Genetic Factors Influencing Severe Atazanavir-Associated Hyperbilirubinemia in a Population with Low UDP-Glucuronosyltransferase 1A1*28 Allele Frequency

Wan Beom Park,[a] Pyoeng Gyun Choe,[a] Kyoung-Ho Song, Jae Hyun Jeon, Sang Won Park, Hong Bin Kim, Nam Joong Kim, Myoung-don Oh, and Kang Won Choe

Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

Background. High prevalence of severe atazanavir-associated hyperbilirubinemia in Asians with low prevalence of the UDP-glucuronosyltransferase (UGT)1A1*28 polymorphism suggests the importance of genetic factors other than UGT1A1*28 for atazanavir-associated hyperbilirubinemia in these populations.

Methods. Serum bilirubin levels were measured in 129 Korean human immunodeficiency virus–infected patients 3 months after initiation of atazanavir (400 mg per day) with good adherence to medication. The multidrug resistance gene 1 (MDR1) C3435T and G2677T/A variations and UGT1A1*6 and *28 were examined by direct sequencing of DNA from peripheral whole blood samples. The associations between genetic polymorphisms and severe (grade 3–4) hyperbilirubinemia were evaluated using multivariate logistic regression analysis including demographic and clinical variables.

Results. The median patient age was 39 years (interquartile range, 34–51 years), and 91% were men. At baseline, the median CD4 cell count was 261 cells/μL (interquartile range, 181–405 cells/μL). Severe hyperbilirubinemia was detected in 27 patients (21%). The independent risk factors for severe hyperbilirubinemia were low baseline CD4 cell count (adjusted odds ratio per 10 cells/μL increase, 0.97; 95% confidence interval, 0.94–0.99), UGT1A1*28 (adjusted odds ratio, 4.15; 95% confidence interval, 1.46–11.84), and MDR1 G2677T/A (adjusted odds ratio, 9.65; 95% confidence interval, 1.09–85.61). Of 19 patients with wild-type alleles for both MDR1 2677 and UGT1A1*28, none developed severe hyperbilirubinemia.

Conclusion. The MDR1 G2677T/A variation and UGT1A1*28 are independent risk factors for severe atazanavir-associated hyperbilirubinemia in Korean human immunodeficiency virus–infected patients.

Atazanavir is a human immunodeficiency virus (HIV) protease inhibitor associated with a clinically benign but potentially stigmatizing unconjugated hyperbilirubinemia; under conditions of severe hyperbilirubinemia, jaundice frequently develops, which often results in drug discontinuation [1]. It is well documented that atazanavir-associated hyperbilirubinemia is linked to a UDP-glucuronosyltransferase (UGT) promoter variant that contains 7 thymine adenine (TA) nucleotide repeats, A(TA)$_7$TAA (UGT1A1*28), compared with the common promoter that contains only 6 TA repeats [2]; the UGT1A1*28 promoter is less transcriptionally active than the common promoter. This pathophysiology is similar to that of Gilbert syndrome, which is the most common inheritable condition leading to transient unconjugated hyperbilirubinemia [3].

The frequency of the UGT1A1*28 allele is much lower in Asians, including Koreans (13%), Chinese (16%), and Japanese (11%), compared with Caucasians (36%–39%) and African Americans (43%) [4–6]. However, we previously found a similar prevalence of severe atazanavir-associated hyperbilirubinemia in Koreans and Caucasians [7]. These findings suggest that genetic

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[a] W.B.P. and P.G.C. contributed equally to this work.

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Reprints or correspondence: Dr Myoung-don Oh, Dept of Internal Medicine, Seoul National University College of Medicine, 28 Yeongun-dong, Chongro-gu, Seoul, Republic of Korea, 110-744 (mdohmd@snu.ac.kr).

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factors other than UGT1A1*28 may play a role in the development of atazanavir-associated hyperbilirubinemia in Asians.

