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Original article

Prevalence of abacavir-associated hypersensitivity syndrome and HLA-B*5701 allele in a Portuguese HIV-positive population

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ABSTRACT

Background: Human Immunodeficiency Virus (HIV)-positive patients treated with the antiretroviral drug abacavir (ABC) may develop a potentially fatal ABC-associated hypersensitivity syndrome (ABC-HS), typically characterized by fever, malaise, rash, vomiting/diarrhoea and/or dyspnoea/cough. ABC-HS has been strongly associated with HLA-B*57:01 carriage and screening for this allele is recommended.
Objective: To determine the prevalence of HLA-B*57:01 and to characterize suspected ABC-HS in the adult HIV population from our hospital during a 7-year period.
Methods: Clinical data on patients under ABC treatment from January 2006 to December 2012 were analyzed to search for symptoms of ABC-HS. Reactions of suspected ABC-HS were characterized. HLA-B*57:01 and patch tests (1% and 10% ABC in petrolatum) with readings at 48 h were performed in those without previous testing. From January 2008 routine HLA-B*57:01 screening was implemented.
Results: From January 2006 to December 2007, 186 patients began treatment with ABC (data from 163 were available): 7 (4%) patients stopped ABC for suspected ABC-HS (71% males, median age 45 years) and the median time for onset of the reaction after starting ABC was 7 days. Four of the 7 patients had the HLA-B*57:01 allele and 2 of these 4 had positive patch tests. After HLA-B*57:01 screening implementation (January 2008), 573 patients were evaluated and 35 (6.1%) were HLA-B*57:01 positive; no suspected ABC-HS were observed since then.
Conclusion: Four patients with suspected ABC-HS (of 6 screened) were HLA-B*57:01 positive. No ABC-HS occurred since January 2008, after HLA-B*57:01 screening was implemented.

Introduction

The frequency of drug-related exanthemas in Human Immunodeficiency Virus (HIV)-positive patients is estimated to be 100 times higher than in the general population.[1] The increase in adverse drug reactions is most likely multifactorial in origin, including immune hyperactivation and changes in cytokine profiles, oxidative stress and drug metabolism, and also a genetic predisposition.[1] HIV itself may work as a danger signal, leading to the development of an immune response instead of tolerance.[1]

There are some obstacles to the diagnosis of drug hypersensitivity in HIV-infected patients, one of the most important concerns the multiple medication regimens used. In fact, antiretroviral agents (along with antibiotics used to treat opportunistic infections) are frequent agents of hypersensitivity reactions.[2] One such agent with particular importance in that context is abacavir (ABC), a nucleoside reverse transcriptase inhibitor (NRTI) which is frequently used in treatment-naïve patients and whose hypersensitivity reactions occur at a frequency ranging from 2% to 9%; this is an intermediate frequency compared to that of adverse reactions reported to other NRTI drugs, such as emtricitabine (17%) and zidovudine (rare).[3–6]

The abacavir-associated hypersensitivity syndrome (ABC-HS) is a distinct and specific clinical syndrome defined by systemic involvement, and with an estimated incidence of 8% and a mortality

Abbreviations: ABC, abacavir; ABC-HS, abacavir-associated hypersensitivity syndrome; ART, antiretroviral therapy; HIV, Human Immunodeficiency Virus; IQR, interquartile range; NRTI, nucleoside reverse transcriptase inhibitors.

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rate of 0.03%.[7,8] The ABC-HS is clinically characterized by at least 2 of the following manifestations typically occurring within 6 weeks after drug introduction – constitutional symptoms (fever, malaise, lethargy, headache, and myalgia), rash, gastrointestinal symptoms (nausea, vomiting, and diarrhoea), and/or respiratory symptoms (dyspnoea, and cough).[6,9]

The potential severity of ABC-HS contraindicates drug re-challenge. In this regard, patch tests with abacavir may be a useful diagnostic tool, although the procedures for patch testing with this drug are not yet standardized nor are the non-irritant drug concentrations fully established. The rationale for patch testing in patients with acute drug-induced hypersensitivity syndromes is the eventual metabolism of the parent drug to a reactive metabolite in skin and the identification of resident CD8+ cells in skin biopsies of such patients.[10]

Hypersensitivity reactions to ABC have been strongly associated with the HLA-B*57:01 allele.[11] The prevalence of the HLA-B*57:01 seems to be variable among different populations and to be the highest in the European white population (about 7%).[9,12] A large multicentric clinical trial from the PREDICT-1 study team established the effectiveness of prospective HLA-B*57:01 screening in preventing the ABC-HS, with positive and negative predictive values of 47.9% and 100%, respectively.[13] This determined, since 2008, the recommendation of routine screening of the allele prior treatment with ABC, eventually limited by its availability and cost, depending on the region. On the other hand, the cost-effectiveness of the screening will lean on several estimates, namely the availability of appropriate laboratory assays, the population studied and the health care setting.[13,14]

To the authors knowledge no previous studies have evaluated the impact of HLA-B*57:01 routine screening in the prevalence of ABC-HS in Portuguese HIV-positive patients. Our aim was to determine the prevalence of HLA-B*57:01 carriage in the adult HIV population followed in our hospital and to characterize suspected ABC-HS during a 7-year period, before and after introduction of routine HLA-B*57:01 screening.

