

Influence of alpha-1 glycoprotein acid concentrations and variants on atazanavir pharmacokinetics in HIV-infected patients included in the ANRS 107 trial

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Abstract

Atazanavir is an HIV-1 protease inhibitor (PI) with high protein binding in human plasma. The objectives were first to determine the in vitro binding characteristics of atazanavir, second to evaluate whether plasma protein binding to albumin and to orosomucoïd (alpha 1 glycoprotein acid) influence the pharmacokinetics of atazanavir in HIV-infected patients. For the in vitro study, atazanavir protein binding characteristics were determined in alpha 1 glycoprotein acid and albumin purified solutions. Atazanavir was found to bind alpha 1 glycoprotein acid on a high affinity saturable site (association constant $4.61 \cdot 10^5$ L/mol) and albumin on a low-affinity non-saturable site. For the in vivo study, blood samples from 51 patients included in the ANRS107- Puzzle 2 trial were drawn prior to drug intake at week 6. For 10 patients included in the pharmacokinetic substudy, five additional blood samples were collected during one dosing interval at week 6. Atazanavir concentrations were assayed by LC-MS/MS. Albumin concentrations, alpha 1 glycoprotein acid concentrations and phenotypes were also measured in these patients. Concentrations of atazanavir were modelled using a population approach. A one-compartment model with first-order absorption and elimination best described atazanavir pharmacokinetics. Atazanavir pharmacokinetic parameters and their interindividual variabilities (%) were as follows: absorption rate constant (k_a) 0.73 h^{-1} (139.3%), apparent clearance (Cl/F) 13.3 L/h (26.7%) and apparent volume of distribution (V/F) 79.7 L (27.0%). Atazanavir Cl/F decreased significantly when alanine aminotransferase and/or alpha 1 glycoprotein acid levels increased ($p < 0.01$). ORM1*S alpha 1 glycoprotein acid phenotype also significantly increased atazanavir V/F ($p < 0.05$). These in vivo results indicate that atazanavir pharmacokinetics is moderately influenced by its protein binding, especially to alpha 1 glycoprotein acid without expected clinical consequences.

MESH Keywords Adult ; Female ; HIV Infections ; blood ; drug therapy ; metabolism ; HIV Protease Inhibitors ; pharmacokinetics ; therapeutic use ; Humans ; Male ; Middle Aged ; Oligopeptides ; pharmacokinetics ; therapeutic use ; Orosomucoïd ; metabolism ; Pyridines ; pharmacokinetics ; therapeutic use ; Serum Albumin ; metabolism

Introduction

Atazanavir is an azapeptide protease inhibitor, with a distinct resistance and tolerance profile approved for use in combination treatment of HIV-1 in the US and Europe (11, 12, 17). In the US, one of the recommended antiretroviral regimens is the combination of atazanavir/ritonavir with tenofovir/emtricitabine. Recommended doses of atazanavir are 400 mg once daily taken with food without ritonavir in therapy-naïve patients or 300 mg in combination with low-dose ritonavir (100 mg) once daily in antiretroviral-experienced patients, or when combined with tenofovir (7). The major advantages of atazanavir are its simplicity of administration and a favourable adverse effects profile, especially on lipid parameters.

Major pharmacokinetic characteristics of atazanavir are a variable absorption through the gut, 86% plasma protein binding on albumin and alpha 1 glycoprotein acid (orosomucoïd) and elimination through biotransformation which involved CYP3A. Although consequences of CYP3A metabolism on first pass effect and drug-drug interactions have been largely studied, there is a lack of information on consequences of protein binding on atazanavir pharmacokinetics. It is now recognized that protein binding is an important modulator of protease inhibitor disposition and unbound concentration inhibitor is considered as the active moiety which is available to cross cell membranes. Therefore variations in the concentrations and structures of orosomucoïd and albumin under physiological or pathological infections such as HIV infection are likely to influence protease inhibitors pharmacokinetics (3). Albumin concentrations could be

significantly reduced in patients with liver disease such as co-infections with hepatitis B virus or C virus. Orosomucoid, also called alpha 1 glycoprotein acid, is a glycoprotein which is controlled by a cluster of three adjacent genes: AGP-A which codes for the major protein ORM1; AGP-B and AGP-B' which code for the protein ORM2 (14). The proteins ORM1 and ORM2 are different by a sequence of 22 amino-acids. The protein ORM1 is polymorphic with three variants: ORM1*F1, ORM1*S and ORM1*F2, whereas the protein ORM2 is generally monomorphic with one variant: ORM2*A (8). This polymorphism could be responsible for interindividual variation in the plasma binding of protease inhibitors, which might influence their pharmacokinetic parameters.

