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Drug Allergy (C Mayorga, Section Editor)

How Mechanism Knowledge Can Help to Management of Drug Hypersensitivity

A. Ariza, PhD[1,*]
T.D. Fernández, PhD[1]
G. Bogas, PhD, MD[1,2]
M.J. Torres, PhD, MD[1,2,3,4]
C. Mayorga, PhD[1,2,3]

Address
[*,1]Allergy Research Group, Instituto de Investigación Biomédica de Málaga-IBIMA, Hospital Civil, Málaga, Spain
Email: adriana.ariza@ibima.eu
[2]Allergy Unit, Hospital Regional Universitario de Málaga, Hospital Civil, Málaga, Spain
[3]Nanostructures for Diagnosing and Treatment of Allergic Diseases Laboratory, Andalusian Center for Nanomedicine and Biotechnology-BIONAND, Parque Tecnológico de Andalucía, Málaga, Spain
[4]Departamento de Medicina, Facultad de Medicina, Universidad de Málaga, Málaga, Spain

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Abstract

Purpose of review To describe the mechanisms involved in the heterogeneous drug hypersensitivity reactions and how a better understanding of them can help in the correct diagnosis, the improvement of the in vitro diagnostic methods, and the management of the reaction.
Recent findings We know that drug hypersensitivity reactions are mediated by different mechanisms and until now some drugs have been reported to be able to activate the immune system by a single mechanism while other drugs can be involved in different mechanisms. Moreover, studies show that important clinical aspects such as risk factors, predictability, and cross-reactivity may depend on the drug action mechanism. In this way, recent genetic association studies have shown different human leukocyte antigen (HLA) associations with hypersensitivity reactions depending on the drug and/or the mechanism involved.
Summary Mechanistically, drug hypersensitivity reactions (DHRs) are classified as allergic and non-allergic reactions. Allergic reactions have been further classified into reactions mediated by IgE, IgG, or IgM; immune complex/complement activation; and T cells. Non allergic

reactions can be associated to nonspecific histamine release, bradykinin increase, complement activation, or changes in the metabolism of arachidonic acid. More recently, a classification based on the mode of action of drugs has been proposed, suggesting three mechanisms involved in DHRs: (i) drugs that bind covalently on macromolecules (e.g., proteins) (allergic/immune reaction); (ii) drugs that bind on immune receptors like HLA and T cell receptors (pharmacological interaction, p-i reactions); and (iii) drugs with the ability to stimulate or inhibit receptors or enzymes of inflammatory cells (pseudo-allergy). An extended knowledge on the mechanisms involved in the heterogeneous DHRs can help to understand differences in sensitization patterns, uncommon clinical manifestations, dependence on drug dose, predictability, and cross-reactivity. For that, a better understanding of them can help in the correct diagnosis and the management of the reaction.

Introduction

Adverse drug reactions (ADR) are defined by the World Health Organization (WHO) as "any noxious, unintended and undesired effect of a drug that occurs at doses used for prevention, diagnosis or treatment" [1]. They are a relevant public health problem, involved in 3–6% of hospitalizations and in 10–15% of hospitalized patients [2, 3]. The pharmacological classification suggested by Rawlins and Thompson in 1974 [4] is the most widely applied and divided the ADRs in predictable (type A) and unpredictable (type B) reactions. Drug hypersensitivity reactions (DHRs) are type B reactions, defined by the WHO as "dose-independent, unpredictable, noxious, and unintended response to a drug taken at a dose normally used in humans" [1, 5].

