International Journal of Antimicrobial Agents xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Short communication

Pharmacokinetic interactions between telaprevir and antiretroviral drugs in HIV/HCV-coinfected patients with advanced liver fibrosis and prior HCV non-responders

Laura Milazzo[a,*], Dario Cattaneo[b], Elisa Calvi[a], Cristina Gervasoni[a], Cristina Mazzali[c], Paola Ronzi[a], Anna Maria Peri[a], Anna Lisa Ridolfo[a], Antonio D'Avolio[d], Spinello Antinori[a]

[a] Department of Biomedical and Clinical Sciences L. Sacco, III Division of Infectious Diseases, University of Milan, Via GB Grassi 74, 20157 Milan, Italy
[b] Unit of Clinical Pharmacology, Luigi Sacco University Hospital, Via GB Grassi 74, 20157 Milan, Italy
[c] Department of Biomedical and Clinical Sciences, Section of Biostatistics, University of Milan, Via GB Grassi 74, 20157 Milan, Italy
[d] Unit of Infectious Diseases, Department of Medical Sciences, University of Turin, Amedeo di Savoia Hospital, Corso Svizzera 164, 10149 Turin, Italy

ARTICLE INFO

Article history:
Received 4 September 2014
Accepted 29 December 2014

Keywords:
Telaprevir
Antiretroviral therapy
Pharmacokinetics
Drug interactions

ABSTRACT

Complex drug–drug interactions have been reported with concurrent administration of telaprevir (TVR) and human immunodeficiency virus (HIV) protease inhibitors (PIs), leading to relevant limitations of the therapeutic options for patients coinfected with hepatitis C virus (HCV) and HIV. However, little is known about the pharmacokinetics and drug interactions between TVR and antiretrovirals in HIV/HCV-coinfected patients with advanced liver fibrosis. Here we report the pharmacokinetics of TVR and antiretrovirals in a cohort of HIV/HCV genotype 1-coinfected patients with advanced liver fibrosis treated with TVR-based triple anti-HCV therapy. No significant differences were observed in the pharmacokinetics of atazanavir, amprenavir or tenofovir at baseline and at Day 15 of TVR, whereas the $AUC_{0-4\,h}$ of darunavir was 36% lower in the presence of TVR ($AUC_{0-4\,h}$ 15 007 ng h/mL and 9563 ng h/mL at baseline and at Day 15 of TVR administration, respectively). Noteworthy, the $AUC_{0-4\,h}$, C_{min} and C_{max} of raltegravir were reduced by 61%, 50% and 64%, respectively. However, none of the patient's plasma levels of tenofovir, atazanavir, amprenavir or raltegravir declined below their minimum effective concentrations even in association with TVR, and no HIV treatment failure occurred. A non-significant trend for lower TVR exposure was seen in patients concomitantly given amprenavir versus those given atazanavir ($AUC_{0-4\,h}$, 9840 ng h/mL and 13 345 ng h/mL, respectively). In conclusion, this study highlighted the feasibility of maintaining the current antiretroviral regimen in HIV/HCV-coinfected patients, even when significant interactions with TVR are predictable, whenever a change of HIV PIs is not deemed appropriate.

1. Introduction

Since its approval in 2011, telaprevir (TVR) has been used in combination with peginterferon alfa (peg-IFNα) and ribavirin (RBV) for the treatment of chronic hepatitis C virus genotype 1 (HCV1) infection both in the USA and Europe, leading to a significant improvement in outcomes both in HCV-monoinfected and HCV/human immunodeficiency virus (HIV)-coinfected populations [1,2]. TVR is an HCV protease inhibitor (PI) primarily metabolised by the cytochrome P450-3A4 isoform, of which it is a substrate and inhibitor, as well as being a substrate of *P*-glycoprotein. Therefore, complex drug–drug interactions have been reported with concurrent administration of TVR with most of the HIV PIs; it has been shown that plasma levels of both TVR and HIV PIs were reduced by their concomitant use [3,4]. This observation led to relevant limitations of the therapeutic options for HCV/HIV-coinfected patients, and currently the only HIV PI recommended in association with TVR is ritonavir-boosted atazanavir (ATV/r) [5]. However, most data on the pharmacokinetic interactions of TVR and HIV PIs derive from pharmacokinetic studies in healthy volunteers, and only a few studies have been performed in HIV/HCV-coinfected patients [2,4], particularly in those with advanced liver fibrosis/cirrhosis [6]. Given that in treatment-experienced patients the use of different HIV PI-based regimens might be necessary, we aimed to report

* Corresponding author. Tel.: +39 02 3904 3350; fax: +39 02 5031 9758.
E-mail addresses: laura.milazzo@unimi.it, laura.milazzo@virgilio.it (L. Milazzo).

http://dx.doi.org/10.1016/j.ijantimicag.2014.12.035
0924-8579/

the pharmacokinetics of TVR and antiretroviral medications in a cohort of HIV/HCV1-coinfected patients treated with TVR-based triple anti-HCV therapy.

2. Methods

2.1. Study population

An open-label, prospective study on HCV/HIV-1-coinfected patients on stable antiretroviral therapy and with advanced liver fibrosis (METAVIR score F3/F4) who started triple therapy for chronic HCV1 infection (TVR 1125 mg twice daily, peg-IFNα-2a 180 μg/week + weight-adjusted RBV) was conducted at Luigi Sacco University Hospital (Milan, Italy). The study was approved by the hospital's Institutional Review Board, and written informed consent was obtained from all of the patients enrolled. Liver stiffness was determined by hepatic transient elastography (FibroScan; Echosens, Paris, France).