The purpose of this work was to determine the *in vitro* binding characteristics of atazanavir. Then we evaluate whether albumin concentration and/or alpha 1 glycoprotein acid concentration and alpha 1 glycoprotein acid variants are pertinent covariates in the population pharmacokinetics analyses of atazanavir used in combination with ritonavir tenofovir in HIV-infected patients included in a clinical trial (ANRS 107 – Puzzle 2) (22).

Methods

Atazanavir *in vitro* binding experiments

Alpha 1 glycoprotein acid and serum albumin solutions were prepared in pH 7.4 phosphate-buffered saline. Concentrations of alpha 1 glycoprotein acid and serum albumin used were those found in normal patients and were 0.7 g/L and 40 g/L respectively. These solutions were spiked with known amounts of atazanavir to yield the following final concentrations: 0, 500, 1000, 1500, 2000, 5000, 10000, 15000 and 30000 ng/mL. Bound and unbound atazanavir were separated by ultrafiltration of 500 µL samples using Centrifree® devices (Amicon, YM-300 filter system, Millipore Corp., Bedford, Massachusetts, USA) at 3000 g during two hours at 30°C. Atazanavir was then measured in the ultrafiltrate according to a method developed for amprenavir (1). The Amicon Centrifree YM-300 filter system (Millipore Corp. Bedford, MA) with a membrane molecular weight cut off of 30,000 Daltons was used to ultrafiltrate plasma samples. The driving force for ultrafiltration was provided by centrifugation (Jouan, GR 4.11) at 2000 g, at 30°C. Duration of centrifugation was 120 minutes to obtain an ultrafiltrate volume of at least 200 mL from a 500-mL. Atazanavir concentrations in ultrafiltrate were measured by HPLC with separation on a C18 column after liquid-liquid extraction and UV detection at 220 nm. The mobile phase consisted of pH 5.6 phosphate buffer/acetonitrile/methanol (480/110/110, vol/vol) and the flow rate was 1.1 mL/min. Retention times for atazanavir and 6,7-dimethyl-2,3-di-(2-pyridyl)-quinoxaline (internal standard from Sigma Aldrich Chemicals) were 15 and 30 minutes respectively in our chromatographic system.

Unbound fraction was the ratio of unbound atazanavir and total atazanavir concentrations. The graph of the drug bound concentration as a function of the drug unbound concentration depicts the protein binding system (24).

Population pharmacokinetic analysis of atazanavir in patients

Study design and population

ANRS 107–Puzzle 2 was a randomised, open-label, multiple-dose trial evaluating the efficacy and safety of a combination of atazanavir/ritonavir and tenofovir in HIV-infected patients with multiple antiretroviral treatment failures. The study design is detailed elsewhere (22). From week 3 to week 26, all patients received atazanavir/ritonavir (300 mg/100 mg QD) plus tenofovir disoproxil fumarate (300 mg QD equivalent to 245 mg of tenofovir disoproxil or 136 mg of tenofovir) and nucleoside reverse transcriptase inhibitors (NRTIs) selected according to the baseline reverse transcriptase genotype of the HIV isolate infecting each patient. Drugs were administered in the morning with a light continental breakfast.

Before inclusion, all patients gave their written informed consent. The protocol was approved by the Institutional Review Board of Saint Antoine Hospital, Paris VI University. HIV-infected patients were eligible for inclusion if they met the following criteria: documented treatment failure with at least two PIs and one non-nucleoside reverse transcriptase inhibitor, HIV RNA >10 000 copies/mL, no change in antiretroviral treatment within the last month before inclusion in this study, normal liver function.

Plasma collection

Blood samples for biochemical and immuno-virological measurements were drawn at screening and at regular time intervals after inclusion. Blood samples for atazanavir plasma concentrations assay were collected prior to drug intake in the morning at week 6, 1 month after starting the full antiretroviral treatment, atazanavir + ritonavir + tenofovir + optimized background treatment, according to the design of the ANRS107 study (22). For 10 patients included in the pharmacokinetic substudy, additional blood samples were collected after dosing at times 1, 2, 3, 5, 8 and 24 hours (23). Plasma samples were kept at -20°C until analysis. The actual times of drug administration and sampling were recorded.

