Pharmacokinetic Properties and Tolerability of Bevirimat and Atazanavir in Healthy Volunteers: An Open-Label, Parallel-Group Study

David E. Martin, PharmD, MBA[1]; Hal Galbraith, PharmD[2]; Jared Schettler, MS[2]; Corey Ellis, MS[1]; and Judy Doto, BSN[1]

[1]Panacos Pharmaceuticals Inc., Gaithersburg, Maryland; and [2]Quintiles Inc., Overland Park, Kansas

ABSTRACT

Background: Bevirimat, an inhibitor of HIV-1 maturation, is currently in clinical development for the treatment of HIV-1 infection. It undergoes glucuronidation via uridine diphosphate glucuronosyltransferases (UGTs). The protease inhibitor atazanavir is a potent inhibitor of UGT1A1. Because of this inhibition, high atazanavir plasma levels are associated with increases in plasma bilirubin.

Objectives: The purposes of this study were to assess the pharmacokinetic (PK) properties and tolerability profiles of bevirimat administered as monotherapy and in combination with atazanavir.

Methods: This was an open-label, parallel-group study in healthy volunteers. Nonsmoking men and women aged 18 to 60 years were eligible for inclusion in the study. After being stratified in a 1:1 ratio by sex, subjects were randomly assigned to 1 of 2 groups to receive bevirimat 200 mg/d for 14 days or atazanavir 400 mg/d on days 1 through 21 and bevirimat 200 mg/d on days 8 through 21. Bevirimat PK properties were assessed on day 14 in the monotherapy group and on day 21 in the combination group. Atazanivir PK properties were assessed on days 7 and 21 in the combination group. Serum bilirubin was assessed daily. Tolerability was assessed by monitoring of adverse events using physical examination and clinical laboratory evaluation, including recording of vital signs and electrocardiography throughout the study.

Results: A total of 48 healthy volunteers (24 men, 24 women; mean age, 33 years; mean weight, 83.6 kg; mean body mass index, 27.8 kg/m^2) were included in the study. There were no significant between-group effects on the PK properties with respect to geometric least squares mean ratios of C_{max} and $AUC_{0-\tau}$ (95.9 [90% CI, 84.5–108.8] and 92.0 [90% CI, 80.5–105.2], bevirimat monotherapy vs bevirimat + atazanivir, respectively; and 93.9 [90% CI, 82.3–107.1] and 94.1 [90% CI, 78.2–113.1], atazanivir monotherapy vs bevirimat + atazanivir, respectively). Bevirimat was not associated with any significant changes from baseline in serum bilirubin concentrations, whereas 7-day atazanavir monotherapy was associated with a ~5-fold increase. Coadministration was not associated with significant bilirubin concentration elevations compared with the administration of atazanavir alone. Dosing was discontinued in 4 subjects (atazanavir-induced hyperbilirubinemia, 3; atazanavir-induced rash, 1). In addition, 17 subjects (35.4%) experienced treatment-emergent adverse events including: ocular icterus, 5; headache, 5; unconjugated blood bilirubin increases, 4; diarrhea, 3; upper respiratory tract infection, 3; and yellow skin, 3.

Conclusions: In this study, there were no significant differences in PK properties in atazanavir or bevirimat administered as monotherapy or in combination in this small, select group of healthy volunteers. The coadministration of bevirimat and atazanavir was reasonably well tolerated. Bevirimat did not significantly increase serum bilirubin concentrations and had no significant effect on atazanavir-induced hyperbilirubinemia, potentially providing a further option in the management of HIV-1 infection following evaluation in HIV-infected patients. (*Clin Ther*. 2008;30:1794–1805) © 2008 Excerpta Medica Inc.

Key words: bevirimat, atazanavir, interaction, pharmacokinetic, tolerability.

