Complicated Atazanavir-Associated Cholelithiasis: A Report of 14 Cases

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Fourteen human immunodeficiency virus (HIV)–infected patients receiving an atazanavir (ATV)–based antiretroviral regimen developed complicated cholelithiasis. ATV was found in biliary calculi in 8 of 11 cases: infrared spectrometry analysis of calculi revealed that ATV made up a median of 89% (range, 10%–100%) of the total calculus composition. Development and management of ATV-associated cholelithiasis are discussed.

Atazanavir (ATV) is one of the most used protease inhibitors (PIs) for the treatment of human immunodeficiency virus (HIV) infection. Although hyperbilirubinemia is a common side effect, its clinical consequences are usually limited to mild scleral icterus. Nephrolithiasis and cholelithiasis were not described in ATV phase III clinical trials [1, 2]. However, post-marketing studies revealed that ATV may be responsible for nephrolithiasis, with an estimated incidence of 7.3 cases per 1000 patient-years [3]. In addition, 2 cases of ATV-associated cholelithiasis have been reported recently [4, 5]. We describe 14 additional cases of complicated cholelithiasis in patients receiving an ATV-based antiretroviral (ARV) regimen, including 8 cases in which significant concentrations of ATV were identified in biliary stones, using infrared spectrometry analysis.

METHODS

The Brittany and Normandy COREVIH network links hospitals and professionals involved in the care of HIV-infected patients in western France. During the study period (2006–2012), an average of 5000 HIV-infected patients were treated through this network annually, and 20% of these were receiving an ATV-based antiretroviral regimen (unpublished data). Cases were identified through computerized databases when available, through COREVIH physicians’ interviews, and through the computerized registries of suspected drug-related adverse events (Centres Régionaux de PharmacoVigilance). Patients where included if they fulfilled the following 3 criteria: (1) they received a diagnosis of cholecystitis, cholangitis, or pancreatitis; (2) cholelithiasis was documented through imaging and/or surgery; (3) they were treated with an ATV-based ARV regimen when complicated cholelithiasis was diagnosed. Data were extracted from medical records through a standardized questionnaire and included comorbidities, nadir CD4 cell count, and ARVs. In addition, we extracted the following data that were collected when cholelithiasis was diagnosed: body mass index (BMI; defined as the weight in kilograms divided by the square of height in meters), alcohol intake, plasma HIV load, time since ATV initiation, cholelithiasis–associated symptoms, liver function test results, serum lipase level, ATV plasma concentration, findings of imaging studies, management of cholelithiasis-related complications, and outcome. For 11 patients, a sample of biliary stones was analyzed by infrared spectrometry [6]. Data are expressed as medians (range).

RESULTS

Between 2006 and 2012, 14 patients fulfilled inclusion criteria; there were 12 males and 2 females. Median nadir CD4 cell count was 103 cells/mm³ (range, 12–433 cells/mm³), and 4 patients had Centers for Disease Control and Prevention class C HIV/AIDS. Seven patients were coinfected with hepatitis C virus (HCV): 4 were successfully treated, and 3 had ongoing HCV replication (including 2 patients with cirrhosis and 1...
with hepatocarcinoma). One patient had had didanosine-related acute pancreatitis 12 years previously, and 3 patients had a history of indinavir-related nephrolithiasis. At the time of complicated-cholelithiasis diagnosis, patients’ median age was 48 years (range, 36–82 years). HIV infection had been known for a median duration of 17.5 years (range, 2–25 years). All patients had an undetectable plasma viral load, and the median CD4 cell count was 585 cells/mm$^3$ (range, 248–1678 cells/mm$^3$). Patients’ median BMI was 25 (range, 17–35). Twelve patients were receiving a ritonavir-boosted ATV regimen. At the time of calculus extraction, the ATV daily dose was 400 mg (for 1 patient), 300 mg (for 9), 200 mg (for 1), and 150 mg (for 3). Associated ARVs were emtricitabine-tenofovir in 9 patients. Upon diagnosis of cholelithiasis, ATV trough plasma concentrations, which were available for 3 patients, were within the therapeutic range.

Cholelithiasis-related symptoms appeared after a median duration of 42 months under ATV-based ARV regimen (range, 1–90 months). All patients presented with abdominal pain. The median bilirubin level was 34.5 µmol/L (range, 7–180 µmol/L). The spectrum of cholelithiasis-associated complications included cholecystitis (in 11 patients), cholangitis (in 1), and acute pancreatitis (in 4). Three patients underwent endoscopic sphincterotomy, and 13 underwent surgery (laparoscopic cholecystectomy). Calculi were sent for infrared spectrometry analysis in 11 cases. Significant levels of ATV were found in calculi from 8 patients, representing 100% of the total calculus composition in 4 patients (median, 89% [range, 10%–100%]). Macroscopic appearance of all ATV-containing calculi was brownish (Figure 1). In the 3 cases with no trace of ATV, calculi were smaller and blackish, and infrared spectrometry yielded mostly calcium bilirubinate, as observed in pigmentary cholelithiasis. All patients survived. For 11 patients, ATV was replaced by another ritonavir-boosted PI (for 8), an integrase inhibitor (for 2), or a nonnucleoside reverse-transcriptase inhibitor (for 1). Three patients initially continued to receive ATV. No relapse of complicated cholelithiasis was observed during the study period. One patient who continued to receive ATV developed compensated cholelithiasis (ATV represented 100% of the calculus composition, according to infrared spectrometry) 11 months after the episode of complicated cholelithiasis. Another patient required cholecystectomy 7 months after ATV was discontinued, because of persisting abdominal pain: infrared spectrometry revealed that ATV represented 78% of the total calculus composition.

