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Efficacy, safety and pharmacokinetics of atazanavir (200 mg twice daily) plus raltegravir (400 mg twice daily) dual regimen in the clinical setting

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ABSTRACT

Background: Unboosted atazanavir with raltegravir has been investigated at 300 mg twice daily showing frequent hyperbilirubinemia and selection of resistance-associated mutations.
Objectives: Atazanavir 200 mg twice daily could increase tolerability and plasma exposure.
Study design: Patients on atazanavir/raltegravir (200/400 twice daily), with self-reported adherence >95% and no concomitant interacting drugs were retrospectively evaluated.
Results: 102 patients [72.5% male, age 46.4 years (42–54), BMI 24 kg/m^2 (22–26)] were included. CD4+ T lymphocytes were 417 cell/μL (302–704) and 76 patients (74.5%) had HIV-RNA <50 copies/ml. After 123 weeks 18.6% patients showed virological failure and 3.9% discontinued for intolerance. Available genotypes showed selection of major integrase (7/10 patients) and protease resistance-associated mutations (5/13 patients). In patients switching with dyslipidemia (n = 67) total, LDL cholesterol and triglycerides significantly decreased. Patients switching with eCRCL<60 ml/min (n = 27) had no significant changes while patients with eCRCL >60 ml/min showed significant decrease (−9.8 ml/min, p = 0.003) at 96-weeks. Atazanavir and raltegravir trough concentrations were 321 ng/mL (147–720) and 412 ng/mL (225–695). Self-reported non-adherence (n = 4) was significantly associated with virological failure (p = 0.02); patients with virological success had borderline longer previous virological control (33 vs. 18 months, p = 0.07).
Discussion: Switch to atazanavir/raltegravir was safe and well tolerated allowing optimal drugs' plasma exposure. However, a concerning rate (18.6%) failed with newly selected mutations and stopped ATV/RAL because of DDI and intolerance issues or were lost to follow-up. This regimen might be considered in selected patients, without history of protease inhibitors failure or HBV infection, showing optimal adherence and prolonged suppression.

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1. Background

The astonishing success of antiretroviral therapy (ART) is limited by long-term toxicity, suboptimal adherence, drug-drug interactions (DDI) and multidrug resistant HIV strands. Recommended regimens include three drugs with nucleoside reverse transcriptase inhibitors (NRTIs) as backbone [1]. NRTIs- and ritonavir (RTV)- sparing regimens provide an interesting choice to reduce drugs' toxicity and improve tolerability in ART-experienced patients. There is growing interest in NRTIs-sparing dual regimens containing HIV integrase inhibitors (INI) and protease inhibitors (PIs) [2,3] as well as for lamivudine containing dual regimens [4,5]. Raltegravir (RAL) associated to unboosted atazanavir (ATV) represents an option for NRTI- and RTV-sparing maintenance therapy.

Raltegravir is mainly metabolized through glucuronidation by uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1), secondarily by UGT1A3 and UGT1A9 and is not a cytochrome P450 (CYP) substrate [6]. Atazanavir 300 mg boosted by RTV 100 mg showed efficacy in treatment- naïve [7–9] and -experienced subjects [10–13]; ATV is mainly metabolized by CYP3A, inhibits CYP3A and UGT1A1. Unboosted ATV dosed 400 mg once daily (qd) showed drug exposure below recommended concentration at the end of dosing interval ($C_{trough,}$ 150 ng/mL) [1,14] in up to 50% subjects [15–18]. Splitting 400 mg daily dosing of ATV in 200 mg twice daily (bid) may favour adequate plasma exposures [19]. Studies in healthy volunteers and HIV-infected subjects [20–24] showed RAL AUC increased by 40–55% through ATV-mediated UGT1A1 inhibition; given its safe toxicity profile, RAL dosage adjustment is not suggested. ATV C_{min} was reduced by 29% with concentrations remaining however above EC_{90} for wild-type HIV-1 (14 ng/mL). The efficacy of this combination has been studied as initial and maintenance strategy with different dosing. A comparative study in treatment-naïve patients with RAL 400 mg and ATV 300 mg bid showed efficacy comparable to standard therapy [25]. Nevertheless the study was stopped at 24 weeks due to high rates of RAL resistances (in those who failed) and hyperbilirubinemia. Small-sized studies in experienced subjects showed viral efficacy and improved tolerability with ATV 200 mg and RAL 400 mg both dosed bid [26,27]. Persistent viral suppression was reported in 90% of patients treated with ATV 400 mg qd plus standard dose of RAL at 48 weeks [28]. A recent study showed efficacy (100% at 48 weeks) and good safety profile in twenty-five experienced patients randomized to RAL 400 mg plus ATV 300 mg bid for four weeks followed by RAL 800 mg plus ATV/ritonavir 300/100 mg qd for four weeks or vice versa [29]. The lowering effect of RAL co-administration could be counterbalanced by increased plasma exposure of ATV given 200 mg bid (higher C_{min}, lower C_{max}), avoiding hyperbilirubinemia observed with higher doses [25].