DHR classification is complex because of the heterogeneity in terms of drug involved, clinical symptoms, and underlying mechanisms. Clinically, DHRs are usually classified as immediate or non-immediate/delayed based on the time interval between the drug exposure and the onset of the symptoms [6]. This classification has limitations and it is controversial because of the subjective cut-off point. Nowadays, a new cut-off point that classified these reactions into immediate (<1–6 h after drug exposure) and non-immediate (>1 h after drug exposure) has been proposed [7], overlapping immediate and non-immediate reactions from 1 to 6 h [6, 8•], originally defined by Levine [6] as "accelerated reactions." Immediate reactions are mostly mediated by an IgE-mechanism and they commonly appear as isolated clinical manifestations like urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, or as systemic reactions like anaphylaxis or anaphylactic shock [9]. Non-immediate reactions are usually mediated by specific T cells; however, other mechanisms can be implicated [7] and the most usual clinical presentations are delayed urticaria and maculopapular exanthemas, as well as more severe reactions like acute generalized exanthematous pustulosis (AGEP), toxic epidermal necrolysis (TEN), Stevens–Johnson syndrome (SJS), and drug reactions with eosinophilia and systemic symptoms (DRESS). Though this classification is very useful in clinical routine, there are weaknesses due to other factors (e.g., administration route, drug metabolites, cofactors, coprescribed drugs) may increase or decrease the time interval between the drug administrations and the onset of the symptoms [10].

Mechanistically, DHRs are classified as allergic and non-allergic reactions [9]. ADRs with and immunological basis (ADRIBs) or allergic reactions have been furthermore classified in accordance with the classification system proposed by Gell and Coombs [11]: type I reactions, mediated by specific IgE with mast cells and/or basophils as main effector cells; type II reactions (cytolytic or cytotoxic), mediated by specific IgG or IgM; type III reactions (immune complex), mediated by immune complex and complement activation; and type IV reactions, mediated by specific T cells that can be subdivided (type IVa–IVd) according to the mechanism involved [12]. On the other hand, there are reactions with clinical symptoms compatible with an allergic reaction that are not true drug allergies. The proposed pathomechanisms for these reactions are (i) nonspecific histamine release by masts cell and basophils, (ii) bradykinin accumulation, (iii) complement activation, (iv) alterations in arachidonic acid metabolism, and (v) bronchospasm induction by the pharmacological action of some drugs [7].

Finally, a classification based on the way drugs interact with the immunological system was proposed by Pichler et al. [13, 14••, 15••] to better comprehend different aspects of DHRs. According to this classification, three mechanisms can be involved in DHRs: (i) drugs that bind covalently on proteins and form carrier complexes (allergic/immune reaction); (ii) off-target action of drugs on immune receptors like human leukocyte antigen (HLA) and T cell receptors (TCR) (pharmacological interaction, p-i reactions); and (iii) drugs with the ability to stimulate or inhibit receptors or enzymes of inflammatory cells (pseudo-allergy). This classification is based on the drug action and is helpful in clinical practice, because it can clarify differences in sensitization patterns and can explain differences in sensitizations, uncommon clinical manifestations, dependence on drug dose, predictability, and cross-reactivity in DHRs. In this review, we focus on the description of mechanisms involved in the heterogeneous DHRs and how a better understanding of them can be helpful in the correct diagnosis with the improvement of the in vitro diagnostic methods and the management of the reaction.

Mechanisms involved and clinical manifestations

Allergic reactions: hapten hypothesis

Most of the drugs and their reactive metabolites are considered haptens, small molecules (<1000 Da) too small to induce a specific immune response. The hapten hypothesis states that haptens are able to covalently bind on endogenous proteins, directly or previous drug metabolism [16], to form an antigenic hapten-carrier complex [17–19] (Fig. 1). The main protein targets for haptens could be serum proteins (e.g., albumin,hemoglobin), intracellular proteins, or specific tissue proteins. According to this hypothesis, both haptens and proteins are relevant for the immunological recognition by specific antibodies or specific T cells. Therefore, it is crucial to fully characterize the haptenic structures to better understand the molecular bases of DHRs. Hapten-protein adducts are processed to peptides and presented as peptide-HLA complexes by antigen-presenting cells (APCs), like dendritic cells and B cells and then finally recognized by TCR, eliciting drug-specific humoral or cellular immune responses [20, 21]. It is important to highlight that although the generation of drug-carrier proteins adducts are required to induce an immune response, more factors are needed, so different studies have shown circulating drug modified proteins are detected in tolerant subjects without hypersensitivity [22••, 23•]. Hapten-like drugs are capable to induce the four types of allergic reactions proposed by Gell and Coombs [11, 12], although the most clinically relevant immune-mediated DHRs are the types I and IV. Some of the drugs are able to bind stably and covalently to proteins as carrier molecule include betalactam antibiotics (benzylpenicillin [24], amoxicillin [25–27], piperacillin [28], flucloxacillin [29], and carbamazepine (CBZ) [30••], as well as other drug such as sulfanilamides, metamizole, quinolones, radiocontrast media, and muscle relaxants [14••, 15••].