Drug assays

Atazanavir concentrations were measured in plasma patients samples by validated LC/MS/MS assays (Bristol-Myers Squibb, Saint Nazaire, France). The lower limits of quantification (LOQ) were 1 ng/mL. Day-to-day variabilities for the quality control samples were 5.7 %.

Biochemical and virological measurements

Absolute numbers of CD4 lymphocytes, plasma HIV RNA levels, blood chemistry parameters (albumin, total bilirubin, total cholesterol, triglycerides, alanine and aspartate aminotransferases) were determined according to standard assays (22).

Determination of alpha 1 glycoprotein acid concentrations and phenotypes

Alpha 1 glycoprotein acid plasma concentrations were measured by nephelometry (BN Prospec, Dade Behring). Alpha 1 glycoprotein acid phenotypes (ORM1*S-ORM2*A, ORM1*F1S-ORM2*A and ORM1*F1-ORM2*A) were determined on plasma samples by isoelectric focusing according to the method developed by Eap and Baumann, with some modifications (10).

Population pharmacokinetic modelling

Data at week 6 were analysed using a population approach with the first-order method (WinNonMix version 2.0.1, Pharsight Corporation, Mountain View, CA, USA) and parameterised with the apparent volume of distribution (V/F), the first order absorption rate constant (k_a) and the apparent clearance (Cl/F). The statistical model for the observed plasma concentrations of the drug C_{ij} in patient i at time t_{ij} was given by: $C_{ij} = f(t_{ij}, \theta_i) + \epsilon_{ij}$ where θ_i is the pharmacokinetic parameter vector of patient i , ϵ_{ij} the residual error and f the pharmacokinetic model.

An exponential random-effect model was chosen to describe inter-individual variability: $\theta_i = \theta \exp(\eta_i)$ where θ is the population mean vector of the pharmacokinetic parameters and η_i represents the random effect vector. Random effects were assumed to follow a normal distribution with zero mean and variance matrix Ω which was supposed to be diagonal. Residual variability was modelled using a proportional error model.

Goodness of fit plots (observed versus predicted population and individual concentrations, weighted residuals versus predicted concentrations and versus time) were examined for each model. Tested covariates were age, weight, body mass index, creatinine clearance at week 6, alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) at baseline, plasma alpha 1 glycoprotein acid and albumin concentrations at week 6, alpha 1 glycoprotein acid phenotypes, coinfections (hepatitis B infection and/or hepatitis C infection), ritonavir trough and average concentrations and combined NRTIs. Continuous variables were centred on their median. The sex of the patients was not tested as a covariate because there were only two females in the population. The effects of covariates were tested on each individual parameter (correlation test for continuous variables and ANOVA for categorical variables) using Statgraphics version 5.1 (Manugistics, Inc. Rockville, Maryland, USA). The covariates that were found to have a significant effect ($p < 0.05$) were then evaluated in the population analysis. The effect of a covariate was assessed by the likelihood ratio test. In the forward inclusion process, a covariate was retained in the model if there was a decrease greater than 3.84 in the objective function ($p < 0.05$, 1 degree of freedom) and if there was a decrease in the interindividual variability of the associated pharmacokinetic parameter. From the best model including covariates, a backward elimination procedure was then used to test whether all covariates selected should remain in the final model. When deletion of a covariate ($p < 0.05$) significantly increased the log-likelihood (> 3.84), that covariate was kept in the model.

Results

Atazanavir in vitro binding

In a solution of 0.7 g/L of alpha 1 glycoprotein acid, atazanavir was found to bind to one high affinity saturable site at about 31.1%. The association constant was $4.61 \cdot 10^5$ L/mol and the number of sites 0.61. In a solution of 40 g/L of serum albumin, mean unbound fraction of atazanavir was found to be 21.3% and was constant up to 15000 ng/mL of total atazanavir. This suggested that atazanavir binds to one low-affinity non-saturable site. The number of sites and the affinity constant were not differentiated and the product was estimated as 6352 L/mol. When atazanavir total concentrations were above 15000 ng/mL, atazanavir unbound fraction increase to 30.9%, protein binding sites becoming saturated (figure 1).

