

Classification of Drug Hypersensitivity into Allergic, p-i, and Pseudo-Allergic Forms

Werner J. Pichler^a Oliver Hausmann^{a–c}

^aADR-AC GmbH and ^bDepartment of Rheumatology, Immunology, and Allergology, University of Bern, Inselspital, Bern, and ^cLöwenpraxis, Luzern, Switzerland

Keywords

Adverse drug effects · Allergic/immune reactions · p-i drug reactions · Pseudo-allergic drug reactions · Classification · Drug hypersensitivity

Abstract

Drug hypersensitivity reactions (DHR) are clinically and functionally heterogeneous. Different subclassifications based on timing of symptom appearance or type of immune mechanism have been proposed. Here, we show that the mode of action of drugs leading to immune/inflammatory cell stimulation is a further decisive factor in understanding and managing DHR. Three mechanisms can be delineated: (a) some drugs have or gain the ability to bind covalently to proteins, form new antigens, and thus elicit immune reactions to hapten-carrier complexes (allergic/immune reaction); (b) a substantial part of immune-mediated DHR is due to a typical off-target activity of drugs on immune receptors like HLA and TCR (pharmacological interaction with immune receptors, p-i reactions); such p-i reactions are linked to severe DHR; and (c) symptoms of DHR can also appear if the drug stimulates or inhibits receptors or enzymes of inflammatory cells (pseudo-allergy). These three distinct ways of stimula-

tions of immune or inflammatory cells differ substantially in clinical manifestations, time of appearance, dose dependence, predictability, and cross-reactivity, and thus need to be differentiated.

© 2016 The Author(s)
Published by S. Karger AG, Basel

Introduction

Adverse drug reactions (ADR) are common. They are due to different mechanisms and result in different clinical pictures. In 1977 and 1981, Rawlins and Thompson [1] proposed a subclassification of ADR, which is still widely used today for an initial approach to ADR [1, 2]: type A reactions are due to the pharmacological activity of the drug. They are influenced by drug pharmacokinetics, comorbidities and/or drug-drug interactions. Overdosing and drug binding to off-target receptors are central to this “pharmacological” reaction type. Type A reactions occur in nearly all individuals, are dose dependent, are considered to be predictable, and their mechanism is mostly understood (Table 1). A typical example would be sleepiness caused by first-generation antihistamines.

KARGER

E-Mail karger@karger.com
www.karger.com/iaa

© 2016 The Author(s)
Published by S. Karger AG, Basel

Karger
Open access

This article is licensed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND) (<http://www.karger.com/Services/OpenAccessLicense>). Usage and distribution for commercial purposes as well as any distribution of modified material requires written permission.

Correspondence to: Prof. Werner J. Pichler
ADR-AC GmbH
Holligenstrasse 91
CH–3008 Bern (Switzerland)
E-Mail Werner.pichler@adr-ac.ch

Table 1. Classification of ADR according to Rawlins and Thompson [1] and others [2, 3]

Type A reaction [1, 2]	Type B reaction [3]
Pharmacological action	Not a pharmacological action
Predictable	Not predictable
Dose dependent	Not dose dependent
Rational	Not rational

Drug allergy is a type B reaction.

Type B reactions comprise about 15% of all ADR. They occur in individuals with a certain predisposition, and were called “idiosyncratic” ADR. They are not readily anticipated and thus were, from a pharmacological perspective, called “bizarre” ADR (Table 1) [3]. A few are due to certain enzyme deficiencies and may appear as a nonimmune-mediated “hypersensitivity” reaction to drugs but should be better classified as exaggerated reactions – to distinguish them from classical immune-mediated hypersensitivities. An example is hemolysis after drugs (antimalarials like primaquine, certain analgesics, and antibiotics) in individuals with glucose-6-phosphate dehydrogenase deficiency [4].

The majority of type B reactions involve the immune system and are drug hypersensitivity reactions (DHR). We will not use the term drug allergy, as this refers to a specific immune response to a drug acting as an allergen (mostly linked to a protein or peptide), while drug hypersensitivity is a term going beyond drug allergy: immune stimulations and corresponding clinical symptoms can also occur when drugs bind *directly* to immune receptors like HLA or TCR (T-cell receptor) proteins (*pharmacological interaction with immune receptor [p-i] concept*) [5–7] or when inflammatory cells are stimulated by drug-receptor or drug-enzyme interactions (*pseudo-allergy*) [8, 9]. Thus, the need of covalent linkage of a drug to a protein carrier molecule to form a new antigen is no more considered a prerequisite for generating a DHR [5–9]. Indeed, a substantial part of DHR follow *pharmacological* but *not immunological* rules and actually show features of a type A reaction. These new findings have an impact on clinical course, management, prediction, dose effect, and cross-reactivity of such DHR, and thus should be considered in the clinical approach to a patient with DHR.

ADR to a therapeutic antibodies or other proteins/peptides follow distinct rules and need a special approach

[10]. Later, additional forms of ADR were described (ADR type C–E), but these subclassifications are rarely used [10]. Recently, ADR under therapy with checkpoint inhibitors were distinguished from other ADR and called immune-related adverse reactions. Some of these immune-related adverse reactions may be related to loss of normal control mechanisms by the immune system due to therapy with anti-PD-1 or -CTLA-4 antibodies [11].