The multidrug resistance gene 1 (MDR1) encodes a transmembrane transporter, the P-glycoprotein (P-gp), that functions in the absorption and distribution of most HIV-1 protease inhibitors [8]. Data on the association between MDR1 polymorphisms and atazanavir-associated hyperbilirubinemia remain controversial [1]. Rodriguez-Nóvoa et al [9] suggested that a polymorphism in MDR1 (C3435T) was associated with lower concentrations of atazanavir and a reduced risk for hyperbilirubinemia in Caucasians. In contrast, Ma et al [10] did not find an association between MDR1 C3435T or G2677T and concentration of atazanavir in several populations, including African-Americans, Caucasians, and Hispanics. However, to our knowledge, no study has investigated the relationship between MDR1 polymorphisms and atazanavir-associated hyperbilirubinemia in Asians.

In addition, other polymorphisms in the UGT gene may also affect the development of atazanavir-associated hyperbilirubinemia in Asians. The UGT1A1*6 polymorphism (G211A, G71R), which is common in some Asians (13%–23%) and rare in Caucasians (0.1%) [3], results in an ~70% reduction in the rate of bilirubin glucuronidation in vitro [11] and is associated with Gilbert syndrome in Asians, irrespective of the UGT1A1*28 allele [6, 12]. In addition, Boyd et al [13] reported that UGT1A1*6 was associated with indinavir-associated hyperbilirubinemia. However, no study has examined the association between UGT1A1*6 and atazanavir-associated hyperbilirubinemia. In the present study, we examined potential genetic factors for severe atazanavir-associated hyperbilirubinemia in Korean HIV-infected patients with a low prevalence of the UGT1A1*28 allele.

PARTICIPANTS, MATERIALS, AND METHODS

Study participants. This study included adult Korean HIV-infected patients who initiated antiretroviral therapy with unboosted atazanavir (400 mg per day) from May 2005 through April 2007 at the Seoul National University Hospital. The 1600-bed, university-affiliated teaching hospital is the largest referral centre for HIV/AIDS in South Korea; one-quarter of all HIV-infected patients in South Korea are seen at this hospital. Patients who did not show viral suppression 3 months after initiating atazanavir, who had active liver disease, or who did not consent to participating in the study were excluded. Viral suppression 3 months after initiating atazanavir was defined as an HIV RNA level <40 copies/mL or at least a 2 $\log_{10}$ decrease in HIV RNA copies/mL [14].

Three months after initiating atazanavir treatment, total bilirubin levels were measured in serum samples. Atazanavir-associated hyperbilirubinemia was defined as hyperbilirubinemia (bilirubin level, >1.3 mg/dL) that developed after initiation of atazanavir therapy in the absence of other causes of hyperbilirubinemia. Hyperbilirubinemia was classified on the basis of the AIDS Clinical Trials Group guidelines for total bilirubin levels as follows: grade 1 (mild), 23–32 μmol/L (1.3–1.9 mg/dL); grade 2 (moderate), 33–53 μmol/L (1.9–3.1 mg/dL); grade 3 (severe), 54–105 μmol/L (3.1–6.1 mg/dL); and grade 4 (serious), >105 μmol/L (>6.1 mg/dL) [15]. Severe hyperbilirubinemia was defined as grade 3 and 4 hyperbilirubinemia. Consent for genetic analyses was obtained from all participants, and the study protocol was approved by the Institutional Review Board of Seoul National University Hospital.

Genetic analyses. Genomic DNA was extracted from peripheral whole blood with use of the AccuPower Genomic DNA Extraction Kit (Bioneer). Primer sequences for polymerase chain reaction (PCR) amplification of both the TATA box of the UGT1A1 promoter and part of UGT1A1 exon 1 were 5′-ATTAACTTGGTGTATCGATTGG-3′ and 5′-AAGCATAGCAGAGTCCTTTTTTA-3′. PCR was performed under the following thermal cycling conditions: 95°C for 15 min, followed by 35 cycles at 95°C for 20 s, 52°C for 40 s, and 72°C for 1 min.