IgE-mediated (type I) allergic reactions

Pathophysiology

IgE-mediated allergic reactions develop due to the production of specific IgE by specific B lymphocytes after a previous sensitization phase

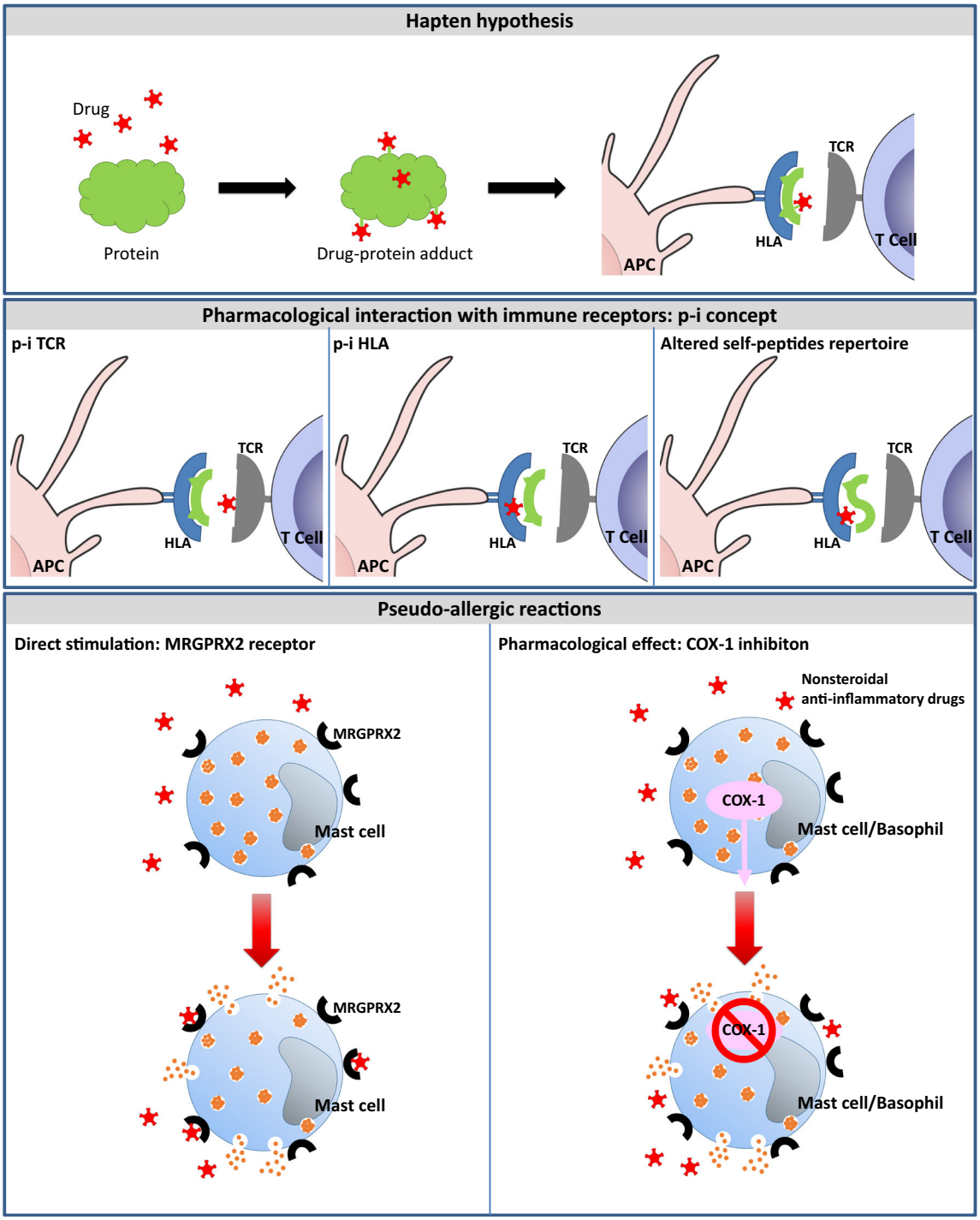

Fig. 1. Mechanisms of drug interaction with the immune system proposed for drug hypersensitivity reactions. COX-1, cyclo-xigenase-1; HLA, human leucocyte antigen; TCR, T cell receptor.>