**DISCUSSION**

This is the first series describing complicated cholelithiasis in patients receiving an ATV-based ARV regimen. The association between complicated cholelithiasis and ATV use may be coincidental, given the common use of ATV in HIV-infected patients and the prevalence of cholelithiasis among adults in Europe and North America (ranging from 8% of men to 16% of women [7]). However, the direct implication of ATV in cholelithiasis pathways was documented in 8 of 11 patients whose calculi were analyzed, with a median ATV proportion of 89% of the total calculus composition. As mentioned above, in 1 patient, although the calculus was extracted 11 months after ATV discontinuation, infrared spectrometry revealed that ATV represented 78% of the composition. Likewise, in the case recently reported by Courbon et al [5], a high concentration of ATV was found in the bile 1 year after ATV discontinuation. These observations are of concern, suggesting that ATV-related cholelithiasis may be long lasting.

Drug-induced cholelithiasis may occur through 2 mechanisms [8]. First, drug precipitation in the bile may lead to the constitution of calculi composed of the drug plus other biliary components, as documented for ceftriaxone-related cholelithiasis. Second, the drug may induce a rise in the production of some components of the calculus, such as cholesterol or bilirubin. For example, fibrates may induce cholelithiasis through increased biliary secretion of cholesterol. The high percentage of ATV found in calculi in our study, including 4 cases in which ATV was the only component identified, suggests the
preeminence of ATV precipitation in the cholelithiasis pathway. ATV is slightly water soluble, and its solubility is dependent on pH. The normal concentration and solubility of ATV in bile are unknown. Biliary pH, usually >6.5, may predispose to ATV crystallization. Indinavir, another PI, has been involved in cholelithiasis [9, 10]. Like indinavir, ATV is an inhibitor of the bilirubin-conjugating enzyme uridine diphosphate glucuronoyl transferase 1A1 (UGT1A1), which is responsible for moderate and usually asymptomatic hyperbilirubinemia. This chronic hyperbilirubinemia may be augmented in subjects with a genetic UGT1A1 polymorphism such as in Gilbert’s syndrome, because of the genotype UGT1A1*28, which is associated with constitutionally decreased UGT1A1 enzymatic activity [11].

Our study was not designed to identify risk factors for ATV-induced cholelithiasis. Conceivably, biliary precipitation of ATV could be enhanced by increased ATV plasma concentrations. As ATV is principally metabolized in the liver, end-stage liver disease is associated with increased ATV concentration in plasma and may contribute to biliary precipitation of the drug. Likewise, combination with ritonavir, a CYP3A4-inhibitor that increases ATV plasma levels, may contribute to the risk of ATV biliary precipitation. In our study, most patients were treated with a ritonavir-boosted PI, as recommended. In addition, 6 of the 8 patients with documented ATV-related cholelithiasis were coinfected with HCV, which is higher than the mean prevalence of HCV coinfec tion (14%) in the Brittany and Normandy COREVIH network. However, the limited sample size does not allow any conclusion regarding the impact of HCV on the risk of ATV-associated complicated cholelithiasis. Last, prolonged biliary impregnation by ATV may be necessary for calculus formation, as suggested by the median duration of 48.5 months between ATV introduction and the first symptoms of cholelithiasis in our study (5 years in the case reported by Courbon et al [5]). This could explain why ATV-associated cholelithiasis could not be identified during phase III studies and was only reported recently, 6 years after ATV introduction in our therapeutic armamentarium. However, in the case reported by Jacques [4], the duration of ATV use was only 6 weeks before documented, ATV-associated cholelithiasis was diagnosed, and ATV duration was even shorter (4 weeks) in one of our patients.

What should be the consequences of the increased awareness of this potentially life-threatening adverse event? It must be outlined that the incidence of ATV-associated cholelithiasis is probably not high, at least during the first years of ATV use. Indeed, although our study was not designed to calculate incidence, as it relied on passive case finding, the 14 cases of complicated cholelithiasis observed within the 6-year study period in a population of 5000 HIV-infected patients (of whom approximately 20% were receiving ATV) translate to an estimated 2.3 cases per 1000 patient-years. Hence, systematic ultrasonography screening for cholelithiasis in all ATV-treated patients would probably not be cost-effective and may lead to unnecessary treatment changes in asymptomatic patients. However, better knowledge of this adverse event is necessary for 2 reasons: (1) physicians and patients must be aware that ATV-treated patients presenting symptoms compatible with cholelithiasis must be investigated using liver function tests, measurement of the serum lipase level, and hepatobiliary ultrasonography; and (2) long-term, systematic prospective studies of ATV-treated patients are required to better evaluate the incidence of and risk factors for complicated cholelithiasis.

Notes

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