PCR primers for amplification of the MDR1 gene, including position 2677 (exon 21), were 5′-TCAGAAAATAGAAGCATGAGTTG-3′ and 5′-AGCAGTAGGGAGTAACAAAATAAC-3′; the PCR conditions were as follows: 95°C for 5 min, followed by 45 cycles at 95°C for 30 s, 56°C for 45 s, and 72°C for 1 min. PCR primers for amplification of the MDR1 gene, including position 3435 (exon 26), were 5′-TCTTGTTTTCAGCTGCTTGATGG-3′ and 5′-AGAGACTTACATTAGGCAGTGAC-3′; the PCR conditions were as follows: 95°C for 15 min, followed by 45 cycles at 95°C for 20 s, 56°C for 30 s, and 68°C for 30 s.

All PCR products were purified and directly sequenced using the AMI 3730XL DNA Analyzer (PE Applied Biosystems); samples were analyzed for the number of TA repetitions in the UGT1A1 promoter, identity of position 211 in the UGT1A1 gene, and identity of positions 2677 and 3435 in the MDR1 gene.

Statistical analysis. All statistical analyses were performed with SPSS software, version 17.0 (SPSS). Descriptive results of continuous variables were expressed as median values and interquartile range (IQR). Fisher's exact test was used to compare categorical variables. Logistic regression analysis was used to determine risk factors for severe atazanavir-associated hyperbilirubinemia. Variables in the models included age, sex, hepatitis B or C infection, baseline CD4 cell count, and genetic polymorphisms. Variables that were not significant in univariate analyses ($P > .10$) were excluded from multivariate analyses. All significance tests were 2-sided.

RESULTS

Study participants. Of a total of 190 patients who were prescribed atazanavir during the study period, 12 patients (6%)

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Table 1. Baseline Patient Characteristics

Characteristic	Patients (n = 129)
Age, median years (IQR)	39 (34–51)
Sex	
Male	117 (90.7)
Female	12 (9.3)
Korean ethnicity	129 (100)
Presumed HIV transmission route	
Male-to-male sexual exposure	45 (34.9)
Heterosexual exposure	42 (32.6)
Injection drug use	0 (0)
Other or unknown	42 (32.6)
Positive for HBV antigen	8 (6.2)
Positive for HCV antibodies	5 (3.9)
Baseline CD4 cell count, median cells/μL (IQR)	261 (181–405)
Baseline HIV RNA titer, median copies/mL (IQR)	4490 (25–59,300)
Total bilirubin, median mg/dL (IQR)	0.75 (0.6–0.9)
Concomitant use of tenofovir	0 (0)

NOTE. Data are no (%) of patients, unless otherwise indicated. HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range.

discontinued treatment within 3 months after starting atazanavir; six patients (3%) did so because of jaundice. One hundred forty-four patients (75%) met the predefined criteria for viral suppression 3 months after initiating atazanavir. By excluding 12 patients who did not furnish informed consent for the study and 3 patients who had active liver disease, a final total of 129 patients were recruited for the study. All patients were Korean, and the median age was 39 years (IQR, 34–51 years); 91% of the patients were male (Table 1). Forty-eight patients (37%) were naive to antiretroviral treatment, and 64 patients (50%) were taking other antiretroviral drugs within 1 month before beginning atazanavir treatment. Previous antiretroviral drug regimens included nelfinavir (n = 24), lopinavir/ritonavir (n = 24), efavirenz (n = 9), indinavir (n = 6), and nevirapine (n = 1). Antiretroviral drugs that were administered concurrently with atazanavir included zidovudine-lamivudine (n = 103; 80%), lamivudine-stavudine (n = 14; 11%), lamivudine-abacavir (n = 7; 5%), and lamivudine-didanosine (n = 5; 4%). No patients received any nonnucleoside reverse-transcriptase inhibitor or tenofovir concurrently with atazanavir treatment.

At baseline, the median plasma HIV RNA load was 4490 copies/mL (IQR, 25–59,300 copies/mL), with 45 patients (35%) having an HIV RNA level <40 copies/mL. The median CD4 cell count was 261 cells/μL (IQR, 181–405 cells/μL). Hepatitis B virus antigen was present in 8 (6%) patients, and hepatitis C virus antibodies were present in 5 (4%) patients. The median total bilirubin level was 0.75 mg/dL (IQR, 0.6–0.9 mg/dL). Three patients were also receiving atorvastatin or rosuvastatin, although none were taking any H_2 blockers or proton pump inhibitors.

