Pharmacogenomics in clinical practice: example of HLA-B*5701 and the hypersensitivity reaction to Abacavir

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Abstract

Pharmacogenomics is the study of variation in the characteristics of nucleic acids relating with response to drugs. It is considered crucial to the development of individualized Medicine. Adverse reactions to drugs increase morbidity, mortality and healthcare costs. Pharmacogenomics holds the potential to reduce drugs adverse reactions. HIV infected patients have a higher incidence of hypersensitivity reactions. Abacavir is a reverse transcriptase nucleoside inhibitor used in the treatment of HIV infection, but causes hypersensitivity reactions in 5 to 8% of the patients. There has been a link of HLA-B*5701 with abacavir hypersensitivity reaction and the analysis of HLA-B*5701 may reduce the incidence of this hypersensitivity reaction.

Key words: pharmacogenomics, HLA-B*5701, Abacavir.

PHARMACOGENOMICS

Pharmacogenomics is defined as "the study of variations in DNA and RNA characteristics related to response to drugs", and it is considered a key factor for the development of personalized Medicine strategies through the increase in knowledge, at molecular level, of disease and the response to treatment.[1]

Recent advances in genomic technologies are increasing our knowledge of the variability of the human genome, including variability at nucleotide level (single nucleotide polymorphisms – SNPs; large insertions and deletions; duplications – copy number variations - CNVs). DNA sequence polymorphisms can affect susceptibility to diseases, pathological manifestations and response to therapy. However, transposing this information to clinical practice continues to present challenges.[1]

Genetics can affect various aspects of therapy, in particular, pharmacokinetic (availability of the drug), pharmacodynamic (efficacy) and adverse effects (which may or may not be dose-related).[1]

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ADVERSE REACTIONS

The adverse reactions to drugs increase morbidity, mortality and costs associated with health care.

A meta-analysis estimated that annually, more than two million hospitalized patients develop adverse reactions to drugs and that these, in 1994, were between the 4th and 6th highest causes of death in the United States of America.[2]

It is calculated that the hospital costs directly attributable to adverse reactions reach 1.56 to 4 thousand million dollars annually in the United States.[3,4]

According to the definition of the World Health Organization, an adverse drug reaction is any harmful or undesirable and unintended response to a drug occurring at doses normally used in man for prophylaxis, diagnosis, therapy or modification of physiological functions.[5]

A probable cause of an adverse drug reaction is genetic variation in the individual metabolization of the drug.[6]

One benefit of Pharmacogenomics is its potential to reduce adverse drug reactions through a modification of the dose or drug used in individuals with lower capacity to metabolize it, due to genetic variation of the enzymes involved in this metabolism, or through the development of drugs that avoid metabolic pathways with adverse genetic variability.[6]

INFECTION BY THE HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Immune deregulation associated with HIV infection has various consequences, including higher incidence

of skin disease and reactions of hypersensitivity to drugs (described as occurring with 100 times higher frequency in individuals infected by HIV).[7]

The reactions of hypersensitivity in individuals infected by HIV are clinically similar to those that occur in non-infected individuals, and are generally characterized by a combination of fever, erythema and involvement of the internal organs within a period of 6 weeks after the start of the drug, and may be associated with significant morbidity and mortality.[8,9] The physiopathology of reactions of hypersensitivity is probably multifactorial, involving host-related, viral, immunological and metabolic factors.[8]

HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY (HAART)

Currently the recommended antiretroviral treatment is a combined regimen. The initial treatment in patients who will start therapy for the first time should include nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and a non-nucleoside reverse transcriptase inhibitor (NNRTI) or an HIV protease inhibitor.[10,11]

The class of NRTIs prevents viral replication by competitive inhibition of viral RNA dependant DNA polymerase (reverse transcriptase). The NNRTIs bind directly with the reverse transcriptase, deactivating it. The protease inhibitors impede cleavage of the Gag protein and of the Gal-Pol protein precursors, making viral replication impossible in a later stage of the replication cycle.[10]