Classifying DHR

The strengths of the type A and B classification is its simplicity and the clear definition of type A reactions with its associated features, whereas type B reactions remain less clear and are essentially defined as “non-A” type (Table 1). What did not fit into type A was classified as type B [1–3]; ADR type B were not due to pharmacological actions, were not predictable, not dose dependent, and result in a nonrational, “bizarre” clinical picture. This “non-A” classification had a substantial negative impact on the clinical management and research of type B reactions. As type B reactions were thought to be due to idiosyncratic, individual features of the patient, *idiosyncrasy* was interpreted as “the drug itself is OK, just the patient is weird.” Type B reactions were considered to be rare but unavoidable. The claim of dose independence ruled out dose reduction as a therapeutic or prophylactic option. No animal models were developed, or if they existed in pharmaceutical industry, they were not analyzed in detail as the drug development was simply stopped if reactions occurred.

In spite of these obstacles, several academic centers tried to improve the understanding of the clinical features and pathomechanisms of DHR. By studying immune-mediated immediate- and delayed-appearing hypersensitivity reactions in the affected patients, it was found that the interaction of a drug with the immune system was more complex than previously anticipated [7].

Different attempts have been undertaken to subclassify DHR, with the aim to better diagnose, manage, and possibly avoid them (Table 2). In clinical practice, these approaches are often combined.

– The *time* until symptoms appear (*within 1 h or thereafter*) is the simplest, useful (for some reactions), and still widely used classification [12]. However, it does not consider the characteristics of the drug, type of the immune response, dose dependence, and individual susceptibility.

Table 2. Examples of subclassifications of drug hypersensitivity

Distinctive features	Clinical symptoms
<i>Timing: appearance of symptoms after drug uptake</i>	
<1 to <6 h	Urticaria, angioedema, anaphylaxis due to IgE (mostly <1 h) and pseudo-allergy
Mostly >6 h, often days	Many symptoms due to T cells, IgG
<i>Immune mechanisms (Coombs and Gell [13])</i>	
Type I: IgE	Rapid, mostly <1 h: urticaria, anaphylaxis
Type II: IgG cytotoxic	Delayed, after 1–14 days: blood cell dyscrasia
Type III: IgG immune complex	Delayed, after 2–14 days: vasculitis, serum sickness
Type IV (a–d): T cells	Delayed, after 2 to >20 days: various exanthems, hepatitis
<i>Type of drug</i>	
NSAID	Respiratory and/or cutaneous diseases and exacerbations; mostly pseudo-allergy
Anticonvulsants	DRESS, SJS/TEN; mostly via p-i, often linked to a certain HLA allele
Biologicals (proteins)	Infusion reactions, IgE, IgG, complement, or neutralization (loss of efficacy)
<i>Mode of drug action with immune/inflammatory cells</i>	
Allergic	IgE mediated penicillin allergy, contact dermatitis, combined IgE and T-cell reactions
p-i (HLA, TCR)	Only T-cell reactions
Pseudo-allergy (e.g. MRGPRX on mast cells or intracellular enzyme blockade)	Urticaria/anaphylaxis bronchospasm (with underlying inflammation); no drug-specific IgE or T cells

- An immune-mediated mechanism linked to certain clinical phenotypes is the basis for the (revised) *Coombs and Gell* [13] classification [14]. The *immediate*-appearing symptoms (urticaria, anaphylaxis) were classified as being due to IgE and mast cell degranulation, and the *delayed*-appearing symptoms (exanthems, hepatitis) as dependent on T-cell activation (and rarely antibody involvement, especially IgG). This classification and attribution of symptoms to an underlying immune mechanism are also important to devise optimal testing strategies, as the type of immune stimulation determines the procedures needed for skin or in vitro testing with the incriminated drug.
- Some reactions known to occur mainly with *certain drugs* were named accordingly, e.g. NSAID intolerance, anticonvulsant hypersensitivity syndrome, or acute infusion reactions to biologicals.

None of these classifications is ideal and per se able to explain and link pathomechanisms, clinical pictures, dose dependency, cross-reactivity, and optimal treatments (Table 2). Moreover, all classifications assumed that the formation of a new antigen by the hapten-carrier concept is essential for DHR. Here, we propose to also consider direct, noncovalent drug-receptor interactions as cause of DHR and to differentiate three major forms of DHR: allergic/immune, pseudo-allergic, and pharmacological stimulations.

Three Distinct Mechanisms Leading to DHR

The Allergic/Immune Stimulation: Hapten and Prohapten Concept

This mechanism is the classical explanation for DHR and represents a true *drug allergy*. It is based on the data generated in the early 20th century [15] and states that small molecules like drugs or drug metabolites are too small to elicit a specific immune response on their own. Only if they bind *covalently* to proteins a new antigen is generated (hapten-protein complex) [16]. Some drugs are prohaptens and gain the ability to bind covalently to proteins only after being metabolized [17]. Table 3 shows a list of drugs acting as haptens. The stable covalent binding is important for two features of haptens:

- The ability to stimulate cells of *innate* immunity (e.g. dendritic cells) [18, 19]: the drug activates pattern recognition receptors – either by direct chemical interaction with such receptors or by induction of endogenous activators. This induces the expression of CD40 or other costimulatory molecules on dendritic cells [18, 19].
- The covalent binding by a drug alters the protein structure and can transform an autologous soluble (e.g. albumin, transferrin) or cell-bound protein (e.g. integrins, selectins) to a novel drug-modified protein, which acts as a new antigen [16, 20, 21] to which no intrinsic

Table 3. Type of drugs eliciting drug hypersensitivity by allergic-immune (hapten), p-i, or pseudo-allergic mechanisms^a