[7, 31, 32]. In this way, specific IgE molecules are released into the bloodstream and then, a proportion of these antibodies are reversible linked to specific high affinity receptors (FcεRI) expressed on the surface of basophils and mast cells [33, 34]. Then, after a new drug exposure, the antigen (hapten-protein adduct) interact with two or more adjacent specific IgE molecules bound on the surface of mast cells and basophils (cross-linking) triggering an intracellular signaling cascade leading to the cellular activation and degranulation, with the extracellular release of preformed inflammatory mediators (e.g., tryptase, histamine, TNF-α), and the synthesis and secretion of lipid mediators (e.g., PAF, prostaglandins, and leukotrienes) and cytokines (e.g., IL-4 and IL-13) [35–39]. All of them are responsible for the clinical manifestations (vasodilatation, smooth muscle contraction, and inflammation) [37]. Betalactam allergic reactions are the best defined IgE-mediated reactions [40].

Clinical manifestations

IgE-mediated reactions are related with two main clinical entities: urticaria, with or without angioedema, and anaphylaxis. Urticaria is characterized and previously described as "rapidly evolving transient pruriginous wheals occurring at different sites of the body, which may represent the first stage of an anaphylactic reaction" [40]. On the other hand, anaphylaxis is defined as "a serious allergic reaction with a rapid onset that may cause death" [41].

T cell-mediated (type IV) allergic reactions

Pathophysiology

The effector mechanism of these reactions include a previous expansion of T cells stimulated by hapten-peptide-HLA complexes, and then a recruitment of inflammatory effector cells to target organs, and finally, after a new antigen exposure, effector cells are activated to secrete cytokines that involved in the immunological reaction and cytotoxins that cause tissue damage [34].

Clinical manifestations

Contrary to IgE-mediated reactions, clinical manifestations in T cell-mediated reactions are heterogeneous and comprise a number of different clinical phenotypes [42•] that can either be diseases with multisystem involvement in which the main affected organ is the skin, such as DRESS [43], severe cutaneous diseases such as SJS and TEN [44], AGEP [45, 46], and generalized bullous fixed-drug eruption (FDE). Moreover, single-organ diseases are associated to this pathomechanism, affecting organs like the liver (drug-induced liver injury (DILI)) [47–50], the pancreas (drug-induced pancreatitis), the lungs (lung infiltrates with eosinophilia) [51, 52], and the kidney (interstitial nephritis) [53].

Pharmacological interaction with immune receptors: p-i concept

Pathophysiology

The pharmacological interaction (p-i) with immune receptors concept suggests that drugs/metabolites may directly, reversibly, and non-covalently bind to immune receptor proteins (TCR, HLA, or HLA peptides) [13, 54, 55]. This drug binding occurs through non-covalent bonds like hydrogen bonds, van der Waals forces, and electrostatic interactions. Drug interaction with TCR or HLA is frequently selective for a specific TCR or HLA molecule, due to only particular amino acid sequences and conformational structures enable relatively strong non-covalent drug interactions [56] that are spontaneous and could induce T cell activation within seconds after drug administration [57, 58]. Functional consequences of these interactions are influenced by the location and orientation of the drug binding site and the drug affinity [13, 59–62]. Moreover, non-covalent interaction of drug with immune receptors can result through different pathways (Fig. 1):

p-i TCR

Drugs can bind directly on TCR (p-i TCR), altering the TCR conformation and increasing the TCR binding affinity, giving them the potential to induce immune reactions [59]. A recent study has shown two types of sulfamethoxazole (SMX) reacting T cell clones that can be stimulated by the binding of SMX to CDR2 region of TCR-Vβ20-1 or CDR3 of the α-chain. Moreover, the study found that the stimulation was only dependent on SMX, with no requirement of peptide and HLA recognition [59].

