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LETTER

Hyperbilirubinemia in atazanavir-treated human immunodeficiency virus-infected patients: the impact of the *UGT1A1*28* allele

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Dear editor

Panagopoulos et al[1] reviewed the effects of the *UGT1A1*28* polymorphism on Reyataz® (atazanavir)-related hyperbilirubinemia in human immunodeficiency virus (HIV)-infected patients that may result in increased severity and drug discontinuation in some patients. The effects of the *UGT1A1* polymorphisms on the pharmacokinetics of other antiretroviral drugs such as Isentress® (raltegravir) and Edurant® (rilpivirine) are also discussed. We respond here on the relevance of the study findings in the South African context.

The antiretroviral protease inhibitor (PI) atazanavir inhibits hepatic uridine diphosphate-glucuronosyltransferase (UGT) 1A1, thereby preventing the glucuronidation and elimination of bilirubin.[2] This may result in hyperbilirubinemia in >50% of patients, with jaundice that can cause premature discontinuation of atazanavir in ~2%–8% of patients.[2] Risk for bilirubin-related discontinuation of atazanavir is substantially increased among individuals who carry two TA_n repeat polymorphisms within the *UGT1A1* loci: TA_7 (*UGT1A1*28*) and TA_8 (*UGT1A1*37*) that reduce gene transcription, with reported positive predictive values for discontinuation ranging from 20% to 60% depending on race or ethnicity.[2]

Prevalence of the *UGT1A*28* polymorphism is reported to be between 9% and 60% in African populations.[1] One study examining the South African population (n=197) reported *UGT1A1*28* and *UGT1A1*37* frequencies as ~34% and 6% of the population, respectively.[3] We recently tested the prevalence of *UGT1A1* polymorphisms in a cohort of 172 tuberculosis patients (73% HIV coinfected) in KwaZulu-Natal, South Africa, within the Improving Retreatment Success study (NCT02114684). The prevalence of *UGT1A1*28* and *UGT1A1*37* was found to be ~23% and 8%, respectively. This suggests that approximately one-third of South African patients may be at potential risk for atazanavir-related hyperbilirubinemia resulting in drug discontinuation.

South Africa is one of the highest HIV-burden countries in the world and has the largest antiretroviral treatment program globally, with >3.4 million people on treatment.[4] The current first-line drug regimen used in South Africa includes efavirenz, emtricitabine, and tenofovir; however, it is estimated that between 8% and 23% of patients will be switched to a second-line regimen within 5 years on treatment.[5] The South African National treatment guideline includes PIs as the backbone of the second-line drug regimens. Aluvia® (ritonavir-boosted lopinavir) is more commonly prescribed; however, atazanavir is the preferred alternate PI in patients who are unable

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to tolerate lopinavir such as those patients with gastrointestinal side effects, or those with dyslipidemia at high risk of cardiovascular events. Atazanivir is also recommended as a part of postexposure prophylaxis in South Africa.

The increasing rates of acquired and transmitted drug resistance seen in patients in HIV-endemic settings clearly indicate a growing demand for second-line drugs such as atazanavir and newer agents including raltegravir and rilpivirine. Data describing the prevalence and impact of genetic variability on antiretroviral drug-metabolizing enzymes (DMEs) such as UGT1A1 from HIV endemic geographical locations including South Africa are lacking. Investigating the extent to which allelic variation of key DMEs impacts pharmacokinetics, drug exposures, therapeutic efficacy, and risk of serious adverse events is critical to ensure safe and sustainable virologic suppression. Moreover, as genetic testing assays for polymorphisms in genes coding for DMEs become cheaper, easier to access, and interpret, more data from studies are needed to guide clinical decision-making based on pharmacogenetics.

Disclosure

The authors report no conflicts of interest in this communication.

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