ABACAVIR AND PHARMACOGENOMICS

Abacavir is a nucleoside analog reverse-transcriptase inhibitor, available in a once-daily dosage formulation, effective, with few drug interactions and a favorable long-term toxicity profile. The most important adverse effect, which limits its use and requires close clinical surveillance, is a reaction of immunologically mediated hypersensitivity that occurs in 5 to 8% of patients during the first six weeks of treatment.[12,13] The symptoms of the hypersensitivity reaction include fever, erythema, constitutional, gastrointestinal and respiratory symptoms, which become more severe with the continuation of treatment. It is necessary to immediately and permanently suspend the drug, which leads to a rapid resolution of the symptoms in 48-72 hours, although the disappearance of erythema can take longer. New exposure to the drug is contraindicated, as this can lead to a faster, more severe, and potentially fatal reaction.[12-15]

Sometimes it is difficult to distinguish the reaction of hypersensitivity to Abacavir from systemic viral diseases or adverse reactions to other drugs (anti--retroviral or antibiotic drugs administered simultaneously).[10,14]

In 2002, two independent groups published results that indicate a statistically significant association between HLA-B*5701 (a marker of the major histocompatibility complex - MHC) and reaction of hypersensitivity to Abacavir.[16,17]

Subsequently, results of prospective trials were reported in which the determination of HLA-B*5701 and the eviction of Abacavir in patients who are positive for this allele reduced the incidence of reactions of hypersensitivity to Abacavir.[18-20]

During this period, an Abacavir skin patch test was developed, which is used as an investigation tool for the identification of patients who present hypersensitivity to Abacavir. An Abacavir adhesive is applied on the back or arm of patients with clinical suspicion of hypersensitivity to Abacavir. It is removed after 24 hours. A positive skin reaction (erythema, hardening and itching) in the site of application of the adhesive is similar to the skin symptoms of the reaction of hypersensitivity to Abacavir, which is compatible with a reaction that is immunologically mediated, and is closely correlated with the clinical diagnosis of hypersensitivity to Abacavir and with the presence of the HLA-B*5701 allele.[14,15]

In 2006, two clinical trials were begun, to investigate the predictive value of HLA-B*5701: PREDICT-1 and SHAPE.

The PREDICT-1 trial was a prospective trial which assessed the clinical utility of the HLA-B*5701 determination in the incidence of reaction of hypersensitivity of Abacavir in more than 1900 patients infected by HIV who had never taken Abacavir. The results revealed that HLA-B*5701 determination can reduce the incidence of reaction to hypersensitivity. The exclusion of HLA-B*5701-positive patients from treatment with Abacavir eliminated the hypersensitivity reactions to Abacavir mediated immunologically, confirmed by the skin test, and significantly reduced the clinical diagnostic rate of hypersensitivity reactions. The determination of HLA-B*5701 enabled a group at high risk of hypersensitivity reaction to be established (in the case of the population of the pre-

sent study, 6% of HLA-B*5701 patients).[12,14]

The SHAPE trial was a retrospective case-control trial that investigated the relationship between HLA--B*5701, and the hypersensitivity reaction to Abacavir could be generalized to non-Caucasian populations. The results support the hypothesis that there is a relationship between HLA-B*5701 and the reaction of hypersensitivity to Abacavir also in non-Caucasian populations.[21,14]

As a corollary to these and other studies, the latest European and North American therapeutic guidelines for the treatment of HIV recommend investigation of HLA-B*5701 before the start of treatment with a regimen that includes Abacavir.[22,23]

It should be mentioned that there is no 100% guarantee that HLA-B*5701 negative patients will not develop a reaction of hypersensitivity to Abacavir.

CONCLUSION

Although there is a growing amount of data and lines of investigation relating to the theme of Pharmacogenomics and anti-retroviral therapy, there are numerous barriers to the direct application of this knowledge, which provides individualized therapy for patients infected by HIV.[9]

The use of HLA-B*5701 detection for the determination and pre-treatment, of patients with a high risk of developing a reaction of hypersensitivity to Abacavir will set an important precedent in the transition from individualized Medicine to clinical practice, and in the use of genetic tests to increase the safety of drugs.[8,14]

Nowadays, there is a moral and ethical obligation to perform HLA-B*5701 detection tests in the clinical practice, in order to avoid reactions of sensitivity to Abacavir. Currently, as requested by the European and American authorities (EMA and FDA), the legal information (Summary of Product Characteristics – SPC) for drugs containing Abacavir now recommend the use of HLA-B*5701 detection tests in clinical practice, as a tool for optimizing therapy.[24,25] ■

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