Severe hyperbilirubinemia according to UGT1A1 and MDR1 polymorphisms. The frequencies of the UGT1A1*6 and *28 alleles in the study participants were 19% and 11%, respectively. The frequencies of the MDR1 2677 (T or A) and 3435 T alleles were 54% and 31%, respectively (Table 2).

Three months after initiating atazanavir, 100 (78%) of the 129 patients developed hyperbilirubinemia and 27 (21%) developed severe hyperbilirubinemia. Table 2 shows the proportion of the patients with severe hyperbilirubinemia according to genetic polymorphisms.

Risk factors for severe atazanavir-associated hyperbilirubinemia. Univariate analyses showed old age, low baseline CD4 cell count, and presence of the UGT1A1*28 allele or MDR1 G2677T/A as potential risk factors for severe hyperbilirubinemia. Multivariate analysis showed that independent risk factors for severe hyperbilirubinemia were low baseline CD4 cell count (adjusted odds ratio per 10 increase of CD4 cell count, 0.97; 95% confidence interval, 0.94–0.99; P = .036), UGT1A1*28 allele (adjusted odds ratio, 4.15; 95% confidence interval, 1.46–11.84; P = .008), and MDR1 G2677T/A (adjusted odds ratio, 9.65; 95% confidence interval, 1.09–85.61; P = .042) (Table 3).

Table 2. Genotyping Results and Prevalence of Severe (Grade 3–4) Hyperbilirubinemia 3 Months after Initiating Atazanavir in 129 Korean Human Immunodeficiency Virus–Infected Patients

Genotype	No (%) of patients	Hyperbilirubinemia, no (%) of patients	
		Any grade	Grade 3–4
UGT1A1*6[a]			
G/G	87 (67.9)	65 (74.7)	18 (20.7)
G/A	34 (26.6)	28 (82.4)	7 (20.6)
A/A	7 (5.5)	6 (85.7)	1 (14.3)
UGT1A1*28			
TA_6/TA_6	103 (79.8)	77 (74.8)	16 (15.5)
TA_6/TA_7	25 (19.4)	22 (88.0)	10 (40.0)
TA_7/TA_7	1 (0.8)	1 (100)	1 (100)
MDR1 2677			
G/G	22 (17.1)	18 (81.8)	1 (4.5)
G/T	54 (41.9)	40 (74.1)	16 (29.6)
G/A	21 (16.3)	16 (76.2)	4 (19.0)
T/A	17 (13.2)	15 (88.2)	3 (17.6)
T/T	9 (7.0)	6 (66.7)	2 (22.2)
A/A	6 (4.7)	5 (83.3)	1 (16.7)
MDR1 3435			
C/C	62 (48.1)	48 (77.4)	10 (16.1)
C/T	55 (42.6)	43 (78.2)	15 (27.3)
T/T	12 (9.3)	9 (75.0)	2 (16.7)
Total	129 (100)	100 (77.5)	27 (20.9)

[a] One patient in whom the genotype of UGT1A1*6 was not determined was excluded.

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Table 3. Clinical and Genetic Factors Associated with Severe Hyperbilirubinemia in Patients Treated with Atazanavir

	Univariate analysis		Multivariate analysis	
Variable	OR (95% CI)	*P*	aOR (95% CI)	*P*
Female sex	…	.999	…	
Age (per year)	0.95 (0.91–0.99)	.014	0.96 (0.92–1.01)	.089
Hepatitis B or C virus infection	0.29 (0.04–2.32)	.243	…	
Baseline CD4 cell count (per 10 cells/μL)	0.97 (0.94–1.00)	.028	0.97 (0.94–0.99)	.036
At least 1 UGT1A1*6 allele	0.93 (0.37–2.36)	.877	…	
At least 1 UGT1A1*28 allele	3.99 (1.55–10.24)	.004	4.15 (1.46–11.84)	.008
At least 1 2677T/A at MDR1	6.74 (0.86–52.58)	.069	9.65 (1.09–85.61)	.042
At least 1 3435T at MDR1	1.77 (0.74–4.23)	.200	…	

