ATAZANAVIR-RELATED JAUNDICE IN A MIDDLE-AGED WOMAN

Icterícia associada com atazanavir em mulher de meia idade

Vitorino Modesto dos Santos[1], Mariely Fernanda da Silva Helbingen[2]

Abstract

HIV infections are associated with high social and economic burdens in the whole world, causing a variable degree of gastrointestinal and hepatic abnormalities mainly due to atazanavir. This protease inhibitor can cause indirect hyperbilirubinemia, without correspondent elevations in the serum levels of canalicular enzymes, or aminotransferases. Lack of hyperbilirubinemia may be a marker of the patient's non-adherence to the treatment. The types of myocardial infarction and stroke have a relationship with high bilirubin levels. This report and commented articles emphasize the role of hyperbilirubinemia in HIV infection and the multidisciplinary approach to better follow-up of the patients treated with atazanavir.

Keywords: Atazanavir; drug adverse effect; jaundice.

Resumo

As infecções por HIV estão associadas a altos encargos sociais e econômicos em todo o mundo, causando um grau variável de anormalidades gastrointestinais e hepáticas principalmente devido ao uso de atazanavir. Esse inibidor de protease pode causar hiperbilirrubinemia indireta, sem elevações correspondentes nos níveis séricos de enzimas canaliculares ou aminotransferases. A falta de hiperbilirrubinemia pode ser um marcador da não adesão do paciente ao tratamento. Os tipos de infarto do miocárdio e acidente vascular cerebral têm uma relação com altos níveis de bilirrubina. Este relato de caso e os artigos comentados enfatizam o papel da hiperbilirrubinemia na infecção pelo HIV e a abordagem multidisciplinar para um melhor acompanhamento dos pacientes tratados com atazanavir.

Palavras-chave: Atazanavir; efeito adverso a medicamento; icterícia

[1] Professor Adjunto da Universidade Católica de Brasília (UCB) e Preceptor do Departamento de Medicina Interna do Hospital das Forças Armadas (HFA).

[2] Médica, Departamento de Clínica Médica do HFA.

Introduction

HIV infections cause high physical, social and economic burdens in the whole world. Specialists in infectious diseases, gastroenterology, and hepatology, take part in management. The major concerns are drug-adverse effects on the liver, mainly related to atazanavir (ATV). ATV is utilized in association with other antivirals to optimize its therapeutic action and is more often well tolerated, despite 40% to 65.3% of induced IB [1-6]. This antiretroviral protease inhibitor can give origin to indirect hyperbilirubinemia (IB) by inhibition of hepatic uridine diphosphate glucuronosyltransferase (UGT), the enzyme that increases the hydro solubility of some substances for their excretion by bile or urine [3,4]. Otherwise, the lack of bilirubin elevation may be utilized as a marker of the patient's non-adherence to treatment [2]. Moreover, a relationship between bilirubin levels and cardiovascular events was described [1]. This report aims to highlight the role of the multidisciplinary approach of HIV patients utilizing ATV.

Case report

We report a 38-year-old previously healthy Brazilian woman who suffered an accidental cutaneous injury by a needle that was contaminated with human blood from an unknown individual. She underwent routine serologic tests and started using ATV, ritonavir, tenofovir, and lamivudine. On D2, she presented yellowish semi-liquid diarrhea and nausea without vomiting or abdominal pain. Three days later she also noticed yellowish skin and sclerotic, with no change in the color of urine, and had nightmares. She denied pain, fever, comorbidities, and drug allergy. Physical examination: BMI 19.6 kg/m², afebrile, hydrated, jaundiced (++), cardiovascular evaluation and abdominal ultrasound without abnormalities. Routine laboratory exams are shown in Table 1, and the direct Coombs test was negative. The serological panel for infections with biological material was negative. On D1: anti-HBS: 10.5 UI/ml, HBSAg: 0.256, anti-HBc IgG: 1.59, anti-HBc IgM: 0.063, anti-HCV: 0.082, anti-HIV 1 and 2: 0.345, and anti-*T. pallidum*: 0.15. On D8: HAV IgG: 60UI/L, anti-HAV IgM: 0.39UI/L, HBSAg: 0.44, and anti-HCV: 0.0855. On D34: anti-HBS: 17.5 UI/ml; HBSAg: 0.41; anti-HBc IgG: 1.94; anti-HBc IgM: 0.066, anti-HCV: 0.093, and anti-HIV 1: 0.43. Abdominal ultrasonography images obtained in D10 revealed normal liver and biliary tract. The CD4 count was found not significant (> 500 cells/microliter). Cardiovascular evaluation, including

