Pharmacokinetics and inhibitory quotient of atazanavir/ritonavir versus lopinavir/ritonavir in HIV-infected, treatment-naive patients who participated in the CASTLE Study

Li Zhu1*, Shanmei Liao1†, Michael Child1, Jenny Zhang1, Anna Persson1, Heather Sevinsky1, Timothy Eley1, Xiaohui Xu1, Mark Krystal1, Awny Farajallah1, Donnie McGrath1, Jean-Michel Molina2 and Richard Bertz1

1Bristol-Myers Squibb, Research and Development, Princeton, NJ, USA; 2Department of Infectious Diseases, Saint-Louis Hospital, AP-HP, Paris, France and University of Paris-Diderot, Paris 7, France

*Corresponding author. Tel: +1-609-818-8155; Fax: +1-609-818-3220; E-mail: li.zhu@bms.com
†Present address: 5/F Tower 1, German Center, 88 Keyuan Road, Pudong Zhongjiang Hi-Tech Park, Shanghai 201203, P. R. China.

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Objectives: To characterize the pharmacokinetics and inhibitory quotient (IQ) of atazanavir/ritonavir- and lopinavir/ritonavir-based regimens in HIV-infected, treatment-naive patients.

Methods: The CASTLE Study was a 96 week randomized study comparing 300 mg of atazanavir once daily with 400 mg of lopinavir twice daily, each with low-dose ritonavir (100 mg) plus tenofovir disoproxil fumarate/emtricitabine in HIV-infected, treatment-naive patients. A subset of patients participated in an intensive pharmacokinetic evaluation of the atazanavir regimen (n=18) and the lopinavir regimen (n=21) at week 4. (ClinicalTrials.gov NCT00272779)

Results: Atazanavir geometric mean (CV%) Cmax, Cmin and AUC over the dosing interval were 2897 (46) ng/mL, 526 (57) ng/mL and 28605 (46) ng·h/mL, respectively, and for lopinavir they were 10655 (51) ng/mL, 5944 (68) ng/mL and 90946 (59) ng·h/mL, respectively. The baseline protein binding-adjusted 90% effective concentration (PBA-EC90) was 16 (44) ng/mL for atazanavir and 173 (44) ng/mL for lopinavir. The median IQ (min, max), calculated as the ratio of Cmin to individual baseline PBA-EC90, was 35 (4, 77) for atazanavir and 34 (11, 129) for lopinavir. The Cmax for ritonavir was 46% higher, while AU0–24 and Cmin were 16% and 72% lower in the atazanavir regimen compared with the lopinavir regimen. Tenofovir exposures were similar with both treatments.

Conclusions: Atazanavir (300 mg once daily) and lopinavir (400 mg twice daily), each with low-dose ritonavir, achieved similar IQs in HIV-infected, treatment-naive patients. These results are supportive of the main clinical finding of the CASTLE Study, that the atazanavir/ritonavir-based regimen is non-inferior in antiviral efficacy to the lopinavir/ritonavir-based regimen in antiretroviral-naive subjects.

Keywords: protease inhibitors, antiretroviral therapy, clinical pharmacology

Introduction

Atazanavir is a potent, once-daily HIV-1 protease inhibitor (PI) used in combination with other antiretroviral (ARV) agents for the treatment of HIV-1 infection. PI-based ARV regimens are among the preferred options for treatment-naive patients, and selecting an initial ARV therapy to achieve sustained virological response requires balanced consideration of pharmacokinetics, efficacy, viral susceptibility, tolerability and dosing simplicity. Most PIs, including atazanavir and lopinavir, are substrates of cytochrome p450 3A4 and therefore benefit from a ‘boost’ in drug exposure when co-administered with low-dose ritonavir, which potently inhibits cytochrome p450 3A4. Inhibitory quotient (IQ) is a concept of maintaining adequate in vivo drug exposure needed for replication inhibition relative to an in vitro measure of viral susceptibility to the ARV agent. There are conflicting results regarding the value of IQ as an independent predictor of virological response, with cases of success reported in PI-experienced cohorts. The utility of IQ may also extend to PI-naive patients, especially in cases where resistant virus is transmitted. This study examined whether IQ can serve as a better surrogate comparator than pharmacokinetic properties or viral susceptibility alone when comparing PI-based regimens.
As HIV becomes a manageable chronic disease, there is a growing need for treatments with favourable safety profiles that promote adherence and improve morbidity and mortality in the long term. Ritonavir, even at low doses, is associated with frequent side effects such as diarrhea and nausea, the severity of which may increase with higher doses or more frequent dosing. In addition, renal toxicities, including acute renal necrosis and Fanconi syndrome, have been reported with tenofovir disoproxil fumarate (TDF). Co-administration with atazanavir/ritonavir or lopinavir/ritonavir increases tenofovir exposures by 32%–37%, thus raising concerns of increased incidence of nephrotoxicity. This study examined the comparative exposures by 32%–37%, thus raising concerns of increased incidence of nephrotoxicity. This study examined the comparative exposures of ritonavir and tenofovir when co-administered in a fixed-dose regimen with atazanavir or lopinavir.