p-i HLA

Drugs can bind directly to the binding groove of HLA (p-i HLA), generating new drug peptide-HLA complex (allo-HLA) or could alter the conformation of peptide-HLA complex that can be recognized as neoantigen by TCRs [13, 63]. For example, CBZ/aromatic antiepileptic drugs have been reported to interact directly with HLA-B*15:02 protein, with no intracellular antigen processing implicated in the HLA-B*15:02 presentation of CBZ [64]. As well as oxypurinol can directly activate specific T cells through HLA-B*58:01 with no intracellular processing [58].

Altered self-peptides repertoire hypothesis

Drug direct binding to HLA molecules can produce alteration of the regular repertoire of peptides presented by HLA [60–62]. The altered peptide repertoire model proposes that drugs interacting with the HLA peptide-binding groove can change the binding cleft and the specificity of peptide-HLA binding, which leads to T cell proliferation [65–67]. Hypersensitivity reactions to abacavir have been reported to be mediated by this model [60, 61]. Studies have shown that abacavir binds to HLA-B*57:01 F-pocket and modify the shape and chemistry of the antigen-binding cleft, altering the repertoire of endogenous peptides and inducing T cell activation and

autoimmune-like systemic manifestations. It is important to remark that, until know, the altered peptide repertoire hypothesis has been only demonstrated for abacavir.

Clinical manifestations

Clinical manifestations in these reactions commonly appear >5–7 days after the drug exposure and only after T cell have expended and migrated into tissues. In p-i reactions, drug doses are relevant for the induction of T cell reactions; however, in some cases, lower drug doses could be enough to elicit symptoms onset if a previous expansion of T cell has occurred [68]. p-i reactions are characterized by relevant clinical aspects like drug dose dependence and rate of symptoms onset depending on the number of stimulated T cells. [56]. Finally, in vitro studies suggest that p-i reactions are implicated in severe reactions like MPE [54], AGEP [69], DILI [70], SJS/TEN [64, 71], and DRESS [58, 72–75].

Pseudo-allergic/non-immunological reactions

Pathophysiology

Pseudo-allergic reactions are heterogeneous reactions induced after drug binds directly to receptors or interacts with enzymes of effector cells without immune mechanisms involved, although the underlying pathomechanisms are not yet completely clarified [7, 9, 76]. No previous sensitization or cells expansion is required in these reactions because they are not mediated by the activation of the immune system [77]. The hypothesis proposed for these reactions is that certain drugs are capable to induce the direct stimulation of mast cells, basophils, eosinophils, and neutrophils with no demonstration of the presence of specific IgE, IgE, or T cells. This process can be mediated through a receptor on mast cells, the MAS-related G protein-coupled receptor-X2 (MRGPRX2), that has been reported to be relevant for the IgE-independent and direct mast cells activation [76, 78, 79]. The interaction of some drugs with MRGPRX2 receptor can elicit the release of histamine, TNF-α, β-hexosaminidase, and PGD_2, responsible of the clinical manifestations. Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequent elicitors of pseudo-allergic reactions [80••, 81], although other drugs like quinolones, vancomycin, radiocontrast media, opioids, dextrans, and neuromuscular blocking agents have been reported to directly stimulate mast cells [76, 79, 82] (Fig. 1).

Clinical manifestations

Most of pseudo-allergic reactions are mild reactions (e.g., acute urticaria), but other more severe even lethal reactions like anaphylaxis can be elicit by pseudo-allergic mechanisms. These reactions are frequently misdiagnosed as immediate hypersensitivity reaction, but the pathomechanism, drug cross-reactivity, and possible prevention strategies are significantly different to those involved in real allergic reactions. For example, pseudo-allergic reactions have been reported to be dose-dependent and higher drug concentrations are often needed to induce clinical symptoms compared with IgE-mediated reactions [83]. Interestingly, NSAIDs may

boost the existing local inflammation in patients with eosinophilic inflammation, producing asthma exacerbations, urticaria, and rhinosinusitis [84]. Moreover, a higher risk to develop NSAID intolerance has been described in patients with severe asthma compared with subject with mild or no asthma [80••, 84–88]. According to this, inflammation is an important cofactor for the development of NSAID-induced pseudo-allergic reactions that can explain the appearance of symptoms in tissues suffering inflammation.