Allergic-immune (hapten)	p-i ^b	Pseudo-allergy
β-Lactam antibiotics: penicillins (e.g. amoxicillin, flucloxacillin), cephalosporins, carbapenem, monobactam; penicillamine	Flucloxacillin, amoxicillin ^d , cephalosporins ^d	NSAID (e.g. acetylsalicylic acid, diclofenac, mefenamic acid, ibuprofen)
Sulfamethoxazole, NO, and other reactive metabolites	Sulfamethoxazole, sulfapyridine, and other sulfanilamides	Muscle relaxants ^c (e.g. rocuronium, suxamethonium)
	Quinolones (e.g. ciprofloxacin, moxifloxacin, norfloxacin)	Quinolones (e.g. ciprofloxacin, moxifloxacin, norfloxacin)
	Iomeprol, iohexol, and other radiocontrast media	Iomeprol ^c , iohexol ^c , and other radiocontrast media
	Carbamazepine, lamotrigine, phenytoin	
	Allopurinol, oxypurinol	
	Metamizole, vancomycin, abacavir	
	Lidocaine, mepivacaine, and other local anesthetics	

^a Only the best-documented mechanisms are listed. Note that the action of a drug as hapten does not exclude action as p-i as well (e.g. flucloxacillin), or that drugs acting via pseudo-allergic mechanisms may also act via IgE or even p-i (e.g. metamizole or radiocontrast media, or muscle relaxants).

^b Note that most drugs involved in p-i-driven stimulations fail to elicit anaphylaxis (e.g. abacavir, carbamazepine, lamotrigine); these are drugs which are not acting via allergic/immune mechanisms. An exception is flucloxacillin, which can stimulate via p-i and hapten mechanisms. Only p-i stimulation leads to hepatitis (linked to HLA-B*57:01), while allergic stimulations lead to exanthems [32].

^c In some of these acute reactions drug-specific IgE reactivity has been documented (serology and/or skin tests). However, it is not clear whether the sensitization developed against the drug *itself* or against a *cross-reactive* compound.

^d Preliminary data of β-lactams in DRESS [D. Yerly et al., in preparation].

tolerance exists. The *adaptive immune* response reacts via specific receptors (TCR for antigen on T cells and immunoglobulin receptor on B cells) with these newly formed antigens [16, 20].

The covalent link of a hapten to its protein carrier is resistant to intracellular processing. Hapten-modified peptides are finally presented on HLA molecules to TCR [16, 21]. In most instances, haptens bind to a specific amino acid (e.g. lysine) in different positions within the protein. Thus, after protein processing to smaller peptides, *various* hapten-peptide conjugates are generated which bind to *different* HLA molecules [16, 20, 22]. The resulting immune responses to hapten-*protein* complexes is therefore *not* restricted to a single HLA molecule (in contrast to some p-i reactions, see below).

In conclusion, a hapten elicits both T- and B-cell reactions simultaneously and is normally not linked to a single HLA allele. Hapten reactions are polyclonal and functionally heterogeneous, involving antibodies, cytotoxicity, and cytokines released by T cells and activated inflammatory cells [14]. They appear rapidly if the *effector* mechanism relies on cell-bound IgE crosslinked by

hapten-*protein* complexes and subsequent mast cell/basophil degranulation. On the other hand, they might appear delayed if the effector mechanism relies on prior expansion of T cells stimulated by hapten-*peptide*-HLA complexes followed by recruitment of inflammatory effector cells.

Pharmacological Stimulation of Immune Receptors: p-i Concept

The concept that drugs are too small to represent full antigens is correct. However, drugs designed to fit into “pockets” of certain protein structures may also *directly* bind to immune receptors like HLA or TCR proteins [5–7]. This drug binding to immune receptors is a *typical off-target effect* of the drug and is analogous to the binding of drugs to other receptor structures: it is based on *noncovalent* bonds like van der Waals forces, hydrogen bonds, and electrostatic interactions. Of note, the drug does *not* bind to the immunogenic peptides presented by HLA. Thus, the drug is *not* acting as an antigen or substituting an antigenic peptide. This reaction type is termed *pharmacological* interaction of drugs with immune receptor (p-i) [5].

The targeted immune receptors are highly polymorphic, both in each individual (TCR) as well as in the population (HLA): one estimates that there are $>10^{11}$ different TCR per individual and $>10,000$ different HLA class I and $>3,000$ class II alleles in the human population (www.allelefrequencies.net). Thus, the chances are relatively high for such an off-target activity of a drug on immune receptors.

Two possibilities have been described for a p-i-mediated drug interaction with the TCR (p-i TCR) or with the HLA molecule (p-i HLA) (Boxes 1, 2) [7]. Docking studies suggest that this off-target drug binding to immune receptors may frequently occur on irrelevant sites of the protein (HLA or TCR) and/or are too labile to elicit a functional consequence [23]. Only occasionally may the drug binding target a critical region of the immune receptor (e.g. peptide binding site of HLA proteins or the CDR3 site of TCR) with a certain affinity and “correct” (stimulatory) orientation of the drug to elicit a profound T-cell activation [7, 23, 24].

The interaction of a drug with HLA or TCR is often selective for a particular HLA molecule or a particular TCR, as only certain amino-acid sequences and 3D structures allow relatively strong, noncovalent drug binding [7, 23, 24]. This explains the idiosyncratic nature of p-i-based DHR. It occurs only in *some* individuals, and persons at risk can be identified by carrying the risk allele.

In contrast to usual off-target activities, where the cell which expresses the off-target receptor is reacting, in p-i exclusively T cells are responsible for the symptoms, even if the HLA molecule of tissue cells is targeted by the drug. This explains the delayed appearance of symptoms mediated by a p-i stimulation, as the initial amount of drug-reactive T cells is often limited and symptoms appear only after T-cell expansion and migration into tissues (similar to hapten-dependent T-cell reactions).