Patients and methods

Study design

The CASTLE Study was a 96 week, randomized, open-label study comparing 300/100 mg of atazanavir/ritonavir once daily with 400/100 mg of lopinavir/ritonavir twice daily, both in combination with 300/200 mg of TDF/emtricitabine once daily in treatment-naive, HIV-infected patients. A subset of subjects provided written informed consent to participate in the pharmacokinetic sub-study reported here. The study was performed in accordance with the ethical principles of the Declaration of Helsinki. (ClinicalTrials.gov NCT00272779)

Blood sampling

Serial blood samples were collected at week 4 after observed dosing. All drugs were dosed with food. Samples for atazanavir/ritonavir and tenofovir were collected at 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 h. Samples for lopinavir/ritonavir were collected at 0, 1, 2, 3, 4, 6, 8 and 12 h. Blood samples were collected in EDTA-containing tubes, centrifuged and stored frozen until analysed. Plasma concentrations for all analytes were determined by validated HPLC/tandem mass-spectroscopy methods.

Pharmacokinetic analysis

Plasma concentrations versus time data were analysed by non-compartmental methods using Kinetica v4.4.1 (Thermo Electron Corporation, Philadelphia, PA, USA). Pharmacokinetic parameters evaluated included Cmax, Tmax and trough plasma concentration (Cmin) at 12 h post-dose (twice-daily regimen) or 24 h post-dose (once-daily regimen); AUC over a dosing interval (AUC0–24) was calculated by linear and log-linear trapezoidal summations. AUC0–24 for the lopinavir/ritonavir regimen was estimated as 2 × AUC0–12.

IQ was defined as atazanavir or lopinavir Cmin at week 4 divided by the respective protein binding-adjusted 90% effective concentration (PBA-EC90) derived from individual clinical isolates collected at baseline. Baseline EC90 was measured using the PhenoSense HIV assay (Monogram Biosciences, Inc., San Francisco, CA, USA) and converted into PBA-EC90 using the following formula:

\[
PBA-EC90 (\text{ng/mL}) = \text{sc} \times \text{MW} \times \text{EC90 (\mu M)/fu},
\]

where sc is the scaling factor to estimate EC90 from EC50 [sc = 3 for atazanavir (unpublished data; Bristol-Myers Squibb internal document) and sc = 2 for lopinavir], MW is the free base molecular weight (704.9 for atazanavir and 628.8 for lopinavir) and fu is the reported unbound fraction in human plasma (14% for atazanavir and 1%–2% for lopinavir). The conservative fu value of 2% was used for lopinavir calculation.

Statistics

Analyses of variance were performed on log(IQ) for the comparison of atazanavir IQ with lopinavir IQ, and on log(Cmax), log(AUC) and log(Cmin) for ritonavir and tenofovir to assess the effect of treatment regimen on ritonavir and tenofovir exposure. Point estimates and 90% CIs for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale. No adjustments were made for multiplicity. All statistical analyses were performed using SAS/STAT® v8.2 (SAS Institute Inc., Cary, NC, USA).

Results

Demographics

Eighteen subjects on the atazanavir/ritonavir regimen and 21 subjects on the lopinavir/ritonavir regimen were evaluated in the pharmacokinetic sub-study. Participants were predominantly male (72%), Caucasian (62%) and from North or South America (69%), with a median (range) age of 39 (22–64) years, weight of 67 (46–100) kg and body mass index of 24.1 (18.3–31.1) kg/m². The demographic characteristics of the pharmacokinetic sub-population were similar to those in the main CASTLE Study. The median (range) baseline HIV RNA values for subjects in the pharmacokinetic sub-study were 5.05 (4.04–5.88) and 4.85 (3.47–5.82) log10 copies/mL for atazanavir/ritonavir and lopinavir/ritonavir regimens, respectively; the corresponding HIV RNA values at week 4 around intensive pharmacokinetic collection were 2.59 (1.69–3.56) and 2.47 (1.69–3.81) log10 copies/mL, respectively. Additionally, at baseline, no subjects in the pharmacokinetic sub-study had major PI-resistance substitutions for either atazanavir or lopinavir.