Management of drug hypersensitivity reactions

The mechanisms involved in DHRs entails differences related to different aspects such as drug cross-reactivity, drug dose, or reaction prediction, all of them relevant in the management of the hypersensitivity disease, as described below.

The first step and the most effective strategy for the management of DHRs must be the avoidance or discontinuation of the culprit drug, as well as the search for safe, effective, and non-cross-reactive alternative medication [89–91]. Cross-reactivity is common in the context of allergic, p-i as well as pseudo-allergic DHRs, although differences have been described.

Cross-reactivity

Allergic reactions

Cross-reactivity is explained by the affinity of specific immune receptors (IgE, TCR) for the eliciting drug (hapten-protein or hapten-peptide complexes) but also related structures [14••]. Focusing on penicillins, the most frequent drugs involved in immunological DHRs [92], the treatment for patients with penicillin allergy is best limited to non-penicillin agents, even in patients with specific IgE directed against a specific side chain of the drug [93]. However, cross-reactivity between penicillins and carbapenems or monobactams are very rare [94–98], as well as third- or fourth-generation of cephalosporins, that may be considered as alternative treatment since the degree of cross-reactivity has been reported to be lower than with first-generation compounds [89, 99, 100]. Clinical cases with a history of DHRs to cephalosporin can be safely treated with negative skin test cephalosporins with a different side chain [101]. Regarding to NSAIDs, patients with a clinical history of ADRIBs should avoid the culprit drug and chemically related compounds, but NSAIDs not chemically related with the drug involved can be administered [102•].

Pharmacological interaction with immune receptors

In p-i reactions, cross-reactivity is common, but needs to be individually analyzed for each group of drugs [14••]. For example, in p-i HLA, abacavir has been reported to bind exclusively to B*57:01, but not to structurally similar HLA-proteins, and drug binding may be prevented by molecule modifications [14••, 103]. In contrast, HLA-B*15:02 protein can bind not only CBZ, but also some

CBZ metabolites, and maybe other anticonvulsants (e.g., lamotrigine and phenytoin) [14••, 104].

Pseudo-allergic/non-immunological reactions

In pseudo-allergy reactions, MRGPRX2 receptor on basophils and mast cells is able to bind a diverse group with a common chemical structure motif with an extensive cross-reactivity [14••, 76]. On the other hand, non-immunologically mediated hypersensitivity reactions to NSAIDs are common and cross-reactivity has been reported between cyclooxygenase (COX)-1 enzyme inhibitory drugs and pyrazolones [80••], although structurally different, they can lead to cross-reactivity due to all have a common mode of action [80••, 85, 105]. The management of these reactions involves avoidance of COX-1 inhibitors to prevent further reactions. Interestingly, selective COX-2 inhibitors are tolerated by most of these patients and can be contemplated as treatment in emergency situations [14••].

Desensitization and dose dependence

Desensitization protocol is the only treatment for DHRs and it is critical for hypersensitivity patients to first-line therapy that needs to be administered [106•, 107•, 108•, 109•, 110]. This method enables the safe re-administration of the drug independently of the mechanism involved [111]. In general, desensitization has been reported to be helpful to prolong the first election treatment in numerous drugs, including chemotherapeutic (platinum agents) and biological agents [108•, 112–115], anticonvulsants [116], antituberculosis medication [117], antibiotics [118–120], NSAIDs [121•, 122, 123••], and others [124, 125]. Regarding to desensitization protocols, dose dependence in DHRs is a relevant factor [126] due to transient tolerance to a drug is induced by initially applying extremely low amounts, which are then steadily increased [14••]. Dose dependence is related with the mechanism involved in the reaction; thereby, immunologically mediated reactions can be elicited at lower doses than therapeutic doses, in contrast with pseudo-allergic reactions, where clinical manifestations usually appear at standard to high doses [14••]. Successful desensitization procedures are well documented in both allergic [107•, 111, 122, 125] and pseudo-allergic reactions [83, 127, 128].