Population pharmacokinetic analysis of atazanavir in patients

Patients

Fifty-one patients completed the study at week 6 and ten patients were included in the pharmacokinetic substudy. The characteristics of these 51 patients are summarised in table 1. The NRTIs combined with ritonavir-boosted atazanavir plus tenofovir were lamivudine (n=40), abacavir (n=30), didanosine (n=18), zidovudine (n=15), zalcitabine (n=5) and stavudine (n=2). Twenty-three patients were hepatitis virus B and/or C co-infected.

Alpha 1 glycoprotein acid concentrations and phenotypes

Alpha 1 glycoprotein acid concentrations were 1.0 g/L (0.6–1.5) at week 6 and were elevated in 15 patients (28.8%) accounting for their age and sex.

Five patients had the phenotype ORM1*S-ORM2*A, 19 ORM1*F1-ORM2*A and 28 were heterozygous and presented ORM1*F1S-ORM2*A. The allele ORM1*F2 was not observed in this rather small sample. The allele ORM2*A was monomorphic and observed in all sera of patients. The ORM1 allele frequencies were as follows: 0.635 for ORM1*F1 and 0.365 for ORM1*S. Good agreement was found between observed and expected values, assuming a Hardy-Weinberg equilibrium ($p > 0.5$). Total plasma concentrations of alpha 1 glycoprotein acid were not found to be significantly dependant on alpha 1 glycoprotein acid phenotypes.

Atazanavir model

Basic model

A one-compartment model with first-order absorption and elimination was used to describe atazanavir pharmacokinetics. The population parameter estimates, their relative standard error of estimation (RSE %) and their inter-individual variability for this basic model are shown in table 2 .

Covariates model building

From this basic model, we tested the effects of the covariates on the individual estimates of the random effects. Using the estimated individual parameters, significant effects of hepatitis B and/or C infection on k_a ($p = 0.030$), of plasma alpha 1 glycoprotein acid concentration, didanosine, ALAT level, ASAT level, ritonavir trough and average concentrations on Cl/F ($p = 0.001$; 0.028 ; 0.037 ; 0.017 ; 0.009 ; 0.006 respectively) and of plasma alpha 1 glycoprotein acid concentration, ORM1*S alpha 1 glycoprotein acid phenotype on V/F ($p = 0.009$; 0.008 respectively) were found.

According to the likelihood ratio test, the final population model had plasma alpha 1 glycoprotein acid concentration (AAG), ALAT level effects on Cl/F ($p < 0.01$; $p < 0.01$ respectively) and ORM1*S alpha 1 glycoprotein acid phenotype (ORM1*S) effects on V/F ($p < 0.05$). The equations are:

$$Cl / F_i = (Cl / F - \beta_{CL/F}^{ALAT} (ALAT_i / 29) - \beta_{CL/F}^{AAG} (AAG / 1.0)) \times \exp(\eta_{Cl/F_i})$$

where 29 (IU/L) and 1.0 (g/L) are the median ALAT and AAG levels.

$$V / F_i = (V / F \times \beta_{V/F}^{ORM1*S}) \times \exp(\eta_{V/F_i})$$

The population parameters of this final model and their relative standard errors of estimation are given in table 2 . The goodness of fit plots (not shown) were all very satisfactory for the basic and final models.

The apparent volume of distribution was estimated to be 79.7 L and increased about 2-fold in patients with the ORM1*S phenotype. Absorption rate constant was estimated to be 0.73/h. The apparent clearance was estimated to be 8.1 L/h when ALAT was 29 IU/L and alpha 1 glycoprotein acid level was 1.0 g/L. Median (range) half-life was 6.9 h (4.0–18.2). We found an increase of 34% in mean atazanavir area under the curve (AUC, 47410 ng.h/mL versus 35432 ng.h/mL, $p=0.0004$) and of 12% in mean half-life (7.8 h versus 6.9 h, $p=0.03$) in patients who had an elevated ALAT level (≥ 40 IU/L), compared with patients with a normal ALAT level. A 36% increase in mean atazanavir AUC (49644 ng.h/mL versus 36529 ng.h/mL) and a 28% increase in mean half-life (9 h versus 7 h) were observed in patients with elevated alpha 1 glycoprotein acid (according to their age and sex), compared with those with a normal alpha 1 glycoprotein acid level.