The induction of a strong T-cell reaction, but not drug-induced B-cell stimulations (IgE and IgG), is a *characteristic feature* of p-i stimulations. It distinguishes p-i from hapten-protein-driven “allergic” DHR, which induce a “complete” T- and B-cell-mediated immune response, with hapten-protein and hapten-peptide specificity (Table 4). Importantly and in spite of the “abnormal,” namely pharmacological T-cell stimulation by p-i, the resulting T-cell activation leads to the secretion of typical cytokines and/or target cell-directed cytotoxicity. Clinical symptoms typically appear $>5-7$ days after the initiation of treatment. In vitro analysis of T cells of patients suggests that p-i reactions are involved in maculopapular eruptions (MPE) [30], acute generalized exanthematous pus-

Box 1. p-i TCR

Besides the classical antigen-dependent T-cell activation two possibilities exist for stimulating a T-cell reaction: direct drug interaction with the TCR (p-i TCR) or with the HLA molecule (p-i HLA) [7]. In *p-i TCR*, the drug fits into some of the innumerable different TCR available [23, 24]. As shown for sulfamethoxazole, the drug might directly interact with the CDR3 regions of TCR which usually interacts with the peptide-HLA complex [23] and then stimulate TCR-triggered signals. Alternatively, the drug binds to the CDR2 region and causes an allogeneic alteration in the TCR. The altered TCR can interact more strongly with an HLA-peptide complex [24]. In both forms of p-i TCR, an additional interaction with HLA molecules is required for full stimulation of the T cell. It is assumed that some of these TCR-mediated stimulations by a small molecule are stimulatory only if the reactive T cells are already preactivated and thus have a lower activation threshold than resting T cells. Such a preactivation may be due to generalized herpes (EBV, CMV) or HIV infection.

Box 2. p-i HLA

In *p-i HLA*, the drug binds directly to the HLA molecule. It may bind preferentially (or exclusively) to a specific HLA allele. This explains the high association of certain DHR with certain HLA alleles, which is seen in reactions to drugs such as abacavir (Table 3) [reviewed in 25]. Two functional consequences of p-i HLA have been described. The drug binding alters the HLA molecule itself and makes it look like a foreign HLA [26]. This is documented experimentally for abacavir hypersensitivity. The binding of abacavir to a crucial self-determining molecule transforms the auto-allele (“HLA-B*57:01”) to look like an alloallele (e.g. HLA-B*58:01), which elicits a strong allo-immune response [26, reviewed in 7]. This scenario helps to explain why some symptoms of drug hypersensitivity are similar to graft-versus-host immune reactions, where the direct allostimulation represents also a direct, dendritic cell-independent T-cell stimulation [26]. Another result of drug binding to the HLA molecule is an alteration in its peptide binding ability. The binding of abacavir to the F-pocket of the HLA-B*57:01 blocks the binding of peptides, which normally bind to the HLA-B*57:01 molecule. Thus, peptides with a smaller amino acid at this F-pocket position are chosen for presentation. This phenomenon is termed altered peptide repertoire and may lead to autoimmunity [27–29]. Note also that p-i HLA is more consistently “stimulatory” than p-i TCR. In p-i HLA, the alteration in the HLA-peptide complex by drug binding, the peptide-drug-HLA protein complex is sufficient for T-cell stimulation independent of drug orientation. In contrast, in p-i TCR, a correct orientation of drug binding to TCR is needed for stimulation [7, 23].

tulosis [31], drug-induced liver injury [32], Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) [33, 34], and drug reaction with eosinophilia and systemic symptoms (DRESS) [35–39]. Typical examples of drugs

Table 4. Distinction of allergic/immune, p-i, and pseudo-allergic reactions

Allergic/immune reactions IgE/T cells	p-i reactions	Pseudo-allergic reactions
<i>Clinical picture</i> Highly variable with the same drug; IgE: anaphylaxis/urticaria/angioedema T cell: exanthema, bullous skin reactions, hepatitis, nephritis	Exclusively T cells: exanths, hepatitis, often severe (SJS/TEN, DRESS)	Respiratory, cutaneous, or anaphylactic reactions (acute urticaria, anaphylaxis, bronchospasm, asthma)
<i>Time, kinetic of appearance</i> Very rapid (<5 min, IgE) to delayed (days to weeks, T cells)	After days to weeks	Mostly within minutes or hours
<i>Need for prior exposure</i> Yes (but sensitization may have occurred to a hidden cross-reactive sometimes environmental compound)	No; often longer exposure and high doses before symptoms appear as cell expansion needs time	No
<i>Need of cofactors like inflammation or cell activation</i> No ^a	Partly: in p-i TCR, costimulation is often required	Eosinophilic inflammation in NSAID-related pseudo-allergy (asthma, rhinosinusitis) In anaphylaxis, prior mast cell activation/expansion
<i>HLA or other genetic associations (e.g. cytochrome P₄₅₀)/possible predictability</i> No	Often (mainly HLA)	Limited and/or unknown
<i>Laboratory and histology</i> Variable Laboratory: tryptase ↑, eosinophilia, lymphocytosis; elevated liver enzymes Histology: cell infiltration with cytotoxic T cells, leukocytoclastic vasculitis	Variable Mainly activated T cells in blood and affected tissue T-cell-mediated cytotoxicity, granulysin ↑	Inflammation: sometimes eosinophilia and eosinophilic infiltrate, sometimes only acute signs of mast cell degranulation (tryptase ↑)
<i>Known chemical characteristics and binding behavior of the drug</i> Penicillins, cephalosporins, SMX-NO are known haptens	Abacavir, allopurinol, carbamazepine via p-i HLA, SMX via p-i TCR	NSAID, quinolones, muscle relaxants, radiocontrast media, and others
<i>Skin tests, LTT</i> Often positive IgE: prick, intradermal T cell: epicutaneous; intradermal late reading	Often positive skin tests and in vitro T-cell activation by drugs in MPE, DRESS, SJS/TEN	Negative
<i>Cross-reactivity</i> Often – depends on drug affinity (complexed to protein or peptide) to specific immune receptors (TCR, Ig); always structure related	Often – depends on drug affinity to HLA, TCR; always structure related	NSAID: related to inhibitory activity on cyclooxygenase; MRGPRX2-related pseudo-allergy; cross-reactivity is very broad and includes different structures
<i>Desensitization</i> Possible in IgE-mediated reactions with a transient but specific effect; unclear in T-cell reactions	Unclear	Well established in NSAID pseudo-allergy; unclear in other pseudo-allergies (MRGPRX-related)

^a Cofactors may not be needed to develop an allergic reaction to a hapten, but when cofactors are present they may enhance clinical manifestations.

known to stimulate via a p-i mechanism are shown in Table 3.

