Raltegravir Pharmacokinetics in Patients on Asunaprevir-Daclatasvir

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New direct active antivirals (DAA) are highly active and well tolerated, including in hepatitis C virus-human immunodeficiency virus (HCV-HIV)-coinfected patients. Among the DAA, the asunaprevir-daclatasvir combination was proven effective, but one remaining concern is whether their coadministration with antiretroviral drugs is safe. Their combination with ribavirin and pegylated interferon (peg-interferon alpha 2a) resulted in a global sustained virologic response at 12 weeks (SVR12) rate of 96%, as shown in 75 patients included in the ANRS HC30-QUADRIH study, sponsored by INSERM-ANRS (1). The objective was to assess the effect of asunaprevir-daclatasvir on the disposition of raltegravir combined with peg-interferon alpha 2a–ribavirin in 20 patients included in the pharmacokinetic (PK) study.

The patients of the pharmacokinetic substudy were treated with raltegravir (400 mg twice a day [b.i.d.]) with tenofovir disoproxil fumarate (DF) and either emtricitabine (n = 18) or abacavir (n = 1) or emtricitabine plus enfuvirtide (n = 1). They received a 4-week lead-in phase of peg-interferon-alpha 2a at 180 μg subcutaneously (s.c.)/week plus ribavirin at 1,000 mg/day (<75 kg of body weight) or 1,200 mg/day (≥75 kg of body weight), followed by a 24-week quadruple therapy combining asunaprevir (100 mg b.i.d.), daclatasvir (60 mg once a day [q.d.]), and peg-interferon–ribavirin. Blood samples were collected on day 0 and on week 8 (after quadruple therapy initiation) prior to and after dosing at times +1, +2, +3, +4, +6, +8, and +10 h. Drugs were administered with a light continental breakfast in the morning. Actual times of drug administration and samplings were recorded.

Raltegravir levels in plasma were assayed by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. Within-run variability was <15%. Asunaprevir and daclatasvir were assayed by a validated LC-MS/MS assay (BMS, West Trenton, NJ). Pharmacokinetic parameters were estimated by a model independent method. The areas under the plasma concentration-time curve from 0 to the last sampling time, 10 h postdosing (AUClast), were determined at steady state and calculated according to the linear up/log down trapezoidal rule (WinNonLin, Pharsight, CA). AUC during a dosing interval (AUCint), could not be calculated in a number of patients as the slope of concentrations of raltegravir versus time of decline was very erratic and therefore could not be used for comparison. The maximum concentration observed (Cmax), the observed predose concentration (Co), and the time of Cmax (Tmax) were obtained visually.

Results are expressed as median (with range in parentheses). Geometric mean ratios (GMR) of pharmacokinetic parameters with and without hepatitis C treatment and 90% confidence interval (CIs) were analyzed using a bioequivalence approach (Statgraphics, Manugistics, Rockville, MD).

Twenty patients completed the study. Eighteen of 20 patients were male, the median age was 49 years (range, 37 to 59 years), the body weight was 74 kg (range, 65 to 78 kg), the CD4 count was 849/mm³ (range, 362 to 1,994/mm³), the plasma HCV RNA level was 6.11 log10 IU/ml (4.98 to 7.41 log10 IU/ml), and the HCV genotypes were 1a in 11 patients and 4 in 9 patients. In addition, 65% were intravenous (i.v.) drug users, all but 1 patient had a plasma HIV RNA level of <50 copies/ml, and 7 (35%) had Child’s A liver cirrhosis. Of note, one patient took 800 mg raltegravir once daily by personal decision.

Raltegravir pharmacokinetic parameters and the ratio of geometric means (day 0 over week 8) and 90% CI for Cmax, Cint, Clast, and AUClast are shown Table 1. Parameters of the patient who took raltegravir once daily were not included. Consequently, comparisons of AUCs between day 0 and week 8 were made using AUClast, knowing that on average the last concentration on a dosing interval was sampled 10 h postdose, whatever the period. Ratios for Cmax and AUClast of raltegravir on and off hepatitis C

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treatment are close to 1, and the 90% CI is close to the bioequivalence range 0.80 to 1.25, which indicates that there is no clinically significant effect of asunaprevir/daclatasvir on raltegravir pharmacokinetics. The C<sub>L</sub> was lower on hepatitis C treatment than at week 0, but the difference was not statistically significant. Raltegravir PK parameters were also similar in patients with or without cirrhosis. The C<sub>max</sub> and AUC of raltegravir on day 0 were 2,247 ng/ml (range, 492 to 7,536 ng/ml) and 7,059 ng · h/ml (range, 1,677 to 21,523 ng · h/ml) in patients without cirrhosis and 2,002 (range, 208 to 4,338 ng/ml) and 10,171 ng · h/ml (814 to 14,568 ng · h/ml) in patients with cirrhosis, respectively. No HIV breakthrough was observed.

Concentrations of asunaprevir and daclatasvir measured on week 8 are listed in Table 1 and remained unchanged in patients with liver cirrhosis (data not shown).

This pharmacokinetic study did not detect any significant PK interaction between raltegravir, asunaprevir, and daclatasvir, whether the patients had liver cirrhosis or not.

Raltegravir concentrations measured in HIV-HCV-coinfected patients are highly variable, as already reported (2–4). Several factors can explain such variability, such as food intake or gastrointestinal pH. Liver disease such as cirrhosis has been demonstrated previously not to affect raltegravir pharmacokinetics (5). Despite such variability, concentrations measured in the patients included in this ANRS HC30 study (day 0) are in the range of previously reported studies (3, 4).

Inpatient comparison of raltegravir concentrations and pharmacokinetic parameters shows that asunaprevir/daclatasvir does not affect significantly raltegravir pharmacokinetics. Raltegravir is metabolized by glucuronidation involving UGT1A1, and very few drug-drug interactions have been reported and involved potent drug-metabolizing inducers such as rifampin or a UGT1A1 inhibitor such as atazanavir (6). It seems that asunaprevir may moderately induce CYP3A4. Interactions between asunaprevir and substrates for influx (organic anion-transporting polypeptide [OATP]) and efflux (P-glycoprotein [Pgp]) transporters have been described, making it very difficult to predict interactions with combined drugs. Daclatasvir is also a substrate of CYP3A4 and Pgp but was shown to mildly inhibit Pgp.

The combined administration of daclatasvir and asunaprevir did not lead to any clinically significant pharmacokinetic interactions in healthy volunteers. However, their complex disposition pathway involving CYP3A, uptake, and efflux transporters that could be affected in liver disease made the study of their disposition in such patients worthwhile. This study demonstrates that in patients with liver dysfunction, concentrations of the three studied drugs remained in the range of previously published data and that the coadministration of asunaprevir and daclatasvir with raltegravir-based antiretroviral therapy is devoid of drug-drug interaction and is safe (7, 8). The high efficacy observed in these HCV-HIV-coinfected patients supports this observation. This study, however, has some limitations since most patients were male. Since no gender effect on raltegravir pharmacokinetics has been reported so far, it is likely that our findings are also relevant for female patients (9).

In conclusion, these data show that in HIV-HCV-coinfected patients, asunaprevir and daclatasvir can be administered safely with raltegravir.

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