Atazanavir and lopinavir pharmacokinetics

All individual Cmin for both atazanavir and lopinavir were well above their respective PBA-EC90 values. Table 1 summarizes the pharmacokinetic parameters, individual PBA-EC90 and IQs. The geometric mean PBA-EC90 (CV%) obtained from these treatment-naive subjects were 16 ng/mL (44) for atazanavir and 173 ng/mL (44) for lopinavir, similar to the previously reported values of 14 ng/mL for atazanavir (data on file) and 140 ng/mL for lopinavir. Although the geometric mean IQ for atazanavir was 24% lower than that of lopinavir (ratio of geometric means 0.76; 90% CI 0.51, 1.14), there was considerable overlap in the observed individual IQ values in the two regimens, and the median IQs for the regimens were similar.

Ritonavir and tenofovir pharmacokinetics

The geometric mean (90% CI) ritonavir Cmax was 46% (0%–112%) higher and the Cmin was 72% (56%–82%) lower in the atazanavir regimen (100 mg of ritonavir once daily) compared with the lopinavir regimen (100 mg of ritonavir twice daily) (Table 2). The ritonavir AUC0–24 was similar in the atazanavir and lopinavir regimens. Tenofovir exposure was similar when co-administered with either atazanavir/ritonavir or lopinavir/
ritonavir (geometric mean ratios for tenofovir $C_{\text{max}}$, $AUC_{t}$ and $C_{\text{min}}$ were all close to 1).

**Discussion**

The CASTLE Study results showed the atazanavir/ritonavir-based regimen to be non-inferior in antiviral efficacy to the lopinavir/ritonavir-based regimen. The pharmacokinetic findings—in particular, comparable IQs between the two regimens—are consistent with these efficacy results. Boosted by ritonavir, both atazanavir and lopinavir plasma concentrations were well above their respective individual as well as historical population mean PBA-EC$_{90}$ values throughout the measured dosing periods.

Plasma protein binding attenuates in vivo ARV activities of PIs, with greater effects on highly protein-bound drugs. When taking plasma protein binding into consideration (86% for atazanavir and 98%–99% for lopinavir), the geometric mean PBA-EC$_{90}$ is 16 ng/mL for atazanavir and 173 ng/mL for lopinavir. This suggests that atazanavir has a protein binding-adjusted potency at least 10-fold higher than lopinavir. Therefore, despite the finding that the geometric mean atazanavir $C_{\text{min}}$ is

### Table 1. Summary of the pharmacokinetic parameters, PBA-EC$_{90}$ and IQs for atazanavir and lopinavir

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Atazanavir</th>
<th>Lopinavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL), geometric mean (CV%)</td>
<td>2897 (46)</td>
<td>10655 (51)</td>
</tr>
<tr>
<td>$AUC_{t}$ (ng.h/mL)$^{a}$, geometric mean (CV%)</td>
<td>28605 (46)</td>
<td>90946 (59)</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (ng/mL)$^{b}$, geometric mean (CV%)</td>
<td>526 (57)</td>
<td>5944 (68)</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h), median (min, max)</td>
<td>3.0 (1.5, 24.0)</td>
<td>4.0 (0.0, 12.0)</td>
</tr>
<tr>
<td>PBA-EC$_{90}$ (ng/mL) at baseline$^{c}$</td>
<td>16 (44)</td>
<td>173 (44)</td>
</tr>
<tr>
<td>geometric mean (CV%)</td>
<td>15 (8, 35)</td>
<td>170 (75, 472)</td>
</tr>
<tr>
<td>IQ at week 4$^{d}$</td>
<td>27 (60)</td>
<td>36 (68)</td>
</tr>
<tr>
<td>geometric mean (CV%)</td>
<td>35 (4, 77)</td>
<td>34 (11, 129)</td>
</tr>
<tr>
<td>GMR$^{e}$ (90% CI) for IQ</td>
<td>0.76 (0.51, 1.14)</td>
<td></td>
</tr>
</tbody>
</table>

$^{a}$ $t$ equals 24 h and 12 h dosing regimens for atazanavir/ritonavir and lopinavir/ritonavir, respectively.

$^{b}$ $C_{\text{min}}$ defined as concentration at 24 h and 12 h for atazanavir/ritonavir and lopinavir/ritonavir, respectively.

$^{c}$ Summary includes all subjects in the pharmacokinetic sub-study who had baseline phenotype data. Three subjects had baseline PBA-EC$_{90}$ missing.