NOTE. aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

In the 100 patients with hyperbilirubinemia, the severity of hyperbilirubinemia was significantly associated with the UGT1A1*28 and MDR1 G2677T/A polymorphisms (Figure 1). Although none of the 15 patients who had wild-type alleles for both UGT1A1*28 and MDR1 2677 developed severe hyperbilirubinemia, we confirmed severe hyperbilirubinemia in 16 (26%) of the 62 patients who had wild-type alleles for UGT1A1*28 and non–wild-type alleles for position MDR1 2677 ($P = .031$), as well as 10 (50%) of the 20 patients who did not have wild-type alleles for both UGT1A1*28 and MDR1 2677 ($P = .002$).

DISCUSSION

To the best of our knowledge, ours is the first study to evaluate the association between genetic polymorphisms and hyperbilirubinemia in Asian HIV-infected patients receiving atazanavir. Previous related studies have only evaluated Caucasian or African-American HIV-infected patients. Furthermore, in contrast to previous studies in which patient adherence to the drug was not considered [2, 9], this study only included subjects who had achieved viral suppression at the time of total bilirubin measurement, indicating good adherence to atazanavir [16].

Our findings confirm that the UGT1A1*28 allele was strongly associated with atazanavir-associated severe hyperbilirubinemia in Korean HIV-infected patients, despite the lower prevalence of the UGT1A1*28 allele in Korean patients, compared with Caucasians. In the present study, the prevalence of the UGT1A1*28 allele was 11%, which is comparable to that previously reported in the general Korean population [5]. In particular, only 1 (0.8%) patient was homozygous for UGT1A1*28 (TA_7/TA_7), compared with 10% of Caucasians who exhibit the homozygous genotype [17]. However, the frequency of severe hyperbilirubinemia in this study was comparable to that previously reported in Caucasians [18].

The relatively high frequency of the UGT1A1*6 allele in Asians may explain the prevalence of Gilbert syndrome in an Asian population with a low prevalence of the UGT1A1*28 allele [11, 12, 19]. In the present study, the prevalence of UGT1A1*6 was as high as 19%, whereas it was rarely found in Caucasians [3]. Our findings did not demonstrate an association between UGT1A1*6 and severe atazanavir-associated hyperbilirubinemia in Korean HIV-infected patients. However, the lack of a statistically significant association could be attributable to the small number of patients in each category who developed severe hyperbilirubinemia.

Our study did identify MDR1 G2677T/A as another independent risk factor for severe hyperbilirubinemia in Korean HIV-infected patients taking atazanavir. Interestingly, among 19 patients who were wild-type for both MDR1 2677 and UGT1A1*28, none experienced severe hyperbilirubinemia, and 8 (53%) of 15 patients who developed hyperbilirubinemia only showed mild (grade 1) hyperbilirubinemia.

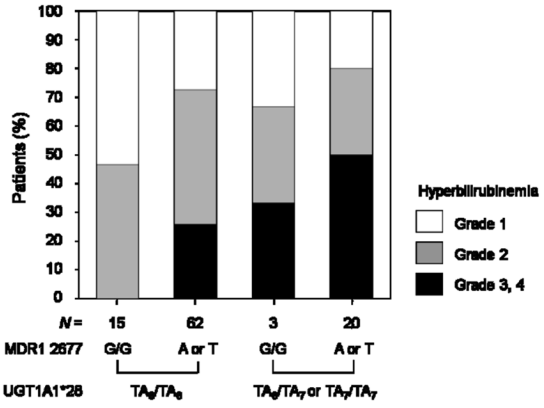

Figure 1. Proportion of severe (grade 3–4) hyperbilirubinemia according to genetic polymorphisms in 100 human immunodeficiency virus–infected patients with different grades of hyperbilirubinemia. G/G, homozygous wild-type genotype; A or T, heterozygous or homozygous genotype for polymorphism MDR1 G2677T/A; TA_6/TA_6, homozygous wild-type genotype; TA_6/TA_7 or TA_7/TA_7, heterozygous or homozygous genotype for UGT1A1*28.

