Therapie (2017) xxx, xxx—xxx

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PHARMACOGENETICS

Pharmacogenetics of hypersensitivity drug reactions

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Received 5 July 2016; accepted 2 September 2016

KEYWORDS
Hypersensitivity drug reactions;
HLA;
Abacavir;
Carbamazepine;
Allopurinol

Summary Adverse drug reactions are a significant cause of morbidity and mortality and represent a major burden on the healthcare system. Some of those reactions are immunologically mediated (hypersensitivity reactions) and can be clinically subdivided into two categories: immediate reactions (IgE-related) and delayed reactions (T-cell-mediated). Delayed hypersensitivity reactions include both systemic syndromes and organ-specific toxicities and can be triggered by a wide range of chemically diverse drugs. Recent studies have demonstrated a strong genetic association between human leukocyte antigen alleles and susceptibility to delayed drug hypersensitivity. Most notable examples include human leukocyte antigen (HLA)-B*57:01 allele and abacavir hypersensitivity syndrome or HLA-B*15:02 and HLA-B*58:01 alleles related to severe cutaneous reactions induced by carbamazepine and allopurinol, respectively. This review aims to explore our current understanding in the field of pharmacogenomics of HLA-associated drug hypersensitivities and its translation into clinical practice for predicting adverse drug reactions.

Abbreviations

ADRs	adverse drug reactions
APC	antigen-presenting cell
DIHS	drug-induced hypersensitivity syndrome
EMA	European Medicines Agency
FDA	Food and Drug Administration
HDRs	hypersensitivity drug reactions
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
MPE	maculopapular eruption
NPV	negative predictive value
PPV	positive predictive value
SJS	Stevens-Johnson syndrome
TCR	T-cell receptor

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http://dx.doi.org/10.1016/j.therap.2016.12.009
0040-5957/

Please cite this article in press as: Negrini S, Becquemont L. Pharmacogenetics of hypersensitivity drug reactions. Therapie (2017), http://dx.doi.org/10.1016/j.therap.2016.12.009

TEN toxic epidermal necrolysis
WHO World Health Organization

Hypersensitivity drug reactions

Adverse drug reactions (ADRs) are defined by the World Health Organization (WHO) as an ''unintended, noxious response to a drug that occurs at a dose usually prescribed for human patients'' [1]. ADRs are recognized as a major health problem, in the United States they are responsible of 6—7% of hospitalization cases and represent the fourth to sixth leading cause of death accounting for 100,000 fatal cases annually [2]. In Europe, it is estimated that 5% of all hospital admission and 197,000 deaths per year are caused by ADRs [3]. Along with the mortality and morbidity burden, it is estimated that the total cost to society of ADRs is $ 177 billion and € 79 billion in the USA and Europe, respectively [3,4]. Moreover, ADRs remain a huge cost burden for pharmaceutical industry representing the main cause of drug withdrawal from the market [5].

The historical pharmacologic classification of ADRs by Rawlins and Thompson classifies these into two main categories [6]. Type A reactions are predictable, dose-dependent, and related to pharmacologic properties of the drug, and Type B reactions, accounting for approximately 10% of all ADRs, are unpredictable, not dose-dependent and correspond to hypersensitivity drug reactions (HDRs). Occurring only in susceptible individuals Type B ADRs are sometimes termed ''idiosyncratic''. Since, terminology used to define HDRs is often confusing due to a lack of commonly accepted definitions, the European Academy of Allergology and Clinical Immunology published a statement paper in order to standardize the nomenclature of allergic diseases, also including drug allergy [7]. The revised nomenclature has been further adopted by the World Allergy Organization [8]. The proposed classification define as ''drug allergy'' those HDRs in which immunologic mechanisms may be demonstrated, while HDRs with symptoms and signs similar to real allergies but not triggered by a specific immunological mechanism are referred to as ''non-allergic drug hypersensitivity'' (e.g. non-specific histamine release, arachidonic acid pathway activation, bradykinin pathway alteration, etc.). With regard to the onset of symptoms, drug allergies may be further classified as immediate or delayed, suggesting also the immunological mechanism underlying the reaction [7,8].