The inter-individual variabilities of absorption rate constant, apparent volume of distribution and apparent clearance were 139.3%, 27.0% and 26.7%, respectively. They were slightly decreased from the basic model by the incorporation of the covariates. Residual variability was 19.9%. Figure 2 shows the model-predicted concentrations and the observed concentrations versus time when ALAT and plasma alpha 1 glycoprotein acid concentrations were 29 IU/L and 1.0 g/L, respectively, in patients with or without the alpha 1 glycoprotein acid ORM1*S phenotype.

Discussion

Atazanavir is a potent and safe HIV PI with a pharmacokinetic profile that allows once daily oral administration and which can be optimised by adding low-dose ritonavir. All patients included in this study received ritonavir boosted atazanavir and a relationship was found between atazanavir clearance and ritonavir concentrations. However variation in ritonavir concentrations was not found to impact atazanavir pharmacokinetics to a significant extent and therefore was not retained in the final model. It is known that protein binding affect

PI disposition (3) and could reduce the antiviral effect of these drugs (13). It was reported that atazanavir binds to both alpha 1 glycoprotein acid and albumin to a similar extent, but binding parameters were unknown (12). Our in vitro data demonstrate that atazanavir has a higher affinity to alpha 1 glycoprotein acid than to albumin. However, alpha 1 glycoprotein acid is present at about 1/40 the concentration of albumin in plasma. Consequently, the binding of atazanavir to alpha 1 glycoprotein acid was saturable above 6000 ng/mL whereas the saturation of albumin appears above 15000 ng/mL of atazanavir. A similar result was already found for saquinavir (15). As for many basic drugs, alpha 1 glycoprotein acid has a high affinity but albumin has a higher capacity for binding (16). In patients treated by atazanavir/ritonavir at the recommended daily dose of 300/100 mg, trough plasma atazanavir concentrations are around 1000 ng/mL. Consequently, alpha 1 glycoprotein acid is the major protein involved in atazanavir binding. These findings are essential because alpha 1 glycoprotein acid concentration can vary considerably as a result of disturbances of homeostasis. It increases during acute or chronic inflammation and infectious disease. HIV-infected patients are therefore likely to exhibit increased concentrations of alpha 1 glycoprotein acid (3, 16, 21). Moreover the alpha 1 glycoprotein acid polymorphism could be responsible for interindividual variation in the plasma binding of protease inhibitors, which might influence their disposition.

The impact of proteins that bind atazanavir on atazanavir pharmacokinetics was evaluated in 51 HIV infected patients having failed several lines of previous antiretroviral treatment and included in the ANRS 107-Puzzle 2 trial. Unfortunately, atazanavir unbound fraction could not be measured in these patients as remaining samples volumes was too low

This is the first population model analysis to explore the possible influence of alpha 1 glycoprotein acid concentrations, alpha 1 glycoprotein acid phenotypes, albumin concentrations, ALAT and ASAT levels and/or hepatitis B and C coinfections on atazanavir pharmacokinetic parameters.

In this very advanced population, alpha 1 glycoprotein acid concentrations remained elevated in 29% of the patients even though they had received a new treatment for 6 weeks. This could be explained by the weak virological response to the new treatment and the lack of effect of the antiretroviral treatment on the inflammation due to HIV infection (22). The relative frequencies of alpha 1 glycoprotein acid phenotypes found here are close to those previously described in healthy subjects or in HIV-infected patients (5, 8). We did not find ORM1*F2 on this population but this variant is present only at a low allelic frequency (9, 19). As already described in healthy subjects, alpha 1 glycoprotein acid plasma concentrations were not found to differ between the 3 phenotypes (18).

To determine atazanavir pharmacokinetic parameters and the influence of protein binding, we used a population approach because only ten patients had a complete pharmacokinetic profile. The pharmacokinetics of atazanavir was described by a one-compartment model with first-order absorption and first-order elimination with random effects on k_a , V/F and Cl/F. This structural model was similar to that of Dailly et al. and Colombo et al., although Colombo et al. described a first-order absorption with a lag time (4, 6). Our estimation of atazanavir pharmacokinetic parameters, apparent volume of distribution, absorption rate constant, apparent clearance and half-life are in the same range as those of previous studies (4, 6, 17, 23). The atazanavir apparent clearance of 9.8 L/h demonstrates that atazanavir has low extraction ratio with clearance depending on the unbound fraction and intrinsic clearance. The atazanavir apparent volume of distribution of 78 L (1.2 L/kg) indicates that plasma protein binding is not a restricting factor to body distribution. Assuming that pharmacologic effect is related to exposure to unbound drug concentrations (AUC_u), which after oral administration, depends on the fraction absorbed through the gut wall, the dose and the intrinsic clearance as demonstrated by Benet and Hoener (2), any change in total drug concentrations should not have clinical consequences. Large inter-individual variability was found for k_a (139.3%) as variable absorption of PIs has already been described.