Prediction of DHRs

At the moment, predictive tests to prevent DHRs are still limited to very few compounds such as abacavir and CBZ [129]. HLA associations to certain DHRs have been reported for an increasing number of compounds [130]; some of them with an almost exclusive association to a specific HLA allele and other drugs associated to different alleles. However, the main limitation for predictive testing is the low positive predictive value, because other risk factors should also be involved in the development of DHRs [14••].

Allergic reactions

Some genetic associations have been found between IgE-mediated allergic reactions to BL antibiotics and single nucleotide polymorphisms (SNPs) of HLA alleles [131, 132]. Thereby, a recent study showed genetic variants in

HLA-DRA and *ZNF300* that predicted positivity to penicillin skin tests and SNPs rs7192 and rs8084 of *HLA-DRA* were found to be significantly associated with penicillin allergy in Italian and Spanish populations and with cephalosporin allergy in Spanish patients [131]. Another study focused on the association of *LGALS3* polymorphisms with BL allergy in Spanish and Italian population showed a genetic association between rs11125 variant and IgE-mediated BL allergy [133]. On the other hand, a study evaluating allergic drug reactions to pyrazolones suggested a genetic predisposition linked to *HLA-DQ* locus, although a limited number of patients was included in the study [134]. In a more recent study, it was found that slow acetylation, related with slow alleles of arylamine N-acetyltransferases 2 (NAT2), was associated with an increased risk of developing selective hypersensitivity to metamizole, and particularly anaphylaxis [135]. Finally, two intronic variants (rs2241160 and rs2241161) for centrosomal protein of 68 kDa encodes gene (*CEP68*) have been recently described in single NSAID-induced urticaria and anaphylaxis [136•], pointing a potential use of this gene in the search and application of clinical biomarkers to detect patients at risk for these reactions. All these data suggest the important relationship between drug metabolism and specific individual genetic variability in the development of immunological reactions to drugs [137, 138], although studies including more participants as well as different geographical populations should be carried out.

Pharmacological interaction with immune receptors

A combination of genetic analysis of HLA and/or metabolizing enzymes could predict p-i-induced DHRs. As mentioned previously, the positive predictive value of HLA associations with DHRs reactions is low (<3%), with the remarkable exception of abacavir, where about 50% of patients with HLA-B*57:01 allele developed a hypersensitivity reaction [139]. In this sense, HLA-B*57:01 screening previous to the administration of abacavir has been widely applied in clinical practice and is part of the US FDA and international human immunodeficiency virus treatment guidelines [140]. HLA association with DHRs has been demonstrated for other drugs with p-i mechanism; for example, it has been reported a strong association of HLA-B*15:02 allele with CBZ-induced SJS/TEN among Han Chinese [141–144]. However, in European and Japanese populations, CBZ-induced hypersensitivity reactions were found to be associated with HLA-A*31:01 [145, 146]. HLA-B*58:01 has been strongly associated to allopurinol-induced SJS/TEN [72, 147–149] and seems not to be ethnic dependent, as well as HLA-B*15:11 with CBZ [145, 146, 150, 151], HLA-B*15:02 with phenytoin [104, 144], and HLA-B*57:01 with abacavir and also associated to DILI development [152, 153].

Conclusions

Nowadays, diagnosis of DHRs is very complex and continues to be a challenge due to the clinical and mechanistic heterogeneity of them. Three clearly distinct mechanisms have been proposed to be involved in DHRs: allergic reactions, p-i with immune receptors, and pseudo-allergic reactions. Mechanisms involved entails differences related to drug cross-reactivity, drug dose, or prediction of the reaction, all of them important in the patient management. However, a better

understanding of the underlying mechanisms involved in each clinical manifestation and each culprit drug is still needed.

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Compliance with ethical standards

Conflict of interest

Adriana Ariza Veguillas declares that she has no conflict of interest. Tahia Diana Fernández-Duarte declares that she has no conflict of interest. Gador Bogas Herrera declares that she has no conflict of interest. María José Torres Jaén declares that she has no conflict of interest. Cristobalina Mayorga declares that she has no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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