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The MDR1 G2677T/A polymorphism may be more common in some Asians than in Caucasians or African-Americans. Previous studies reported that 12%–17% of Japanese, Chinese, and Koreans carry the wild genotype (G/G) for MDR1 2677, compared with 31%–33% of Caucasians [20–24]. This difference may be partly attributed to the higher frequency of the MDR1 G2677A mutation in Asians (4%–18%), compared with Caucasians or African-Americans (0%–2%) [25]. In the present study in a Korean population, the proportion of patients who carried the wild genotype for MDR1 2677 was 17%, and the frequency of the 2677A allele was 19%.

The 2 single-nucleotide polymorphisms in MDR1 2677 result in distinct amino acid changes, Ala893Ser (G2677T) and Ala893Thr (G2677A) [8]. Most studies suggested that polymorphisms in MDR1 G2677T/A were linked to an increased level of the P-gp drug substrates [26–29], although some contradictory data have been reported [30]. Although the blood levels of atazanavir were not evaluated in the present study, an increased concentration of atazanavir, which was associated with MDR1 G2677T/A, might cause severe hyperbilirubinemia.

Other studies suggested that the MDR1 C3435T polymorphism was linked to a lower incidence of atazanavir-associated hyperbilirubinemia in Caucasians [9], although the association was not observed in a separate study by the same group analyzing ritonavir-boosted atazanavir [18]. However, results from another study [10] and our study showed no association between MDR1 C3435T and atazanavir-associated hyperbilirubinemia.

Some possibilities may explain this discrepancy. First, the difference may be attributable to differences among the study populations, including ethnicity [31, 32]. The frequency of the MDR1 C3435T allele was as low as 31% in this study, compared with 48%–54% in Caucasians [24, 31]. Second, because of linkage disequilibrium between MDR1 C3435T and G2677T/A, the previously observed findings that were attributed to the synonymous C3435T single-nucleotide polymorphism, which does not result in amino acid changes, might be due to the associated nonsynonymous G2677T/A polymorphism [30].

In the present study, low CD4 cell count was significantly associated with severe hyperbilirubinemia. In contrast, Torti et al [33] demonstrated an association between high CD4 cell count and the development of severe hyperbilirubinemia, although their results could be influenced by adherence to medication. In our study, poor medical conditions in patients with low CD4 cell counts might increase the risk and severity of hyperbilirubinemia. However, after adjusting this clinical variable, the association of the genetic polymorphisms with severe hyperbilirubinemia remained significant.

This study has several limitations. First, we excluded patients with active liver disease, and there was no patient concomitantly receiving tenofovir or a proton pump inhibitor, which could significantly affect the concentration of atazanavir. However, other confounding factors, such as medical conditions or medications, might affect bilirubin levels 3 months after initiating atazanavir. Second, other genetic polymorphisms that were not evaluated in this study might affect the atazanavir-associated development of hyperbilirubinemia. For example, atazanavir concentration can be influenced by the single-nucleotide polymorphisms in the pregnane X receptor (C63396T), which regulates the expression of CYP3A4 and MDR1 [34], or in SLCO1B1 (T521C), which codes for organic anion-transporting polypeptide 1B1, an influx transporter that is responsible for the uptake of protease inhibitors and unconjugated bilirubin [35]. Third, the outcome of the present study was severe hyperbilirubinemia because this parameter could be measured objectively. However, jaundice and possible treatment interruption because of severe hyperbilirubinemia might be more clinically relevant than hyperbilirubinemia per se. Finally, blood concentrations of atazanavir were not evaluated in this study. Although bilirubin levels after atazanavir initiation correlated well with plasma drug levels in other studies [18], the bilirubin levels in this study may not directly reflect the atazanavir concentration.

In summary, we identified MDR1 G2677T/A along with UGT1A1*28 as independent risk factors for severe atazanavir-associated hyperbilirubinemia in Korean HIV-infected patients. The common prevalence of severe atazanavir-associated hyperbilirubinemia in some Asians despite low prevalence of the UGT1A1*28 allele may be attributable to the frequent MDR1 2677 polymorphisms in these populations.

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Potential conflicts of interest. All authors: no conflicts.

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