Immunological basis of hypersensitivity drug reactions

Immediate reactions occur immediately after drug exposure, are IgE-dependent, and derive from mast cell degranulation and release of pro-inflammatory mediators. Clinical manifestations include erythema, urticaria, angioedema, bronchospasm, and anaphylactic shock. Delayed hypersensitivity reactions generally occur days, or even weeks, after drug exposure and are mediated by antigen-specific T lymphocytes. Examples of delayed-type HDRs include both systemic syndromes (e.g. drug rash with eosinophilia and systemic symptoms) and organ-specific toxicities (e.g. hepatitis, pneumonitis, etc.). Delayed-type hypersensitivity reactions correspond to type IV hypersensitivity according to the classification system of Gell and Coombs [9]. Since T-cells can orchestrate different immune responses resulting in different clinical entities, delayed reactions can be further classified into IVa (Th1 cells), IVb (Th2 cells), IVc (cytotoxic T-cell), and IVd (neutrophils) [10].

Since drugs are generally too small to stimulate an immune response (molecular weights < 1000 Daltons), several, non-mutually exclusive, models have been proposed to explain how drugs can become immunogenic and trigger T-cells: the ''hapten/pro-hapten model'', the ''Pi (pharmacologic interaction with immune receptors) concept'', the ''altered peptide repertoire hypothesis'' and the ''danger signal'' theory. The ''hapten/pro-hapten model'' proposes that a chemically reactive drug, acting as hapten, can bind covalently to self-proteins (carriers) creating fully antigenic complexes. These neo-antigens are processed by an antigen-presenting cell (APC), loaded onto the HLA molecules and then presented to appropriate T-cells. The pro-hapten is a chemically non-reactive drug that becomes reactive upon metabolism [11]. According to ''pi-concept hypothesis'', a chemically inert drug, unable to covalently bind to proteins, is able to structurally ''fit'' into the T-cell receptor. This interaction needs neither metabolism nor antigen processing. The initial stimulation of the T-cell receptor (TCR) is further supplemented by TCR-HLA interaction and probably must take place in a context of hyper-reactive T-cells with a low threshold level of activation [12—14]. The ''altered peptide repertoire hypothesis'' proposes that the drug binds the antigen-binding groove of HLA thus modifying the antigen-binding cleft thus altering the repertoire of self-peptides that are bound and presented. Since T-cells are educated to be tolerant to a specific pool of peptides during thymic maturation, the presentation of these neo-self-peptides may induce T-cell activation. Recent observations provide strong evidence that this model is implicated in HDRs related to abacavir and carbamazepine [15]. Last hypothesis proposes that the drug itself or concomitant situations (e.g. viral infections) can provide ''danger signals'' capable of upregulating costimulatory molecules and cytokines in innate immune cells, thus facilitating the immune activation [11].

The human leukocyte antigen (HLA) molecules plays a crucial role in T-cells activation by presenting processed antigens to the T-cell receptor expressed on T lymphocytes. Broadly speaking, there are two main types of HLA molecules: the HLA class I molecules, expressed on most nucleated cells, and the HLA class II molecules, expressed by APCs, such as monocytes or dendritic cells. HLA class I molecules are encoded by three loci known as HLA-A, HLA-B, and HLA-C; HLA class II molecules are encoded by three loci known as HLA-DR, HLA-DQ, and HLA-DP. HLA class I and class II molecules initiate the adaptive immune response by presenting antigens to CD8+ (cytotoxic) and CD4+ (helper) T-cells. Because the HLA molecules need to present an huge variety of ''self'' and ''non-self'' peptides, the HLA genes are both numerous and extremely polymorphic. Taking into account the crucial role of HLA in immune response it is not surprising that particular HLA alleles have been associated with susceptibility to diseases in which the immune system is considered the principal mediator, like infectious or autoimmune disorders [16,17]. In the same way, certain HLA alleles have been associated with an increased risk of delayed HDRs.

Please cite this article in press as: Negrini S, Becquemont L. Pharmacogenetics of hypersensitivity drug reactions. Therapie (2017), http://dx.doi.org/10.1016/j.therap.2016.12.009