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HLA-B*57:01 genotype and Abacavir therapy: first report from genomic lab in AORN dei Colli Naples -Italy

Abstract

AIDS (acquired immunodeficiency syndrome) is an infectious disease caused by the HIV virus (human immunodeficiency virus). The core of HIV treatment is antiretroviral therapy (ART). Abacavir, an antiretroviral drug used to treat HIV infections, is widely used in the treatment of HIV-supported infections. The active ingredient of the drug is not able to completely eradicate the infection, leading to a patient's recovery, but it reduces the amount of virus in the body, keeping it at low levels. Pharmacogenetic tests are used in clinical practice to optimize the choice of medication or clinical management of the patient. Before starting treatment, it is necessary to perform a genetic exam to assess the presence of the HLA allele B57:01. Patients with the HLA B57:01 allele are therefore at increased risk of hypersensitivity to Abacavir. An adverse effect of abacavir is a hypersensitivity reaction, which can be severe and potentially life-threatening, and may limit treatment with the drug. The abacavir-induced hypersensitivity reaction was therefore associated with the presence of the class I allele of the major histocompatibility complex HLA-B*5701. Screening patients for HLA-B*57:01 before starting abacavir therapy reduces the incidence of hypersensitivity reactions. The study we carried out aims to evaluate the presence of the HLAB57:01 allele in the HIV-positive population present in our territory.

Keywords: HLAB57:01, Abacavir, hypersensitivity, HIV+, AIDS.

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Introduction

The major histocompatibility complex (MHC) is a group of cell surface proteins that can bind to foreign molecules to be recognized by corresponding T cells, followed by induction of the immune system.[1] MHC is highly conserved and present in all vertebrate species. In humans, MHC is also known as the human leukocyte antigen complex (HLA), which consists of more than 200 genes on chromosome 6 and can be classified into three subgroups: class I, class II and class III.[2] The class I region contains genes coding for the HLA HLA-A, HLA-B and HLA-C molecules. HLA molecules consist of a heavy and a light chain (α and β 2-microglobulin respectively).[3]

An important role of class I HLA molecules is to present peptides (processed fragments of antigens) to immune cells (CD8+ T cells). Recruitment and activation of CD8+ T cells is achieved through the specific interaction of the T cell receptor (TCR) with peptides bound to human leukocyte antigen (HLA).[4] Generally, old proteins in cells will be broken down to synthesize new peptides. Some of these broken peptide pieces attach to MHC molecules and are recognized by immune cells as "self". When a cell is infected with pathogens, the pathogenic peptides attached to MHC molecules will be recognized as "non self" from CD8+ T cells which will activate to release inflammatory cytokines and activate an immune response for the elimination of the pathogen.

HLA genes are numerous and highly polymorphic in order to bind various types of peptides originating from either own or foreign antigens. Variations in HLA genes play an important role in determining susceptibility to autoimmune diseases and infections.

Several HLA-B alleles have been identified and each of them has been assigned an identification number, such as HLA-B*57. The subtype HLA-B*57:01 is associated with a considerable sensitivity to treatment with Abacavir, a drug that delays the spread of HIV-1.[5] In most patients, antiretroviral therapy includes two nucleoside reverse transcriptase inhibitors (NRTIs) and an integrase filament transfer inhibitor (InSTI). These inhibitors function to stop viral replication and slow down the progression of infection. Abacavir is one of the NsRT, it has been shown to cause an oversensitive response in 5-8% of treated patients.[6,7] An oversensitive reaction can be life threatening in case of new system stimulation; therefore, understand the mechanism and predictive power of the major histocompatibility complex allele, class I, B 5701 (HLA B 5701) as regards hypersensitive reactions is crucial to shaping the best clinical practice.[8]

The mechanism of hypersensitivity reactions to abacavir is thought to be due to the formation of a complex between short peptide fragments derived from the drug and the HLA-peptide, specifically with HLA- B 57:01.[9] This complex activates CD8+ T cells, which release inflammatory cytokines and initiate the hypersensitivity response. More recently, it has been shown that abacavir may occupy a space below the HLA region, which leads to an altered presentation of the peptide and triggers an autoimmune reaction. Screening for HLA-B*5701 before starting abacavir therapy is recommended by the Panel on Antiretroviral Guidelines for Adults and Adolescents (a working group of the Office of AIDS Research Advisory Council) Department of Health and Human Services (DHHS) and the Panel on Antiretroviral Therapy and Medical Management of HIV-infected children.[10]

Symptoms associated with adverse reactions usually occur within the first six weeks (average onset time: 11 days) of abacavir treatment, although such reactions may occur at any time during the course of therapy. Almost all hypersensitivity reactions (HSR) to abacavir

include fever and/or rash, many other adverse reactions, as follows (nausea, vomiting, diarrhea, fever, lethargy, rashes), frequently occur in patients with hypersensitivity to Abacavir.[11]

Genotype

All patients should be screened for the HLAB57:01 allele before starting treatment with Abacavir.

To test the HLA-B*5701 allele, a whole blood sample is collected in EDTA. The gene sequences coding for HLA -B*5701 are probed and reported as positive if allele is present, or negative if allele is absent, no intermediate phenotypes.