2. Objective

Aim of our study was to further investigate efficacy, safety and pharmacokinetics of the dual NRTI- and RTV-sparing combination of ATV 200 mg and RAL 400 mg, both given bid in clinical setting.

3. Study design

HIV-1 infected patients receiving ATV 200 mg and RAL 400 mg, both bid, were retrospectively evaluated. Inclusion criteria were: treatment with ATV + RAL from at least three months, self-reported adherence of 95% or more, no concomitant interacting drugs. Subjects were outpatients of Infectious Diseases Department of Torino University, Genova University, Ospedale Galliera, Ospedale Papa Giovanni XXIII of Bergamo and Milano University, Ospedale Luigi Sacco. We could identify approximately 95% (200) of total patients starting ATV + RAL in study period from drugs registry of each Hospital Pharmacy involved in the study. Patients receiving ATV + RAL and responding to inclusion criteria were identified and data were collected from clinical records and referent physicians between December 2012 and February 2013. Informed consent request was waived by Hospitals due to the retrospective study design. A subgroup of patients underwent an intensive pharmacokinetic (PK) study. Study regimen was introduced because of toxicity, tolerability, or resistance issues. Virological response was considered as last HIV viral load <50 copies/mL without previous confirmed viral rebound above 50 copies/mL. ATV and RAL resistance associated mutations (RAMs) were calculated according to Stanford University database.

3.1. Pharmacokinetic evaluation

ATV and RAL plasma concentrations were measured by HPLC-UV/PDA-validated method using a solid phase extraction procedure with lower quantification limit 46.8 ng/mL and of 23.4 ng/mL respectively, lower detection limit of 11.7 ng/mL for both drugs [30]. Samples collected 10–14 h after drug intake were considered trough concentrations (C_{trough}). Patients undergoing 12-h intensive ATV and RAL PK evaluation were instructed to take tablets at 8 a.m. and 8 p.m. Blood samples were obtained at the end of dosing interval (8 a.m.), 0.5, 1, 2, 3, 4, 8, 12 h after morning dose given with standard light meal. Plasma was separated within 1 h from drawing and samples stored at −70 °C until analyzed. PK parameters were calculated with a non-compartmental model using the software Kinetica (vers. 5.0, Thermo Scientific, MA, USA). Area under the concentration-time curve (AUC) over 12 h (AUC_{12}) was calculated by the linear-log trapezoidal rule. Maximum concentration (C_{max}), T_{max}, C_{12h} (concentration at 12 h post-dose) and C_0 (concentration pre-dose) were obtained.

3.2. Statistical analysis

Quantitative variables were described as median (interquartile range, IQR), categorical ones by number (percentage). Non-parametric tests were used for all analysis and tests are specified in the text. Factors with $p < 0.2$ at univariate analysis were compared through binomial logistic regression for multivariate analysis. Data analysis was performed using SPSS software for Mac (version 20.0, IBM Corp. Released 2011. Armonk, NY: IBM Corp).

4. Results

Of 200 patients in ATV/RAL in the study period in different centers, 102 patients responding to inclusion criteria were enrolled. Subjects excluded were taking ATV/RAL for less than three months, or were assuming potential interacting drugs (mainly proton pump inhibitors or antacids), showed incomplete compliance to study visits or timing required for blood samples. Subjects were 72.5% male, aged 46 years (42–53) (Table 1). CD4+ cell count was 417 cell/μL (302–704) and 76 patients (74.5%) had HIV-RNA below 50 copies/ml. In patients with measurable viral replication (n = 26), HIV-RNA was 525 copies/mL (82–10.462). Thirty-four patients (33.3%) were HCV-coinfected (7 with liver cirrhosis). Patients had been previously treated for 102 months (37–138). Last regimen was boosted PI-based in 81 patients (79.4%), mainly boosted ATV (60, 58.8%), NRTIs-based (3, 2.9%), NNRTIs-based (11, 10.7%), INI-based (7, 6.8%). Eight (7.8%) and 12 patients (11.7%) had previous virological failure to NNRTIs and PIs, respectively. Switch to ATV/RAL was due to toxicity in 61 subjects (59.8%) 35 of which (57.3%) showed renal abnormalities, 17 (27.8%) dyslipidemia and or lipodystrophy, 6 (9.8%) gastro-intestinal intolerance. In ten patients (9.8%) change