We found that the apparent clearance of atazanavir decreases with increasing plasma alpha 1 glycoprotein acid concentration. A similar effect was previously reported for lopinavir and indinavir clearance (5). This result suggests that elevated alpha 1 glycoprotein acid concentrations could decrease the protein unbound fraction of atazanavir, leading to increased total atazanavir concentrations, but without change in unbound atazanavir concentrations linked to drug efficacy (2).

Interestingly, we found that atazanavir apparent volume of distribution decreases with increased with alpha 1 glycoprotein acid concentrations and increases with the ORM1*S phenotype. This suggests that atazanavir may preferentially bind to the ORM1*F1 variant, compared with the ORM1*S variant. Unfortunately, this hypothesis could not be tested in vitro as human plasma samples tested for alpha 1 glycoprotein acid variants were not available. In contrast, it was suggested that lopinavir and indinavir may preferentially bind to the ORM1*S variant (5). There are conflicting data on preferential binding of neutral and basic drugs such as quinidine to ORM1*S and ORM1*F1 (18, 20). In vitro drug-binding studies are warranted to determine the possible different capacities of the ORM1 variants.

Overall, increases in alpha 1 glycoprotein acid lead to a modest 28% increase in atazanavir half life which should not have any clinical consequence, but could contribute to the interindividual variability of atazanavir pharmacokinetics although to a lesser extent than absorption or CYP3A activity.

We found that the apparent clearance of atazanavir decreases with increasing ALAT. This was expected as atazanavir, like other PIs, is extensively metabolised by hepatic CYP3A isoenzymes, which are decreased in patients with liver failure and directly affect the intrinsic

clearance. However, such a relationship is remarkable as liver dysfunction was mild to moderate in our patients. A 42% increase in AUC and longer terminal half-life (12 versus 6 hours) have been reported in volunteers with hepatic impairment (Child-Pugh grade B or C), compared with healthy volunteers (12). In the present study, we found a similar increase in atazanavir AUC and half-life in patients who had an elevated ALAT level. Our data, although limited, could suggest that high atazanavir concentrations are expected with severe liver dysfunction. As previously described, age, body weight and body mass index did not influence atazanavir pharmacokinetics (4). Most of our patients were males, so no influence of sex on atazanavir pharmacokinetics could be detected. In keeping with our *in vitro* data, atazanavir pharmacokinetics was not influenced by albumin concentrations; however in these patients, there was a small variability in albumin concentrations.

In conclusion, this study demonstrates that atazanavir pharmacokinetics is modestly influenced by its protein binding, especially to alpha 1 glycoprotein acid. The effect of alpha 1 glycoprotein acid concentrations or polymorphisms or liver enzyme elevations on the unbound moiety able to cross biologic membranes and exert a pharmacologic effect is unknown as is therefore, the potential clinical significance, and that this is a limitation of this work.

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Figure 1

Bound atazanavir concentrations versus unbound atazanavir concentrations in solutions of orosomucoid (solid circles) and albumin (open circles). The curve is an ordinary least-square fit of the Emax model to the data using WinNonLin.

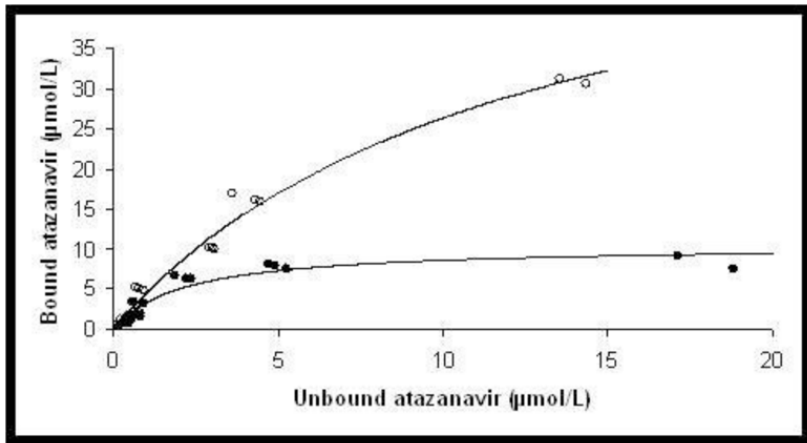


Figure 2

Observed atazanavir concentrations (solid circles in patients with the ORM1*S phenotype and open circles in patients without the ORM1*S phenotype) and predicted population concentrations for median ALAT (29 IU/L) and median orosomucoid (1.0 g/L) in patients with (continuous line) or without (dashed line) the ORM1*S phenotype versus time, at week 6.