Methods

The study has been conducted in a tertiary hospital, in the city of Porto, located in Northern Portugal. In our hospital, routine HLA-B*57:01 screening prior to treatment with ABC has been implemented since January 2008.

We first identified HIV-positive patients that underwent ABC treatment at some point between January 2006 and December 2007, consulting the dispensing records from the hospital pharmacy (**group A**). We also identified all HIV-positive patients who had an indication to start ABC therapy from January 2008 to December 2012 (**group B**); these patients had been previously screened for HLA-B*57:01 carriage (by real-time polymerase chain reaction).

Medical records of the patients were then reviewed. For patients from both groups, we identified those with any symptoms suggestive of ABC-HS (fever, constitutional symptoms, exanthema, gastrointestinal tract symptoms, and/or respiratory symptoms) and the characteristics of the reaction were recorded. Information regarding HLA-B*57:01 carriage status was also retrieved for patients of both groups.

Patients with suspected ABC-HS were called to undergo patch testing with ABC. Patch tests were performed between January and July 2013, with 300 mg ABC-tablets crushed in petrolatum at 1% and 10% concentrations, prepared in our Pharmacy Department, with readings at 48 h and 72 h.[10] Positive results on patch tests were graded according to the International Contact Dermatitis Research Group: (+) mild reaction, possible erythema, infiltration and papules, (++) strong reaction, erythema, infiltration, papules and vesicles, and (+++) very strong reaction, intense erythema, infiltration and coalescing vesicles.[15]

This study was approved by the local ethics committee and all patients gave their informed consent for any diagnostic procedures performed.

Statistical analysis

The characteristics of the population were summarized with descriptive statistics. For qualitative data, absolute and relative frequencies were determined; for quantitative data, medians and interquartile ranges (IQR) were calculated as measures of central tendency and of dispersion, respectively. Data were analyzed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA).

Results

There were 186 HIV-positive patients initiating treatment with ABC from January 2006 to December 2007 (group A). We could access the medical records of 163 of these patients, identifying 7 (4.3%) cases of suspected ABC-HS, 5 of them fulfilling the generally accepted clinical diagnostic criteria – Table 1. The patients' median [IQR] age at the time that the reaction occurred was of 45.0 [35.0–59.0] years, and affected patients were all Caucasian and predominantly males ($n = 5$). The median [IQR] time to symptoms onset after treatment started was 7.0 [3.0–12.0] days. Three patients had liver enzymes elevation, 3 presented with exanthema and 3 other with fever; 1 patient had respiratory involvement. The median time between the onset of symptoms and ABC treatment withdrawal was 1.0 day (range: 0–8 days). All reactions were managed on an outpatient basis. Only one patient needed additional treatment for the reaction (case 2), where antihistamine and corticosteroid were used. We were able to assess 6 patients for the presence of HLA-B*57:01 allele, and to perform patch tests with ABC in 6 (one patient was unable to return to the hospital to perform this test). Two patients had a positive patch test (Fig. 1). Four patients with suspected ABC-HS (of 6 screened) were positive to the HLA-B*57:01 allele (Table 1).

After the implementation of routine HLA-B*57:01 testing, from January 2008 onwards, 573 patients with an indication to start treatment with ABC were screened. Thirty-five (6.1%) had the allele, contraindicating the use of ABC. In the remaining patients from group B that started treatment with this drug, no suspected ABC-HS cases were observed.

Discussion

In this study, we report a prevalence of suspected ABC-HS of 4.3% (3.1% using strict clinical criteria) before implementation of routine HLA-B*57:01 screening, in a predominantly white population from a reference Infectiology Department in Portugal. ABC-HS has been described as a treatment-limiting event in approximately 4% of patients treated with ABC,[8] which is in accordance with our findings. However, if we consider patients with confirmation of an underlying immunologic mechanism, the prevalence would be lower (1.2%).

The nonspecific symptoms that characterize ABC-HS may lead to an over-diagnosis of the syndrome (preventing patients from receiving an ABC containing regimen), a problem that may be addressed by validated patch testing procedures, assuming that a delayed immunologic mechanism underlies the ABC-HS.[10,16] That fact possibly explains why in our study not all patients with suspected ABC-HS had a positive patch test. Another possible reason for the reported negative skin test results is the fact that