-type HIV in vitro in all individuals (median, 4.5-fold higher than the IC_{50} for wild-type HIV). The concentrations in CSF are consistent with the physicochemical characteristics of RAL, including its low molecular weight and its relatively low level of plasma protein binding. Although only total drug concentrations were measured, it appears unlikely that protein binding in CSF would result in unbound RAL concentrations below the IC_{50} for wild-type HIV, given the much lower concentration of binding proteins, such as albumin and alpha-1 acid glycoprotein, in CSF than in plasma (100 to 1,000-fold lower) and the findings of a recent pharmacokinetic study measuring bound and unbound indinavir in plasma and CSF (1, 11). The correlation between RAL concentrations in CSF and those in plasma, although statistically significant, demonstrated some variability, which may suggest some limitation in using plasma RAL concentrations to estimate RAL concentrations in the nervous system. RAL is 83% bound to plasma proteins, and assuming that all free drug penetrates into the CSF, one would expect the concentrations in CSF to be approximately 15 to 20% of those in plasma. The lower CSF-to-plasma ratio of 0.058 suggests that there may be other barriers to CSF penetration, but these barriers are not as great as those seen with protease inhibitors (2, 4, 13). The discordance between the CSF and plasma RAL concentration curves in the population pharmacokinetic model suggests that the influx into and efflux from the CSF are slower than elimination from plasma. The biphasic plasma pharmacokinetics of RAL, and the fact that samples were not evenly distributed during the postdosing interval corresponding to this biphasic pattern, with more samples between 0 and 4 h, may have led to some underestimation of the CSF RAL concentrations. However, population pharmacokinetic modeling partly helps compensate for the uneven sampling times of a formal intensive pharmacokinetic sampling approach.

Although 38% of the pairs had detectable plasma viral loads, HIV was undetectable in all but one CSF sample. This relatively high proportion of subjects with detectable plasma viral loads despite a median RAL use duration of 4 months is consistent with the fact that RAL is often used in highly treated experienced patients with suspected or proven resistance to other classes of antiretrovirals. Although no pretreatment CSF viral loads were measured in this analysis, the high rate of HIV suppression in CSF supports the potency of RAL in the CNS. The single subject with persistently detectable viral loads in CSF (222 copies/ml) was reported receiving 400 mg of RAL twice daily for 33 months, was on a five-drug regimen, and the fact that samples were not evenly distributed during the postdosing interval corresponding to this biphasic pattern, with more samples between 0 and 4 h, may have led to some underestimation of the CSF RAL concentrations. However, population pharmacokinetic modeling partly helps compensate for the uneven sampling times of a formal intensive pharmacokinetic sampling approach.

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had a CSF RAL concentration below the median (9.0 ng/ml), and had the highest plasma viral load (60,100 copies/ml) of the cohort.

The 33% dissociation observed between HIV RNA suppression in plasma (62% of pairs) and in CSF (95% of pairs) suggests that RAL may have relatively greater potency in microglia and macrophages, which primarily produce HIV in the nervous system, than in lymphocytes, which primarily replicate HIV in the blood. A second explanation, not necessarily excluded by the first, is that HIV may have adapted to (or “compartamentalized” in) the nervous system, with RAL-susceptible strains in the CSF and resistant strains in blood. A third explanation, which is compatible with the preceding two explanations, is that the nervous system is relatively protected by the limited immune activation that can occur with failing antiretroviral therapy (compared with no antiretroviral therapy at all) (22). Although an antiretroviral regimen with drugs with greater effectiveness at CNS penetration and/or a higher bound fraction could cause such dissociation, the 7 pairs with plasma-CSF dissociation came from patients on various antiretroviral regimens, suggesting that this is a less likely explanation here. Prospective, controlled clinical trials are needed in order to better understand the contribution of these and other mechanisms to the control of HIV in the nervous system, but the data support the notion that RAL-containing antiretroviral regimens continue to control HIV in the nervous system even after they fail in blood.

The CSF RAL concentrations in this analysis (median, 14.5 ng/ml) are comparable to those recently reported in another small study (median, 18.4 ng/ml), by Yilmaz et al. (26). Our somewhat lower median RAL concentration in CSF may be explained by the lower plasma concentrations in our analysis (medians, 260.9 ng/ml versus 448 ng/ml). This difference between plasma concentrations likely accounts for the differences in CSF-to-plasma ratios between the studies (0.058 versus 0.03). Other potential factors responsible for the differences include specimen collection, processing, and storage; the RAL assay system; baseline subject characteristics (e.g., age, body mass index); and RAL adherence. The distribution of postponing sampling times appears similar to ours, making this factor unlikely to explain the difference. The reports also differ in their conclusions about how well RAL may treat HIV in the nervous system: our report concludes that all CSF RAL concentrations fall in the therapeutic range, but Yilmaz et al. conclude that approximately 50% do. This apparent disagreement is due to the standard used to support the conclusion. The IC<sub>50</sub> was used in this and prior reports, since it is generally less variable than the standard used by Yilmaz et al., the 95% inhibitory concentration (IC<sub>95</sub>), and is commonly referenced in clinical resistance testing reports. Each approach has its merits, and combining them in the interpretation of antiretroviral concentrations in CSF may enable additional differentiation between drugs in the future. In this instance, for example, 100% of our concentrations exceed the IC<sub>50</sub> of 3.2 ng/ml, and 48% (10 of 21) exceed the upper limit of the IC<sub>95</sub> range referenced by Yilmaz et al. (15 ng/ml). On the other hand, approximately 20% of the concentrations reported by Yilmaz et al. were below the IC<sub>50</sub> of 3.2 ng/ml, compared to none in this study. Therefore, our data appear to indicate more consistent CSF activity than previously reported. However, the best approach to estimating the effectiveness of antiretrovirals in the nervous system has yet to be determined and will likely require additional in vitro and in vivo work.

In summary, we conclude that RAL achieves therapeutic concentrations in CSF and, as a component of a combination antiretroviral regimen or as the main antiretroviral, likely contributes to the control of HIV replication in the nervous system. Control of HIV in the nervous system should protect individuals from HAND and support neurocognitive recovery for those who have been diagnosed with HAND previously. Additional work, such as a prospective clinical trial, will be required to definitively characterize the effectiveness and safety of RAL in the CNS.

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