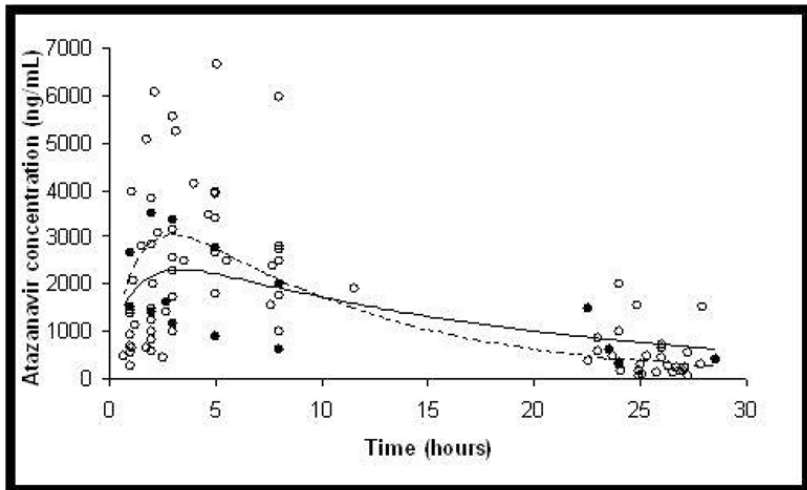


Table 1

Characteristics of the 51 patients included in the population pharmacokinetic analysis

	Median	min-max
Age (years)	41	29–62
Week 6 weight (kg)	65.6	45.0–105.6
Week 6 body mass index (kg/m ²)	21.3	17.0–33.6
Baseline ALAT level (IU/L)	29	5–114
Baseline ASAT level (IU/L)	29	16–149
Week 6 ALAT (IU/L)	38	7–175
Week 6 creatinine clearance (mL/min)	87	23–178
Week 6 albumin (g/L)	40.4	31.2–47.7
Week 6 orosomuroid (g/L)	1.0	0.6–1.5

ALAT: alanine aminotransferase

ASAT: aspartate aminotransferase

Table 2

Population pharmacokinetic parameters of atazanavir (estimates and relative standard errors of estimation) for the basic model and for the final model

Parameters	Basic model		Final model	
	Estimate	RSE (%)	Estimate	RSE (%)
ka (h ⁻¹)	0.75	7.6	0.73	10.7
Cl/F (L/h)	7.8	9.0	13.3	13.2
$\beta_{Cl/F}^{ALAT}$	-	-	0.86	35.0
$\beta_{Cl/F}^{AAG}$	-	-	4.3	46.9
V/F (L)	78.2	10.5	79.7	10.5
$\beta_{V/F}^{ORM1*S}$	-	-	1.9	32.8
ω_{ka} (%)	138.7	21.0 ^a	139.3	26.2 ^a
$\omega_{Cl/F}$ (%)	43.4	54.4 ^a	26.7	27.8 ^a
$\omega_{V/F}$ (%)	31.1	64.8 ^a	27.0	102.2 ^a
σ (%)	18.3	37.2 ^a	19.9	50.3 ^a

^a RSE for ω_{ka}^2 , $\omega_{V/F}^2$, $\omega_{Cl/F}^2$ and σ^2

ka: absorption rate constant, Cl/F: apparent clearance, V/F: apparent volume of distribution

 $\beta_{Cl/F}^{ALAT}$: facteur associated with ALAT concentrations on atazanavir Cl/F $\beta_{Cl/F}^{AAG}$: facteur associated with AAG concentrations on atazanavir Cl/F $\beta_{V/F}^{ORM1*S}$: facteur associated with ORM1*S phenotype on atazanavir V/F ω_{ka} , $\omega_{Cl/F}$, $\omega_{V/F}$: inter individual variabilities for ka, Cl/F and V/F respectively σ : residual error