Some drugs may induce immune reactions either by hapten/allergic or by a p-i mechanism, resulting in distinct clinical manifestations. An interesting example is flucloxacillin. Similar to other β -lactam antibiotics, it can act as a hapten (Table 3). However, flucloxacillin-induced liver injury was independent of hapten-linked features of flucloxacillin and showed noncovalent (direct, p-i) binding to HLA B*57:01 [32]. Recent data by D. Yerly et al. [in preparation] show that amoxicillin- and cephalosporin-linked DRESS are also due to p-i stimulations.

Pseudo-Allergy (Non-Immune-Mediated DH)

There is another, in itself also quite heterogeneous, form of ADR, which was previously referred to as *nonallergic DH, drug intolerance; or pseudo-allergy* [12, 40]. We prefer the term pseudo-allergy, as it emphasizes the close relationship and similarity to allergic symptoms without an underlying drug-specific sensitization [8].

The pathomechanism of pseudo-allergic reactions is not yet completely clarified and is most likely heterogeneous. The symptoms of pseudoallergy can be best explained by the hypothesis that certain drugs activate the effector cells of allergic inflammation, namely mast cells, but also eosinophils, basophils, and probably also neutrophils without evidence of drug-specific IgE, IgG or T cells. We are aware that pseudo-allergic reactions are actually *not* immune stimulations, and their classification as DHR is thus debatable. But as the clinical picture of pseudo-allergy is so similar to allergic reactions, it makes sense to discuss it together with the other forms of DHR involving the adaptive immune system.

Pseudo-allergic reactions are at least as frequent as IgE-mediated reactions to drugs. Common elicitors of pseudo-allergic reactions are NSAIDs. These drugs act by inhibiting cyclooxygenases and prostaglandin synthesis, resulting in a shift in the arachidonic acid metabolism to leukotriene synthesis [9, 41]. In patients with an ongoing, often eosinophilic inflammation like chronic rhinosinusitis, chronic asthma, and chronic spontaneous urticaria, NSAIDs may boost the already existing local inflammation and cause exacerbations of asthma symptoms, rhinosinusitis, and also of urticaria, where inflammatory cells are also present in the skin [42]. Patients with severe asthma have a higher risk to develop NSAID intolerance than individuals with mild or no asthma, and patients with chronic spontaneous urticaria may experience a bout of their urticaria after the intake of NSAIDs [9, 42–46]. Thus, the inflammation per se represents the relevant *co-*

factor for the clinical manifestation of NSAID-related pseudo-allergy and explains the localization of symptoms to the inflamed tissue (respiratory tract and/or skin). The intensity of inflammation may even be decisive for the clinical manifestation as the reduction in tissue inflammation may even eliminate the pseudo-allergic symptoms after NSAID intake [45, 46].

Many other drugs (e.g. radiocontrast media, muscle relaxants, quinolones, and vancomycin), which have no pharmacological action on prostaglandin synthesis, may also cause pseudo-allergic reactions, in particular acute urticaria and anaphylaxis [8, 47]. Also, NSAID may cause acute urticaria and anaphylaxis independent of a preexisting inflammation [42]. Some of these side effects appear to be linked to a single receptor on mast cells, known as MRGPRX2 (Mas-related G-protein-coupled receptor member X2) in humans. This receptor which is recognizing a certain chemical motif was found to be crucial for IgE-independent, direct mast cell stimulation [8]. Fluoroquinolone antibiotics and neuromuscular blocking agents are known to bind to this receptor and to cause systemic pseudo-allergic reactions.

The majority of pseudo-allergic reactions are mild (acute urticaria), but some cause anaphylaxis and can even be lethal, sometimes at the first encounter with the drug as no sensitization is required. Pseudo-allergy is – like IgE-mediated drug allergy – classified as an *immediate* hypersensitivity reaction, but the mechanism, cross-reactivity, and prevention strategies differ substantially from true allergic reactions (Table 4). Pseudo-allergic reactions are elicited by a limited number of drugs (Table 3), and they are clearly dose dependent. Indeed, they usually require substantially higher doses to elicit clinical symptoms than IgE-mediated reactions, which may occur with the same drugs (e.g. metamizole; Table 3).

Pseudo-allergic reactions are still not predictable, but the detection of relevant and functional off-target receptor(s) on inflammatory cells may allow a better screening of drugs for such an off-target activity. In NSAID-exacerbated respiratory diseases, some links to interleukin-4 promoter polymorphisms and N-acetyl transferase-2 polymorphisms have been described in Korean patients [48, 49].

Mode of Action of the Drug: Impact on Drug Safety

The pharmaceutical industry and regulatory agencies are familiar with the hapten theory of immune-mediated side effects and try to avoid the development of drugs

Box 3. Clinical features of allergic/immune (hapten), p-i, or pseudo-allergic reactions

Allergic/immune (hapten) reactions

Drugs acting as a hapten (e.g. β -lactam antibiotics) can stimulate both B and T cells and consequently elicit different types of immune reactions (e.g. in one patient IgE-mediated anaphylaxis and in the other patient T-cell-mediated exanthema or IgG-related hemolytic anemia)

p-i reactions

The drug stimulating via p-i elicits a restricted pattern of exclusive T-cell-mediated symptoms: MPE, DRESS, SJS/TEN, or hepatitis. Antibody-mediated reactions like anaphylaxis or antibody-mediated hemolytic anemia are absent.