$^{d}$ IQ values were not available for one subject in the atazanavir regimen and two subjects in the lopinavir regimen due to missing baseline phenotype data.

$^{e}$ Geometric mean ratio (atazanavir over lopinavir).

### Table 2. Summary of the pharmacokinetic parameters for ritonavir and tenofovir

<table>
<thead>
<tr>
<th></th>
<th>Ritonavir</th>
<th>Tenofovir</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>atazanavir/ritonavir</td>
<td>lopinavir/ritonavir</td>
</tr>
<tr>
<td>$n$</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL), geometric mean (CV%)</td>
<td>960 (55)</td>
<td>657 (60)</td>
</tr>
<tr>
<td>$AUC_{0-24}$ (ng.h/mL)$^{a}$, geometric mean (CV%)</td>
<td>6725 (63)</td>
<td>8012 (51)</td>
</tr>
<tr>
<td>$C_{\text{min}}$ (ng/mL), geometric mean (CV%)</td>
<td>50.5 (99)</td>
<td>179 (87)</td>
</tr>
</tbody>
</table>

$^{a}$ The dose of ritonavir is 100 mg once daily with atazanavir and is 100 mg twice daily with lopinavir.

$^{b}$ One subject on the atazanavir/ritonavir regimen and one subject on the lopinavir/ritonavir regimen had tenofovir pharmacokinetic samples missing.

$^{c}$ Geometric mean ratio (atazanavir over lopinavir).

$^{d}$ One subject was excluded due to reduced renal function subsequent to pneumonia with dehydration at the time of intensive pharmacokinetic sampling. The excluded values for $C_{\text{max}}$, $AUC_{t}$, and $C_{\text{min}}$ were 1802 ng/mL, 25386 ng.h/mL and 757 ng/mL, respectively.

$^{e}$ For ritonavir, $AUC_{0-24}$ is defined as $AUC_{t}$ for the atazanavir/ritonavir regimen and $2 \times AUC_{t}$ for the lopinavir/ritonavir regimen.
approximately 1/10 that of lopinavir, the calculated IQs are in fact comparable between the two compounds. This supports the similar in vivo ARV activity of the two regimens observed in these HIV-infected, treatment-naive patients.

Lambert-Niclot et al.\textsuperscript{10} recently studied a population of 100 treatment-naive patients who received 300/100 mg of atazanavir/ritonavir once daily with two nucleoside reverse transcriptase inhibitors (NRTIs) and reported a median atazanavir trough level of 635 ng/mL and median protein binding-adjusted IQ of 45, approximately 20% higher than that observed in the current study. This discrepancy might be partly attributable to the fact that only 41% of patients in the report of Lambert-Niclot et al.\textsuperscript{10} received TDF, compared with all subjects in this study. Co-administration with TDF is known to decrease atazanavir AUC\textsubscript{0–24} administered with either atazanavir/ritonavir or lopinavir/ritonavir regimen.

These results suggest lopinavir may contribute to treatment-related gastrointestinal adverse events observed with the lopinavir/ritonavir regimen.

Tenofovir exposure increases approximately 32%–37% when administered with either atazanavir/ritonavir or lopinavir/ritonavir.\textsuperscript{5} In the current study, the tenofovir geometric mean C\textsubscript{max}, AUC\textsubscript{0–24}, and C\textsubscript{min} differed by no more than 5% between the two regimens, suggesting similar effects of atazanavir/ritonavir or lopinavir/ritonavir on tenofovir pharmacokinetics. These observations are consistent with the finding of the main study that creatinine clearance changes at 48 weeks were minimal with either regimen (−1%).\textsuperscript{5}

Conclusions

The comparative pharmacokinetic sub-study results show that 300 mg of atazanavir once daily and 400 mg of lopinavir twice daily, each with low-dose ritonavir, achieved similar IQs and are supportive of the efficacy findings of the main CASTLE Study that the atazanavir/ritonavir regimen has similar (non-inferior) efficacy compared with lopinavir/ritonavir in HIV-infected treatment-naive patients.

Acknowledgements

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Transparency declarations

L. Z., M. C., J. Z., A. P., H. S., T. E., X. X., M. K., A. F., D. M. and R. B. are employees of Bristol-Myers Squibb and own stock or options in the company. S. L. was an employee of Bristol-Myers Squibb at the time of the study and analysis. J.-M. M. has received consulting and speaker fees from Bristol-Myers Squibb, Abbott Laboratories and Gilead Sciences.

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