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BRIEF REPORT

Pharmacokinetics of Darunavir/Ritonavir With Etravirine Both Twice Daily in Human Immunodeficiency Virus-Infected Adolescents and Young Adults

Tim R. Cressey,[1] Ram Yogev,[2] Andrew Wiznia,[3] Rohan Hazra,[4] Patrick Jean-Philippe,[5] Bobbie Graham,[6] Amy Gonzalez,[6] Paula Britto,[7] Vincent J. Carey,[7] Courtney V. Fletcher,[8] Edward P. Acosta,[9] for the IMPAACT P1058A Team

[1]Program for HIV Prevention and Treatment, Department of Medical Technology, Faculty of Associated Medical Sciences, Chiang Mai University, Thailand, [2]Children's Memorial Hospital, Northwestern University Feinberg School of Medicine, Chicago, Illinois, [3]Jacobi Medical Center, Bronx, New York, [4]National Institutes of Health (NIH), Eunice Kennedy Shriver National Institute of Child Health and Human Development, Maternal and Pediatric Infectious Disease Branch, [5]The Henry M. Jackson Foundation-Division of AIDS, a Division of The Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., Contractor to National Institute of Allergy and Infectious Diseases, NIH, US Department of Health and Human Services, Bethesda, Maryland, [6]Frontier Science & Technology, Amherst, New York, [7]Harvard School of Public Health, Boston, Massachusetts, [8]University of Nebraska Medical Center, Omaha, and [9]University of Alabama at Birmingham

Data on the combination of darunavir/ritonavir and etravirine both given twice daily in adolescents/young adults are lacking. In this study, we assessed the pharmacokinetics of darunavir/ritonavir 600/100 mg with etravirine 200 mg twice daily in 36 treatment-experienced human immunodeficiency virus-infected adolescents and young adults and found that exposures were comparable to those reported in adults.

Keywords. antiretrovirals; darunavir; etravirine; pediatrics; ritonavir.

Darunavir-boosted with low-dose ritonavir (DRV/r) is one of the preferred protease inhibitor (PI) regimens for perinatally human immunodeficiency virus (HIV)-infected adolescents and young adults who have developed substantial multi-PIs resistance. Darunavir-boosted with low-dose ritonavir can inhibit several cytochrome P450 enzymes, ie, CYP3A and CYP2D6, and has the potential for drug-drug interactions when combined with other antiretroviral (ARV) drugs [1]. Etravirine (ETR) is a nonnucleoside reverse-transcriptase inhibitor (NNRTI) approved for children >6 years of age (≥16 kg) and is metabolized by CYP3A, CYP2C9, and CYP2C19 [2]. Based on their common metabolic pathways, the coadministration of DRV/r with ETR could impact the plasma concentrations of either compound and consequently alter their therapeutic effect or adverse reaction profile. In adults receiving DRV/r 600/100 mg twice daily (BID) with ETR, DRV plasma concentrations were similar to values measured in the absence of ETR, but ETR exposure was reduced by 30% [3]. Age-associated physiological changes can influence the pharmacokinetics (PKs) of ARV drugs [4] so it is important to investigate the PKs and potential drug-drug interactions across the pediatric continuum. We describe the PK assessment of DRV/r 600/100 mg BID coadministered with ETR (200 mg) BID in treatment-experienced HIV-infected adolescents and young adults.

MATERIALS AND METHODS

Study Design

The International Maternal Pediatric and Adolescent AIDS Clinical Trials Group (IMPAACT) protocol P1058A was a multicentered observational study designed to evaluate the PK of ARV drug combinations commonly used by HIV-infected children, adolescents, and young adults in the United States (clinicaltrials.gov: NCT00977756). In the current study, the PKs of DRV/r with ETR BID are reported. Informed consent was obtained from each subject or his/her legal guardian, and assent was signed when appropriate.

Eligible subjects included stable HIV-infected patients ≥6 to <21 years of age receiving DRV/r, dosed per body weight, and ETR 200 mg, both BID, for ≥30 days without any additional NNRTI or PI. Only subjects receiving DRV/r 600/100 mg BID were included in the current PK analysis. The ARV regimen was chosen at their physician's discretion. Subjects were excluded if, at screening, they had any clinical or laboratory toxicity that was grade ≥2 according to the Division of AIDS table for grading the severity of adult pediatric adverse events (http://rcc.tech-res-intl.com/), or hemoglobin of ≤8.5 g/dL, or were receiving a drug that might interact with the drugs of interest. A negative pregnancy test was required at enrollment for females of childbearing capacity. Pharmacokinetic results were communicated to the local investigators "real-time", but there were no protocol-mandated dosage adjustments. Any adverse events occurring from study enrollment until completion of the PK analysis were reported on an expedited basis. This study was

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Correspondence: T. R. Cressey, PhD, Program for HIV Prevention and Treatment (PHPT-IRD174), Faculty of Associated Medical Sciences, 6th Floor, 110 Inthawaroros Road, Muang, Chiang Mai 50200, Thailand (tim.cressey@phpt.org).