Pseudo-allergic reactions

The clinical reactions are related to the type of effector cell stimulated by the drug; activation of mast cells results in urticaria, angioedema and anaphylaxis, and activation of eosinophils results in acute asthma attacks or rhinitis.

which might act as haptens and modify proteins. Their risk to elicit immune-mediated reactions is considered too high. Indeed, β -lactam antibiotics, which frequently act as haptens, are still the leading cause of drug allergy in daily clinical practice (mainly MPE, urticaria, and anaphylaxis).

However, severe T-cell-mediated DHR appear to be mainly due to a p-i mechanism (see below). Thus, it would be important to avoid such reactions. Screening of novel drugs for their ability to bind to HLA alleles or certain constant regions of TCR, e.g. binding to a TCR-V β 20.1 [7, 24], would be one approach. As the HLA polymorphism is immense, one might first use computational modelling and in silico docking studies. If a strong interaction of a drug with a certain HLA allele at a crucial position is observed, it may be a sign of a relevant off-target activity on the HLA molecule [36]. This needs to be verified by in vitro studies with human cells or possibly humanized animal models to prove the assumed immune-stimulatory potential on human immune receptors. As shown, the orientation of the drug binding to its off-target immune receptor as well as cofactors (e.g. generalized immune stimulations by viral infections) are often crucial to effectively elicit clinical reactions [7, 23]. Thus, in silico studies alone are insufficient to predict the hazard. Importantly, in vitro stimulation of drug-specific responses from *drug-naïve* donors was proven to be possible in quite a number of drugs already if one considered the relevant HLA allele [26, 32, 36, 50]. Thus, a combined *computational* and *biological* approach may help to better predict severe, p-i-mediated DHR.

Relation of Allergic-Immune, p-i, and Pseudo-Allergic Reactions to Dose, Predictability, and Cross-Reactivity

A further rationale for the proposed DHR subclassification is an optimized clinical management: allergic-immune, p-i, and pseudo-allergic reactions lead to distinct recommendations for the affected patient as they differ in relation to drug dose, prediction/HLA linkage, and cross-reactivity (Table 4; Box 3).

Dose Dependency

Type B reactions are labelled as dose *independent*. This postulation results from observations of rapid anaphylaxis after minimal drug doses, e.g. immediately after the start of an infusion or after skin testing. As the concentrations applied were substantially below the dose needed for a pharmacological effect, the reaction was termed “dose independent.”

In immune reactions, one has to differentiate between the antigen concentration required for the initiation (sensitization) and for the effector phase. This distinction is also relevant in allergic and p-i reactions: the concentrations needed for the initiation (sensitization/cell expansion) are relatively high compared to the concentrations needed for eliciting effector mechanisms and clinical symptoms.

In *allergic-immune DHR*, the sensitization takes time (>4 days) and occurs to therapeutic drug concentrations. During this time span, the reactive cells expand and mature to effector cells: in antibody-mediated reactions, the B cells generating the antibodies to the hapten-protein complex differentiate and undergo affinity maturation. Interestingly, in IgE-mediated reactions, no symptoms appear during the sensitization phase. In T-cell-mediated reactions, however, symptoms may appear directly following sensitization, namely when the amount of reactive T cells is high enough and homes to the affected organs (mainly the skin).

In already *sensitized* individuals (having drug-affine IgE or memory T cells), especially on repeated encounter, the reaction appears immediately (IgE, minutes) or rapidly (T cells, hours or a few days) after reexposure and can be elicited by doses which are substantially lower than the ones needed for initiation (sensitization). However, the fact that IgE-mediated reactions can occur already at *minimal* doses does not mean the reaction is dose independent. Further reducing the dose eliminates symptoms. This allows for drug desensitization procedures [51], where transient tolerance to a drug is induced by

initially applying extremely low amounts, which are then steadily increased. After hours to days, even a full drug dose is usually tolerated.

In *p-i reactions*, drug concentrations are important for eliciting T-cell reactions: symptoms often appear after 7–10 days, the critical time needed for T-cell expansion and migration to the tissue [14]. In DRESS, symptoms may occur even later (>17 days) and rather frequently after further increasing the drug dose or when drug elimination is impaired (renal insufficiency) as well as when drug metabolism is influenced. In allopurinol hypersensitivity, kidney disease with reduced allopurinol clearance and increased allopurinol (oxypurinol) plasma levels is a known cofactor for the development of SJS [52]. In phenytoin hypersensitivity, the presence of the CYP2C9*3 variant, known to reduce phenytoin clearance, was identified as an important genetic factor associated with phenytoin-related severe cutaneous adverse reactions [53].

On the other hand, in highly sensitized individuals (with DRESS or massive MPE), even a minimal drug amount applied for example by intradermal skin testing with the incriminated drug may elicit generalized symptoms like a mild rash (own observation). Thus, lower amounts of the drug may be sufficient to cause symptoms in *p-i reactions* if a massive expansion of drug-reactive T cells has already taken place.

Pseudo-allergic reactions do not require prior sensitization or cell expansion. Symptoms can appear after the first dose. The clinical symptoms of urticaria or anaphylaxis usually appear at standard to high doses, which is an important distinction to sensitized individuals having IgE reactions. The dose dependence is also well documented by successful desensitization procedures in various pseudo-allergic reactions [54, 55]. In NSAID-related pseudo-allergy, the underlying inflammation and effector cell hyperreactivity influences the clinical severity [56].