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INTRODUCTION

Although highly active antiretroviral therapy (HAART) regimens are effective in reducing mortality and morbidity in patients with HIV-1 infection, problems resulting from antiretroviral resistance and drug interactions necessitate the continuing development of new therapies.[1] This need has focused attention on new therapeutic targets, such as HIV-1 maturation. Cleavage of the Group-specific antigen (Gag) precursor protein, Pr55Gag, by viral protease, yielding mature Gag proteins such as matrix, capsid, nucleocapsid, and p6 proteins, is a critical step in HIV-1 particle assembly[2] and results in a highly ordered Gag-processing cascade.[3–5] The efficiency with which viral protease cleaves its target sequences varies widely. However, even partial inhibition of Gag processing markedly impairs viral maturation and infectivity,[6] making this a potentially valuable therapeutic target in the management of HIV-1 infection.

Bevirimat* is an inhibitor of the final stage in Gag processing (ie, the release of the viral capsid protein [CA or p24] from its precursor). This step causes a conformational change in the viral core resulting in the formation of the mature, infectious conical core structure[7]; hence, inhibition of this step by bevirimat results in defective core condensation and the release of noninfectious particles from infected cells, thereby blocking the spread of infection.[8] Bevirimat has been reported to be a potent inhibitor of HIV-1 maturation, including strains resistant to other antiretroviral agents, both in vitro[9] and in vivo.[10] Bevirimat undergoes glucuronidation mediated by uridine diphosphate glucuronosyltransferases (UGT)-1A3 and -2B7[11] and is a weak inhibitor of UGT1A1 at high concentrations.[12]

The protease inhibitor atazanavir† is a potent inhibitor of UGT1A1, and this inhibition is believed to be associated with the hyperbilirubinemia that has been reported with this agent.[13] Elevations in bilirubin during coadministration of bevirimat with atazanavir were therefore considered to be associated with increased atazanavir levels due to drug interaction.[13] Because bevirimat and atazanavir may be coadministered in future anti-HIV-1 regimens, this study sought to investigate the potential impact on bilirubin concentrations and pharmacokinetic (PK) interactions between bevirimat and atazanavir in healthy volunteers.

SUBJECTS AND METHODS

This open-label, parallel-group study was conducted at Bio-Kinetic Clinical Applications, Inc., Springfield, Missouri. The study protocol was approved by the local institutional review board at Bio-Kinetic Clinical Applications, Inc., and written informed consent was obtained from all subjects prior to the commencement of the study. All study procedures were carried out in accordance with the Good Clinical Practice guidelines.

Subjects

Nonsmoking men and women aged 18 to 60 years were eligible for inclusion in the study. Subjects were recruited through local newspaper advertisement. Subjects were required to be in good health, as determined by medical history, physical examination (performed prior to study commencement), and clinical laboratory evaluation, including serum chemistry, coagulation, hematology, and urinalysis. An additional inclusion criterion was a body mass index of between 18.5 and 35 kg/m^2. Women were required to have a documented negative pregnancy test and to be willing to use double-barrier contraception throughout the study if they were of childbearing potential. Principal exclusion criteria included significant medical or psychiatric illness, Gilbert's syndrome (diagnosed on the basis of clinical history), positive screening results using standard laboratory tests for hepatitis B or C, positive test results for HIV-1 antibodies (enzyme immunoassay confirmed by Western blot), and use of prescription or over-the-counter medication within 1 week prior to receiving study treatment (or 60 days for drugs with an elimination phase $t_{1/2}$ >10 days). The subjects received compensation for their participation in the study.

Study Design

After being stratified in a 1:1 ratio by sex, subjects were randomly assigned to 1 of 2 groups to receive bevirimat 200 mg/d for 14 days or atazanavir 400 mg/d on days 1 through 21 and bevirimat 200 mg/d on days 8 through 21. Medication was administered once daily with 240 mL of water following a light snack. All drugs were administered at the clinic under medical supervision. The use of caffeine or xanthine-

*Formerly PA-457 (Panacos Pharmaceuticals Inc., Gaithersburg, Maryland).

†Trademark: Reyataz® (Bristol-Myers Squibb Company, Princeton, New Jersey).