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performed at IMPAACT sites in the United States and approved by the Institutional Review Board at each site.

Pharmacokinetic Design, Bioanalysis, and Parameter Determination

Medication adherence was checked by phone calls 3 days before the PK visit. On the day of the PK sampling, ARV drugs were administered in an open-label fashion with food (full meal or light snack, high or low fat). Blood samples were collected at 0, 1, 2, 4, 6, 8, and 12 hours post observed dose. Blood samples were processed, and plasma was stored at or below −20°C until analysis. Details of the DRV, RTV, and ETR assays methodologies have been previously described [5]. The primary outcome measure was the area under the plasma concentration-time curve (AUC) over the dosing interval. The study design was based on evaluation of the probability that the 90% confidence interval (CI) for the ETR mean AUC would lie entirely below 20% of the adult ETR mean AUC_{0-12} of 5.5 mg × hour/L [6] (ie, 4.4 mg × hour/mL, otherwise the reduction would not be expected to be clinically significant). Using a standard deviation for ETR AUC of 4.5 [6], a simulation-based estimate of this probability is 70% for a sample of size 36. Pharmacokinetic parameters for DRV, RTV, and ETR were determined using noncompartmental methods (WinNonlin Phoenix version 6.30.395; Pharsight Corp., Mountain View, California).

RESULTS

Forty-three subjects were enrolled and had PK sampling performed. Seven subjects were not included in this PK analysis: 4 subjects because of poor drug adherence (at least 1 of the ARV drugs under study were undetectable) and 3 subjects because they did not receive DRV/r 600/100 mg BID. Among the 36 subjects with PK data available receiving DRV/r/ETV 600/100/200 mg, 22 (61%) participants were male, their median (range) age was 18 (13 to 21) years, weight 61 (36 to 109) kg, body surface area 1.7 (1.2 to 2.5) m^2, HIV-1 ribonucleic acid viral load (VL) 49 (20 to 316 000) copies/mL (61% VL <50 copies/mL, or below detection limit), and CD4 cell count 412 (10 to 1434, n = 34) cells/μL. Other ARVs prescribed with DRV/r/ETV included the following: raltegravir (RAL) (n =14); tenofovir-disoproxil furmate (TDF)/emtricitabine (FTC) (n = 8); TDF/FTC/RAL (n = 6); TDF (n = 1); TDF/RAL (n = 1); abacavir/lamivudine (n = 1); stavudine (d4T)/FTC (n = 1); TDF/FTC/zidovudine (n = 1); RAL/d4T/FTC (n = 1); and RAL/d4T/didanosine-EC (n = 1).

Darunavir and ETR PK parameters for subjects receiving DRV/r/ETV 600/100/200 mg are listed in Table 1. The AUC 90% CI of the mean for ETR was 3.6 to 6.8 mg ×hour/L, and this did not lie entirely below the preset target interval lower bound of 4.4 mg × hour/L. The geometric mean (90% CI) AUC_{12}, maximum plasma concentration, and concentration at 12 hours postdose (C_{12}) for DRV were 67.4 (90% CI, 59.1–76.9), 8.8 (90% CI, 7.8–9.9), and 3.3 (90% CI, 2.6–4.1) and for ETV 3.8 (90% CI, 2.9–4.9), 0.48 (90% CI, 0.38–0.59), and 0.22 (90% CI, 0.16–0.29), respectively.

Due to suboptimal exposure, 6 subjects receiving DRV/r/ETV 600/100/200 mg had a dose increase and PK sampling repeated: 4 subjects had a DRV AUC below the target of 46.7 mg × hour/L (corresponding to a 20% reduction of the mean AUC in adults [58.4 mg × hour/L] [1]), and their physician decided to increase their DRV dose to 800/100 mg BID but kept the same ETR dose; whereas 2 subjects had low ETR AUC (1.12 and 2.8 mg × hour/L; target range, 4.4 to 6.9 mg × hour/L), and their physician decided to increase their ETR dose to 300 mg BID but kept the same DRV/r dose. The HIV VL was detectable in 2 of the 6 subjects who had a dose increase (138 and 190 copies/mL) at the time of PK sampling. All subjects achieved drug exposures within the expected range after the dose increases. Two subjects receiving DRV/r 800/100 mg BID had an approximate 2.5-fold increase in DRV exposure compared with the 600/100 mg dose. There were no reported side effects during the study period.

