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Short Communication

Doravirine and Rilpivirine Intra Cellular Accumulation in the Clinical Setting

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Abstract

Background: Doravirine (DOR) and Rilpivirine (RPV) are the NNRTIs currently most used in the clinical setting, in dual and triple drug regimens (2DR and 3DR). Intracellular (IC) Pharmacokinetics (PK) of these drugs has not been fully elucidated. Our aim was to compare plasma PK and IC accumulation in real-life experienced patients (pts).

Methods: Pts on DOR- and RPV-including Antiretroviral (ARV) regimen were considered. DOR and RPV plasma and IC (PBMCs) concentrations were measured at 12 (37%) (T12) and 24 ± 4 hours (63%) (T24) after last drug intake by means of UHPLC-MSMS validated methods.

Results: 90 pts (65% on 3DR and 35% on 2DR) were included: 52% on DOR- and 48% on RPV-containing ARV. RPV IC/plasma ratio was significantly higher than DOR IC/plasma ratio: 6.034 (4.878-7.186) vs. 1.479 (1.256-1.702) (p=0.001) independently from timing T12 (p=0.003) and T24 (p<0.001). RPV in 3DR resulted to have higher plasma and IC accumulation compared to 2DR. Linear and significative correlations between DOR and RPV plasma and IC concentrations were found (+0.749, p<0.001 and +0.733, p<0.001). No significative correlation between overall DOR and RPV PK and creatinine, BMI or age or difference by gender was found.

Conclusion: RPV proved to accumulate in PBMCs at a higher degree as compared to DOR: RPV and DOR IC levels were 498% and 50% higher than in plasma. RPV showed an IC PBMC/plasma ratio 3-fold higher than DOR. Potential explanation could rely on the higher lipophilicity of RPV. Clinical significance of these data needs to be investigated in further studies.

Keywords: HIV; Antiretroviral drugs; Doravirine; Rilpivirine; Pharmacokinetics; Intracellular concentration

Abbreviations

HAART: Highly Active Antiretroviral Therapy; IC: Intracellular; ARV: Antiretroviral; DRV: Darunavir; RTV: Ritonavir; PBMCs: Peripheral Blood Mononuclear Cells; NNRTIs: Non-Nucleoside Reverse Transcriptase Inhibitors; DOR: Doravirine; RPV: Rilpivirine; 2DR: Dual Drug Regimen; 3DR: Three Drug Regimen; CYP3A4: Cytochrome P-450 3A4; PK: Pharmacokinetics; GM: Geometric Means; C_{trough}: Plasma through Concentration; CNS: Central Nervous System; EC50: Half-Maximal Effective Concentration; CSF: Cerebrospinal Fluid; EC90: 90% Effective Concentration; SP: Seminal Plasma; CVF: Cervicovaginal Fluid; T12: 12 hours ; T24: 24 hours; CI95%: Confidence Interval 95%; TDF/FTC: Tenofovir Disproxil Fumarate/Emtricitabine; TAF/FTC: Tenofovir Alafenamide/ Emtricitabine

Introduction

In patients infected by HIV, the efficacy of Highly Active Antiretroviral Therapy (HAART) through the blockade of different steps of the retrovirus life cycle is now well established. As HIV is a retrovirus that replicates within the cells of the immune system, Intracellular (IC) drug concentrations are important to determine Antiretroviral (ARV) drug efficacy and toxicity. The number of clinical studies in that area is however rather limited, most studies being small and not always adequately designed.

For instance, the correlation between IC and plasma darunavir (DRV, an HIV protease inhibitor) levels in patients receiving HAART including both DRV and Ritonavir (RTV) was showed to be poor, due to the slow efflux rate of DRV from cell. Therefore, the concentration of DRV in Peripheral Blood Mononuclear Cells (PBMCs) may reflect the average exposure to the drug and the clinical efficacy [1].

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) are not prodrugs, as opposite to NRTIs, and they exert their activity by inhibiting enzyme targets directly. Efavirenz IC concentration, previously widely used NNRTI, was showed to be significant predictors of CD4 gain during HAART [2].

Rilpivirine (RPV) and Doravirine (DOR) are the most currently used NNRTIs, both in dual and triple Antiretroviral (ARV) drug regimens (2DR and 3DR). RPV has also been recently approved as a long-acting drug in a dual regimen with Cabotegravir as administration in experienced patients [3].

RPV is metabolized by cytochrome P-450 3A4 (CYP3A4) and has a favourable Pharmacokinetic (PK) profile for once daily dosing with a standard dose of 25 mg. Its absorption depends on gastric pH; hence it should be administered with food [4]. There is no clinical relevant

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effect of age, sex, weight, race, estimated glomerular filtration rate, or hepatitis B/C coinfection status on RPV PK in adults [5].

RPV pharmacokinetic characteristics were previously analysed in a real life intraclass switch study from a 3DR regimen nevirapine-including to RPV-including. Geometric Means (GM) for RPV plasma through concentration (C_{trough}) increased from 29.7 ng/mL (95% CI: 23.8-37.0) on day 3 to 58.2 ng/mL (95% CI: 49.1-69.1) on day 60 after switch. Furthermore, RPV exposure in sanctuaries such as Central Nervous System (CNS) and genital tract have been described and the overall exposure exceeded the half-maximal Effective Concentration (EC50) in Cerebrospinal Fluid (CSF) and the 90% Effective Concentration (EC90) in Seminal Plasma (SP) [6].