2238-5339 © Rev Med Saúde Brasília 2020; 9(2):143-147

electrocardiography and echocardiography, was normal. The patient herein reported had nausea, diarrhea, jaundice and nightmares, some side effects of the antiretroviral drug. Currently, she remains asymptomatic and undergoing regular medical specialized follow-up.

Table 1. Blood tests of a middle-aged woman with atazanavir-related jaundice

Parameters (normal ranges)	**D8**	**D10**	**D34**
Red cells (3.9-5.1 x 10^{12}/L)	4.52	4.38	4.22
Hemoglobin (11.7-15.7 g/dL)	14.0	13.5	13.3
Hematocrit (35-47%)	41.0	40.2	39.0
Leukocytes (4-10 x 10^{9}/L)	5.74	**3.66**	4.05
Platelets (140-450 x 10^{9}/L)	259	226	252
Gamma-glutamyl transferase (5-36 IU/L)	-	18	33
Procalcitonin (< 0.5 ng/mL)	-	0.037	0.036
Sodium (135-145 mmol/L)	-	138	141
Potassium (3.5-5.5 mmol/L)	-	4.7	4.4
Urea (10-50 mg/dL)	37.0	-	28.7
Creatinine (0.7-1.3 mg/dL)	0.70	-	0.72
Aspartate aminotransferase (< 38 IU/L)	18.0	17.4	16.4
Alanine aminotransferase (< 41 IU/L)	17.1	16.0	21.4
Lactate dehydrogenase (< 250 IU/L)	152.5	-	158.7
Direct bilirubin (0.1-0.4 mg/dL)	0.38	0.29	0.23
Indirect bilirubin (0.2-0.9 mg/dL	**7.25**	**7.49**	0.48
Albumin (3.5-5.0 g/dL)	-	3.9	4.4

Admission: March 11th; discharge: March 20th. Abnormal data are shown in bold.

Discussion

Causes of unconjugated jaundice include neonatal disorder, genetic change, and drug catalytic side effects [2-6]. Poor adherence to the scheduled treatment is the main factor for drug resistance and treatment failures of HIV patients; anemia, hypersensitivity, digestive changes, and jaundice are common causes of drug discontinuation [4,6]. Worthy of note is the low frequency of concomitant elevations in the serum levels of canalicular enzymes, and of aminotransferases, which would be indicative of injury in hepatocytes [2,3,5,6]. Moreover, this IB is neither associated with a decrease of hemoglobin levels nor with hemolysis [5]. One should be aware of a possible ATV discontinuation in some patients, mainly if they are Asian descents homozygous forUGT1A1 genotypes, or have Gilbert syndrome [2,3,5,6]. Challenges in this setting involve limitations to UGT1A1 genotyping in most of the low-income countries and non-genetic factors as fasting and diet that can influence indirect the bilirubin levels [2].

Additional concerns in HIV patients treated with ATV and presenting IB includes coexistent changes in liver enzymes by viral hepatitis co-infection and urinary disorders [3,6]. In industrialized countries, approximately 33% of the HIV patients have HCV co-infection that can

add diagnostic pitfalls and pose challenges about an option for invasive approaches. In this group of patients, doubtful cases should be submitted to evaluation by hepatologists [3].