DISCUSSION

The combination of DRV/r with ETR has been demonstrated to be efficacious and safe in HIV-infected, treatment-experienced adults (DUET-1 and DUET-2 trials) [7, 8], but data on DRV/r plus ETR in adolescents and young adults are sparse. We found that the PK parameters of DRV/r given BID in a cohort of adolescents and young adults in the United States were not affected by the addition of ETR and were comparable to those reported in adults; however, the mean DRV values were higher in the present study, AUC_{0-12} was 72.5 vs 58.4 mg × hour/L and C_{12} was 4.2 vs 3.5 mg/L [1]. In addition, the values we observed were also slightly above those levels reported by the Darunavir Evaluation in Pediatric, HIV-Infected (Delphi) study in treatment-experienced patients 6 to 17 years of age (ie, median DRV AUC_{0-12} of 61.6 mg × hour/mL and C_0 of 3.7 mg/L) who received DRV without coadministration of ETR [9].

The ETR PK parameters we observed (AUC_{0-12} 5.2 mg ×hour/L and C_0 0.33 mg/L) were similar to those reported in the DUET study in adults [6] and in a recent population PK analysis of ETR in HIV-infected children aged 6 to 17 years (5.2 [4.3] mg × hour/L and 0.35 [0.34] mg/L, respectively) (PIANO study, NCT00665847) [10] and consistent with the levels observed when ETR was combined with DRV/r once daily [5].

Of note, the interpatient variability for the PK parameters of DRV and ETR were very high in our study. Although the coefficient of variation for the AUC_{0-12} (81%) and C_{12} (97%) of ETR are relatively high, in adults they were even higher with AUC 108% and C_{12} 124%, respectively. The 90% confidence for the ETR AUC_{0-12} did not fall entirely below the predefined target (20% reduction in adult exposure), providing some reassurance that patients are not likely exposed to substantially lower drug

Table 1. Darunavir and Etravirine Pharmacokinetic Parameters[a]

	Darunavir	Ritonavir	Etravirine	DRV/r Adults (Historical) [1]	ETR Adults (Historical) [6]
Parameter	600/100 mg BID		200 mg BID	600/100 mg BID	200 mg BID
N	36	36	36		
AUC_{12} (mg × hour/L)	72.5 ± 28.8	6.4 ± 4.4	5.2 ± 5.6	58.4 ± 16.8	5.5 ± 4.5
C_{12h} (mg/L)	4.1 ± 3.0	0.28 ± 0.22	0.33 ± 0.41	3.5 ± 1.4	0.39 ± 0.38
C_{max} (mg/L)	9.3 ± 3.2	1.0 ± 0.75	0.60 ± 0.54		
C_{min} (mg/L)	2.9 ± 2.4	0.19 ± 0.18	0.27 ± 0.42		
CL/F (L/hour)	9.6 ± 3.8	24.0 ± 17.2	70.0 ± 65.7		

Abbreviations: AUC_{12}, 12-hour area under the curve; C_{12h}, concentration at 12 hours postdose; C_{max}, maximum plasma concentration; C_{min}, minimum concentration within the dosing interval; CL/F, apparent clearance at steady state; DRV, darunavir; ETR, etravirine.

[a]Values are mean ± standard deviation.

concentrations, if at all. The observed interpatient variability of DRV was much lower than with ETR, with AUC 39% and C_{12} 73%, but these were also slightly higher than those reported in adults (AUC 28% and C_{12} 40%) [1]. The high variability observed may also explain the relatively high number of children receiving DRV/RTV/ETR 600/100/200 mg BID with drug exposure below the target range (4 DRV and 2 ETR); these children had a dose increase and achieved target concentrations. The more than proportionally increase in DRV exposure observed in 2 patients after the dose increase was not expected, and no clear explanation can be drawn at this time, but this result emphasizes the need for close monitoring after dose adjustment. However, evidence supporting robust minimum drug exposure targets for DRV and ETV are not available, so it is difficult to determine whether drug level monitoring in the context of the wide interpatient variability observed would be beneficial.

Given that DRV/r and ETR are often among the remaining active drugs for perinatally HIV-infected adolescents with multidrug resistance, it is important to determine the optimal dosing. Due to the observational nature of the study, a detailed assessment of the efficacy and safety was not possible; however, comparable exposure with the adult drug exposure data demonstrating safety and efficacy is indicative that the DRV/r/ETV dosing studied is appropriate. Recent results of once-daily DRV/r with ETR (400 mg QD or 200 mg BID) have also suggested that the interaction is minimal in this population [5]. In conclusion, our data suggest that the current recommendation of DRV/r (600/100 mg) with ETR (200 mg) BID ETR is appropriate in adolescents and young adults.

Notes

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