2.2. Pharmacokinetic analysis

Plasma levels of HIV PIs, raltegravir and tenofovir were measured at baseline (before the introduction of TVR-based triple anti-HCV therapy) and after 15 days of triple anti-HCV therapy, when TVR plasma levels were also evaluated. Blood samples were collected immediately before and at 1, 2, 3 and 4 h after supervised drug intake following a standard breakfast.

The following pharmacokinetic variables were evaluated for TVR, HIV PIs (atazanavir, amprenavir and darunavir), raltegravir and tenofovir: area under the concentration–time curve from 0 to 4 h ($AUC_{0-4\,h}$); maximum observed plasma concentration (C_{max}); time to C_{max}; and minimum observed plasma concentration (C_{min}).

Plasma concentrations of antiretroviral drugs were assessed by a validated chromatographic method coupled with ultraviolet detection (atazanavir, darunavir) or with triple quadrupole mass spectrometry (raltegravir, amprenavir, tenofovir) [7]. TVR pharmacokinetic parameters were reported as total drug amount and as single S and R isomers using a previously published UPLC–tandem mass spectrometric method [8].

2.3. Statistical analyses

The pharmacokinetic parameters of TVR and antiretroviral drugs were described by the geometric mean and 95% confidence interval (CI). Differences in pharmacokinetic data for atazanavir, amprenavir, raltegravir and tenofovir before and after TVR exposure were compared using Student's *t*-test for paired samples. $AUC_{0-4\,h}$ values of total, and S and R isomers of TVR between two groups of patients (those treated in combination with atazanavir versus amprenavir) were compared by the Mann–Whitney–Wilcoxon non-parametric test (rank-sum test). Differences between plasma concentration curves (0–4 h) of TVR in the same groups were analysed by a linear fixed-effects model for repeated measures to estimate the effect of time and group (amprenavir versus atazanavir) using PROC MIXED. Possible interactions between groups and time were also evaluated. All of the analyses were performed using SAS v.9.2 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Patients characteristics

Fifteen HCV/HIV-coinfected patients were enrolled in the study. Their baseline characteristics are reported in Table 1. Most of the patients were male (12/15; 80%) and carried HCV genotype 1a (11/15; 73%). All patients had normal renal function and advanced liver fibrosis (METAVIR score F3/F4), with no clinical signs of liver decompensation. Thirteen patients were on antiretroviral treatment with a PI; six were receiving ATV/r (300 mg/100 mg daily), six were receiving ritonavir-boosted amprenavir (APV/r) (700 mg/100 mg twice daily) and one was receiving ritonavir-boosted darunavir (800 mg/100 mg daily). Nine patients were on treatment with raltegravir and eight patients were receiving tenofovir as backbone. Sustained virological response at 12 weeks post treatment (SVR12) (i.e. HCV-RNA undetectable at post-treatment Week 12) was achieved in 8 (53.3%) of 15 patients; 1 patient discontinued all HCV treatment at Week 8 based on his own decision.

Table 1
Patient characteristics at study inclusion ($n = 15$).

Characteristic	
Age (years) [median (range)]	50 (38–66)
Male sex [*n* (%)]	12 (80)
BMI [median (range)]	21.4 (17.9–27.6)
Creatinine (mg/dL) [median (range)]	0.79 (0.4–1.1)
eGFR (mL/min) [median (range)]	104 (74–177)
CD4 count (cells/μL) [median (range)]	758 (603–1152)
HIV-RNA <37 copies/mL [*n* (%)]	15 (100)
Baseline HCV-RNA (log_{10} IU/mL) [median (range)]	6.43 (5.4–7.2)
HCV genotype [*n* (%)]	
1a	11 (73)
1b	4 (27)
Baseline ALT (IU/L) [median (range)]	78 (23–248)
Fibrosis stage [*n* (%)]	
F3	8 (53)
F4	7 (47)
IL-28 genotype [*n* (%)]	
CC	7 (47)
CT	5 (33)
TT	3 (20)
Previous response [*n* (%)]	
Naïve	1 (7)
Null responder	7 (47)
Partial responder	5 (33)
Relapse	2 (13)
Antiretroviral therapy [*n* (%)]	
Atazanavir/ritonavir	6 (40)
Fosamprenavir/ritonavir	6 (40)
Darunavir/ritonavir	1 (7)
Raltegravir	9 (60)
Tenofovir	8 (53)
Abacavir	1 (7)

BMI, body mass index; eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; HCV, hepatitis C virus; ALT, alanine aminotransferase; IL, interleukin.

3.2. Pharmacokinetics and drug–drug interactions

There were no significant differences in the pharmacokinetic parameters of atazanavir and amprenavir at baseline and at Day 15 of triple anti-HCV therapy (Table 2; Fig. 1A and B). Plasma levels of darunavir were shown to be significantly lowered by the addition of TVR in the single patient treated with darunavir. The $AUC_{0-4\,h}$ of darunavir was 36% lower in the presence of TVR ($AUC_{0-4\,h}$ 15 007 ng h/mL and 9563 ng h/mL at baseline and at Day 15 of TVR administration, respectively). Finally, TVR co-administration was shown to decrease the $AUC_{0-4\,h}$, C_{min} and C_{max} of raltegravir by 61%, 50% and 64%, respectively, although only the decrease for C_{max} was significant ($P = 0.02$) (Table 2; Fig. 1C). Nevertheless, no HIV viral rebound occurred in any of the patients studied. Plasma levels of tenofovir were also measured and no significant differences in the pharmacokinetic parameters of tenofovir with or without

Please cite this article in press as: Milazzo L, et al. Pharmacokinetic interactions between telaprevir and antiretroviral drugs in HIV/HCV-coinfected patients with advanced liver fibrosis and prior HCV non-responders. Int J Antimicrob Agents (2015), http://dx.doi.org/10.1016/j.ijantimicag.2014.12.035