Angbalaga *et al*. studied 410 HIV patients using antiviral drugs (270 females, with 31-40 years of age) and correlated the ultrasound data with CD4 cell count and hepatic enzymes. The changes (47.3% of the total) included: enlarged gallbladder (33.5%), hepatic hyper echogenicity (26.3%), hepatomegaly (23.7%), thickened gallbladder (7.8%), biliary sludge (6.6%) and gallbladder stone (2.1%). These disorders had a significant correlation with the CD4 cell count, and with the serum levels of aminotransferases and alkaline phosphatase [7].

Crane *et al*. recently published an interesting multisite clinical cohort study that included 25,816 people living with HIV in the US, aiming to evaluate the relationships between the total bilirubin levels and events like myocardial infarction (MI) and stroke [1]. Worthy of note, higher bilirubin levels were associated with less type 2 MI as well as type 1 MI combined with ischemic strokes in the group of individuals utilizing ATV. In these patients, the high levels of bilirubin have a significant association with type 2 MI in contrast with findings in HIV patients treated without ATV. The authors emphasized differences in the role of high bilirubin levels due to diverse causes, and of the individual outcomes instead of the composite ones with unequal relationships. They also commented about the possible effect of viral hepatitis and alcohol ingestion on the elevations of serum bilirubin, and the usefulness of bilirubin determination as a marker of good adherence to treatment [1].

These data should highlight the role of the cardiologic evaluations in this group of patients.

Conclusion

Herein are included a case study and comments about articles that can contribute to better knowledge about increased risks of hyperbilirubinemia in patients utilizing ATV. One should ever obtain the ultrasonography abdominal images and a panel of hepatic enzymes. Further research can clarify the risk of type 2 MI in women with a 2-fold increase in bilirubin.

References

1. Crane HM, Nance RM, Heckbert SR, Ritchings C, Rosenblatt L, Budoff M, et al. Association between bilirubin, atazanavir, and cardiovascular disease events among people living with HIV across the United

States. J Acquir Immune Defic Syndr. 2019;81(5):e141-e7.

2. Gammal RS, Court MH, Haidar CE, Iwuchukwu OF, Gaur AH, Alvarellos M, et al. Clinical pharmacogenetics implementation consortium (CPIC) Guideline for UGT1A1 and atazanavir prescribing. Clin Pharmacol Ther. 2016;99(4):363-9.

3. Kaspar MB, Sterling RK. Hyperbilirubinaemia in HIV-HCV co-infected patients on antiretroviral therapy: drug effect or liver disease severity? BMJ Open Gastroenterol. 2016;3(1):e000072.

4. Kim MJ, Kim SW, Chang HH, Kim Y, Jin S, Jung H, et al. Comparison of antiretroviral regimens: adverse effects and tolerability failure that cause regimen switching. Infect Chemother. 2015;47(4):231-8.

5. Subashini D, Dinesha TR, Boobalan J, Samuel LC, Poongulali S, Pradeep A, et al. Incidence of atazanavir-associated adverse drug reactions in second-line drugs treated south Indian HIV-1 infected patients. Indian J Pharmacol. 2016;48(5):582-5.

6. Teófilo E, Rocha-Pereira N, Kuhlmann B, Antela A, Knechten H, Santos J, et al. Long-term efficacy, tolerability, and renal Safety of atazanavir/ritonavir-based antiretroviral therapy in a cohort of treatment-naive patients with HIV-1 infection: the REMAIN Study. HIV Clin Trials 2016;17(1):17-28.

7. Angbalaga A, Ani CC, Atsukwei D, Eze ED, Afodun AM, Igoh EO, et al. Correlation of hepatobiliary ultrasonographic findings with CD4 cell count and liver enzymes in adult HIV/AIDS patients in Jos. J AIDS HIV Res. 2018;10(6):83-95.