DOR is a novel NNRTI that has demonstrated good efficacy and tolerability both in naïve and experienced HIV-positive subjects, with and a high genetic barrier to resistance, as demonstrated by two multicenter phase III studies [7,8].

Further studies in healthy volunteers and HIV-infected positive individuals have shown that DOR has a favorable PK profile for a once-daily dosing of 100 mg, with an approximately 15 hours half-life. DOR absorption is guaranteed in fasted state, differently from RPV. It is metabolized by CYP3A4and less than 10% of elimination occurs *via* the renal pathway. DOR PK is not greatly influenced by sex, age, race, or hepatic impairment [9]. Moreover the effects of severe renal impairment on DOR PK are not anticipated to be clinically meaningful [10].

Protein-unbound DOR PK in CSF [11], SP and Cervicovaginal Fluid (CVF) [12] have been already explored and resulted to exceed the half-maximal effective concentration for wild-type HIV-1 (EC50: 5.1 ng/mL) respectively by 9-, 20- and 60-fold. Intracellular PK of RPV and DOR has not been so far investigated in HIV-positive persons.

Therefore, our aim was to compare DOR and RPV plasma exposure and IC accumulation in real-life experienced patients both in triple and dual ARV regimens.

Materials and Methods

Patients on DOR- and oral RPV-including antiretroviral regimens were included, after informed consent given. DOR and RPV plasma and PBMC concentrations were measured at 12 (37%) (T12) and 24 ± 4 hours (63%) (T24) after last drug intake. Plasma concentrations were measured using HPLC/MS-MS method validated at the Laboratory of Clinical Pharmacology and Pharmacogenetics of the University of Turin. IC quantification was performed in PBMCs, which were isolated using CPT Vacutainers (Becton, Dickinson and Co., Franklin Lakes, NJ, USA), and cell numbers and mean cell volumes were measured using an automated cell counter (Z2 Beckman Coulter, Instrumentation Laboratory, Milan, Italy), as previously described in the literature [13]. Mann-Whitney analysis and Spearman's rank test were used as appropriate. Non-compartmental PK parameters were expressed as geometric mean (CI95%).

Results

Ninety patients (65% on 3DR and 35% on 2DR) were included: 52% patients were on DOR and 48% on RPV-containing regimens. Of these patients 61% were male and 49% female, age and BMI were 54 years (52-57) and 25.6 kg/m^2 (24.6-26.6), respectively, with no significant differences between DOR and RPV groups.

Overall DOR plasma and IC concentrations were 768.5(609.0-927.0) and 1146.7(875.9- 1417.6) ng/ml, respectively, while RPV plasma and IC levels were 187.4 (152.4-222.5) and 1121.7(823.8-1419.6) ng/ml, respectively. Furthermore, a significant difference between RPV as part of 3DR or 2DR was observed in plasma (p=0.002), IC concentration (p=0.001) and IC/plasma ratio (p=0.021). 3DR-RPV plasma, IC and IC/plasma ratio was found to be respectively 222.7 (174.1-271.2), 1476.9(1010.7-1943.1) ng/mL and 6.929 (5.143-8.715), whereas 2DR-RPV resulted to be 141.6 (94.7-188.5), 659.9 (433.8-886.0) ng/ml and 4.866 (3.585-6.147).

No significant difference in DOR-2DR and 3DR concentrations was observed in plasma (p=0.297), IC (p=0.702) and IC/plasma ratio (p=0.335). Overall RPV IC/plasma ratio was significantly higher than DOR IC/plasma ratio: 6.034 (4.878-7.186) *vs.* 1.479 (1.256-1.702) (p=0.001). Even after stratification by time points (T12 or T24) difference between DOR and RPV IC/plasma ratios was found to be significant (T12: p=0.003 and T24: p<0.001). Moreover we observed a linear and significative correlation between DOR and RPV plasma and IC concentrations (+0.749, p<0.001 and +0.733, p<0.001, respectively). DOR IC concentration showed an inverse correlation with CD4+T cell count (-0.322; p=0.028).

No significative correlation between overall DOR and RPV PK and creatinine, BMI or age and no difference by gender was found.

Conclusion

In this first evaluation in the clinical setting, RPV and DOR PK profile was not influenced by age, renal function and gender, in line with previous data [5,9]. RPV proved to accumulate in PBMCs at a significantly higher degree as compared to DOR: RPV and DOR IC levels were 498% and 50% higher than in plasma, respectively. RPV showed an IC/plasma ratio 3-fold higher than DOR, independently from the time of drug intake. The potential explanation of different IC penetration could rely on the higher lipophilicity of RPV compared to DOR. Moreover, RPV proved to accumulate in PBMCs 2-fold higher when dosed in 3DR than 2DR. Previous reports highlighted the increased concentration above the EC50 and EC90 in different sanctuaries when RPV was dosed in standard triple ARV regimen (TDF/FTC) [6]. In our analysis, the increased RPV plasma exposure and concomitantly IC accumulation was observed in presence of backbone (TAF/FTC). Mechanisms at the basis of this result need to be further elucidated as well as their clinical relevance. The interplay between the extent of IC accumulation and the potential role on selection of resistance mutations and drug forgiveness is yet to be thoroughly understood.

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