In conclusion, drug concentrations needed for initiation and elicitation of DHR may vary substantially and differ for allergic, *p-i*, or pseudo-allergic reactions. *Reducing the dose is a useful (although not always sufficient) advice to avoid or minimize DHR.*

Predictability

At present, *allergic reactions* are not predictable, as they can bind to various epitopes (peptide sequences), which are then presented by different HLA alleles [22]. However, if a prior metabolism of a prohaptent to a haptent is involved, differences in the metabolizing enzymes may influence the manifestation of DHR [52, 53].

In *p-i stimulations*, the pharmacological activity of the drug on immune receptors is often linked to the presence of a certain immune receptor in the individual: HLA associations of certain DHR are described for a growing number of drugs [25], some of them with an almost exclusive association to a certain HLA allele, providing a negative predictive value close to 100%, while other drugs were associated with various alleles. On the other hand, the positive predictive value was mostly low (<3%), with the notable exception of abacavir, where about 50% of HLA-B*57:01 carriers developed a hypersensitivity reaction upon drug exposure [57]. The majority of high-risk alleles were HLA class I, but some less stringent associations were also found for HLA class II alleles [58, 59].

Predictive testing to avoid DHR is still limited to very few drugs [57, 60]. A main problem is the low positive predictive value, suggesting that other factors also play a role for disease manifestation. Such factors may be cytochrome P₄₅₀-related genes [53] or the presence of certain TCR, shown for HLA-B*15:02-related severe carbamazepine hypersensitivity reactions [61]. Thus, a combined genetic analysis of HLA and/or metabolizing enzymes may render *p-i*-elicited DHR predictable and therefore avoidable.

Cross-Reactivity

Cross-reactivity within DHR is a common problem. For *allergic DHR*, it is usually explained by the affinity of specific immune receptors (IgE antibodies, TCR) for the eliciting drug (haptent-protein or haptent-peptide complexes) but also related structures. The extent of cross-reactivity is dependent on structural similarity and affinity of the drugs to the available immune receptors (TCR, HLA, IgE).

In most instances, the cross-reactive compound binds with *lower* affinity to the specific immune receptors than the original trigger. This would imply that a higher concentration of the cross-reactive compound is needed to elicit comparable clinical symptoms. Consequently, no symptoms may appear to the cross-reactive compound in T-cell reactions, as the cross-reactive, less-affine compound is not reaching the required dose, which is often similar to the standard dose. In contrast, in IgE-mediated reactions, already very low doses of the original drug are sufficient to elicit symptoms, and a cross-reactive, low-affine compound may still be stimulatory, as the dose given is still in excess.

In *p-i reactions*, cross-reactivity is based on pharmacology. In the sulfamethoxazole model of *p-i TCR*, the

TCR (“H13”) bound only 6 or all 12 structurally related sulfanilamides at the relevant binding site. In TCR “1.3,” 12 structurally related sulfanilamides bound to the same binding site, but only 1 was functionally active (stimulatory); the orientation of drug binding was crucial for functional activity [7, 23, 24]. In *p-i* HLA, abacavir shows a rather restricted ability to bind exclusively to B*57:01, but not to structurally similar HLA-proteins, and modification of the molecule may already abrogate drug binding [62]. In contrast, the carbamazepine-binding HLA-B*15:02 protein binds carbamazepine, some carbamazepine metabolites, and possibly even other anticonvulsants like lamotrigine and phenytoin [63]. Thus, in *p-i* reactions, cross-reactivity is common, may concern binding to TCR or HLA, and needs to be investigated for each group of compounds separately.

In *pseudo-allergy*, the secretagogue receptor MRG-PRX2 on mast cells binds a structurally heterogeneous group of drugs based on a *common chemical motif* and thus shows a wide cross-reactivity which cannot be foreseen by structural data [8]. Similarly, in NSAID-induced pseudo-allergy, structurally different NSAID can lead to exacerbations of the disease – as they all have a *common mode of action* [9, 43, 44]. This needs to be considered in patient advice and prevention of further reactions.

In conclusion, cross-reactivity in the frame of allergic, *p-i*, and pseudo-allergic DHR is common, and seems to be most problematic when low drug doses are sufficient to elicit symptoms (IgE-mediated allergy).

SJS/TEN and DRESS Are *p-i* Reactions

An interesting issue is the pathomechanism of SJS/TEN and DRESS. We propose to categorize SJS/TEN and DRESS (including abacavir hypersensitivity syndrome) as *typical p-i* reactions. This is based on the following arguments:

- When the mode of action of various drugs was analyzed in severe DHR (SJS, DRESS), the stimulation was consistently found to be *p-i* mediated [32–39]. While this does not rule out that regular T-cell stimulations via an allergic-immune (hapten) mechanism can also lead to such reactions, this seems to be rare.
- Many severe DHR were linked to the presence of a certain HLA allele due to direct drug binding to a critical region of the HLA protein and thus represent a typical “*p-i* HLA”-type reaction [25, 27–29, 32–36].
- While many of the SJS/TEN/DRESS-causing drugs were shown to stimulate T cells via *p-i*, B-cell stimula-

tions were not found, and convincing reports on IgE-mediated anaphylaxis to allopurinol, carbamazepine, phenytoin, or abacavir are lacking. An exception are sulfanilamides, where DRESS/SJS and anaphylaxis are known to occur. But sulfanilamide-induced anaphylaxis to SMX is probably elicited by the metabolite SMX-NO, which acts as a hapten, while SJS/DRESS is due to *p-i* reactions to the parent compound (*p-i* TCR) [17, 23, 24].