Therefore, abacavir is contraindicated in HLA-B57:01 positive subjects and patients with a previous hypersensitivity reaction to Abacavir.[12]

The absence of the HLA-B57:01 allele (negative) results in a very low risk of hypersensitivity unlike HLA-B57:01 positive patients who therefore cannot take the drug ABACAVIR. It is known that some HIV-positive individuals expressing the HLA-B57:01 allele have the ability to control the virus and maintain a low viral load, without needing care. This ability delays progression in AIDS.[13,14]

Materials and methods

Our study was carried out on 760 HIV-positive patients, evaluated in the period from 2019 to 2024 at the Molecular Genomics lab in Monaldi Hospital - Azienda Ospedali dei Colli, Naples, Italy, and written consent was obtained from all the participants.

The tests were performed on gDNA extracted from peripheral blood samples. Current Abacavir hypersensitivity tests detect the subtype HLA-B*57:01 by allele-specific polymerase chain reaction (PCR). In our study we performed real-time allele-specific PCR using the Cobas z480 instrument by Roche in combination with the "AMPLI HLAB*5701 REAL TIME" kit by DIACHEM srl, following the producer's protocol. The kit uses TaqMan probes, and the multiplex also contains a primer for human beta-globin as internal control for DNA amplification.[15]

Results

The Food and Drug Administration (FDA) guidelines, the Clinical Pharmacogenetics Implementation Consortium (CPIC) and the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP), recommend that HLA-B*57:01 should be performed for all HIV+ patients before starting Abacavir therapy and an alternative drug should be administered to allele positive patients. Abacavir is also contraindicated in patients with a previous hypersensitivity reaction to the drug.

Our study analyzed, over 6 years, a cohort of 760 patients from 16 to 80 years old (median age 40 years old) as well described in Tables 1–5.

Table 1 Distribution of screened population by gender

Gender	No.	%
Male	676	89%
Female	84	11%

Table 2 Distribution of patients in our cohort by ethnicity

Ethnicity	No.	%
Italian UE citizens	500	65.70%
Non-Italian UE citizens	72	9.40%
African citizens	88	11.50%
Sub American citizens	79	10.70%
Asian citizens	21	2.70%
Total	760	100%

Table 3 Distribution of positive patients by sex

Gender	No. of positive patients	%
Female	12	28%
Male	30	72%
Total	42	100%

Table 4 Distribution of positive patients by ethnicity

Ethnicity	No.	%
Non-Italian UE citizens: Ukrainian	1	2.40%
Italian UE citizens	32	76.10%
African citizens	9	21.50%
Sub American citizens	0	0%
Asian citizens	0	0%
Total	42	100%

Table 5 Comparison between positive and negative tests

Genotype	Phenotype implications	No (%)
HLA B57:01 Positive	High hypersensitivity to Abacavir: do not use the drug, as explained in the guidelines	42 (5.5%)
HLA B57:01 Negative	Low hypersensitivity to Abacavir: use the drug according to the guidelines	718 (94.5%)

Limitations of the study

One of the main limitations of this study is the uneven distribution of ethnicities among patients. As the research was conducted in a hospital located in Italy, there is a significant representation of Italian nationality within the sample.

The sample size for Asian ethnicity is insufficient and there is a significant lack of representation of other ethnic groups. The samples are based on the hospital's catchment area, which is predominantly composed of patients of Caucasian ethnicity and Italian nationality. Consequently, the conclusions drawn from this study may not accurately reflect the diversity of HLA-B*57 allele prevalence and clinical implications between different ethnicities. Future research should aim to include a more balanced and diverse sample to better understand the impact of the allele across ethnicities.

Conclusion

Our results highlight that the prevalence of HLA-B*57 is low as reported in literature.[16] However, it appears that the allele is more expressed in patients of Caucasian and African ethnicity. Extensive cohort studies in Caucasian and African populations infected with HIV-1 have shown that the HLA-B*57 allele has a protective effect against disease progression.

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The advantage of HLA-B*57 can be explained by a strong ability of Gag-specific HLA-B*57 T cells to suppress replication of HIV-1 and reduce the suitability of mutants selected from these T cells.[17]

HLA-B*57 screening was added to clinical care guidelines in 2008 to reduce the risk of hypersensitivity reaction (HSR) from Abacavir. HSR represent an important clinical problem in the treatment of HIV positive patients. Screening of HLA-B*57 has the potential to eliminate confirmed immune hypersensitivity reactions: the presence of the HLA-B*57 allele has a negative predictive value of 100% and a positive predictive value of 47.9% for immunologically confirmed HSR.[8]

Screening for HLA, in addition to avoiding adverse reactions brings cost savings that relate to the management of the patient with an ongoing HSR. The patient with HSR either accesses the emergency room or needs to be treated in the ward, often HSR is then followed by hospitalization or a prolonged hospital stay. It is therefore more cost-effective to perform the screening test than to manage an emergency department access, hospitalization and therapies to intervene in the hypersensitivity reaction.

Therefore, the HLA-B*57 test to prevent hypersensitivity to Abacavir was also reported to be cost effective. Routine testing are a dominant strategy, less expensive and more beneficial than not testing and led to an incremental cost-effectiveness ratio of 22.811 euros per hypersensitivity reaction avoided. Pre-treatment genetic screening can improve patient management in hospital in financially, too.[18,19]

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None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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