- The clinical picture of DRESS or SJS/TEN with severe blistering of the skin or a fulminant, possibly lethal hepatitis, carditis, or colitis, for example, after the intake of a small chemical/drug is difficult to comprehend. From a biological point of view such a “suicidal” immune reaction does not make sense. It has been shown that *p-i* stimulations bypass important control mechanisms inherent in the development of a *normal* immune reaction [7] (Boxes 1, 2). *p-i* stimulations can occur without prior activation of dendritic cells or in the absence of danger signals, and naïve and memory T cells are directly activated (shown for abacavir) [26]. Such T-cell stimulations are reminiscent of allostimulations. Indeed, the drug binding to a self HLA molecule may render it to look like an allo-HLA molecule, which elicits a strong allostimulation by T cells [26]. Thus the direct, “at random,” but still affine interaction of drugs with HLA or TCR molecules can lead to a situation comparable to an *acute-graft-versus-host reaction* [7, 26]. Apart from DHR, only graft-versus-host disease is a well-documented cause of SJS/TEN and DRESS [64–66]. Thus, severe DHR like SJS/TEN or DRESS may represent a self-destructive reaction against their own cells due to drug modification of their own HLA.

Combine Timing, Type, Drug Characteristics, and Testing to Subclassify DHR

Already in 2003, Aronson and Ferner [67] proposed a classification system of ADR (DoTS), which combined properties of the drug and its dose with properties of the reaction (the time course of its appearance and its severity) and of the individual (the genetic, pathological, and other biological differences that confer susceptibility). Here we propose a similar approach to dissect DHR, namely to *combine* different criteria to define allergic, *p-i*, and pseudo-allergic DHR subforms (Table 4; Fig. 1).

These criteria are:

- *Timing of appearance* of symptoms: <1 h (IgE), <1–6 h (pseudo-allergic), or >6 h (delayed/T cells).

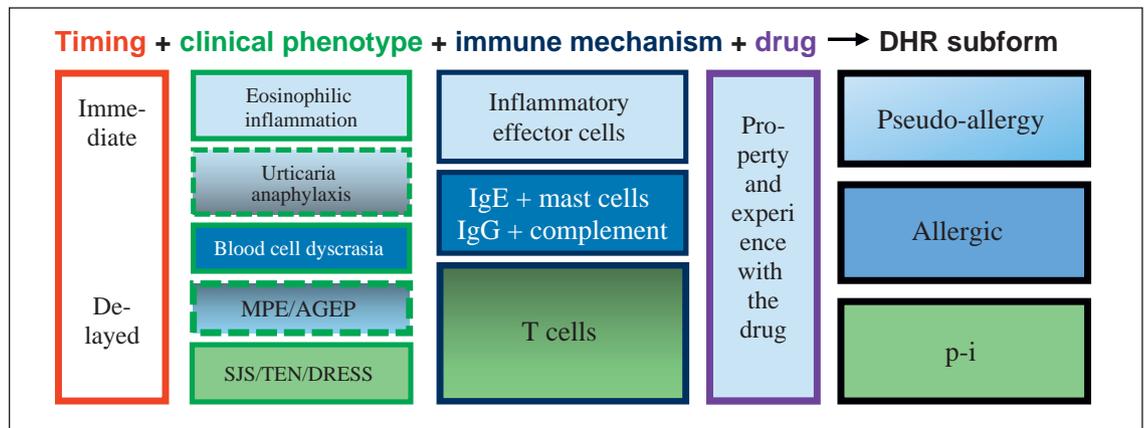


Fig. 1. DHR subclassification: combining time of appearance, phenotype/symptoms, possible immune pathomechanism, property, and experience with the drug often allows to conclude which mode of action is involved in the specific DHR of the patient. AGEP, acute generalized exanthematous pustulosis.

Box 4. Case histories illustrating DHR subclassifications

- A A 34-year-old patient had recurrent febrile rhinosinusitis and bronchitis; 15–20 min after the 1st dose of 750 mg amoxicillin, he developed generalized erythema, palmar and plantar pruritus, bronchoconstriction, hypotension (80/? mm Hg) and syncope for ca. 30 s, and upper-thorax urticaria. He tolerated the same drug 1 year ago. The rapidity of symptoms, the type of symptoms, the known hapten-like features of β -lactams suggest the diagnosis of an allergic (IgE-mediated) anaphylaxis to amoxicillin. Other penicillins/ β -lactams may also cause reactions due to cross-reactivity. Allergy workup is needed.
- B A 60-year-old patient with neuralgia developed malaise, erythema, a swollen face, fever (38° C), and an exanthema after 3 weeks of carbamazepine (3 × 400 mg/day). The laboratory investigation showed CRP 14 mg/L (normal <5 mg/L), eosinophilia ($1.4 \times 10^9/L$, normal $<0.5 \times 10^9/L$), and elevation in liver enzymes (ALAT/ASAT >450 IU/L, normal <70 IU/L). The type of drug known to cause DRESS, the time interval between starting treatment and appearance of symptoms (due to expansion of T cells), the kind of symptoms (T-cell-mediated cytotoxicity), and the laboratory findings allowed the diagnosis of DRESS to carbamazepine, which is a p-i reaction.
- C A 29-year-old lady developed an acute urticaria with massive swelling of the lips and in the periorbital region after 50 mg diclofenac taken for lower-back pain 20 min previously. She had chronic spontaneous urticaria for 3 months about 1 year ago, but was symptom free ever since. She remembered a history of similarly severe generalized urticaria once after 1,000 mg of aspirin 6 months ago. The type of drugs, the acute appearance, and the type of symptoms, the previous urticaria, and the fact that different NSAID elicit similar symptoms speak for a pseudo-allergic reaction to diclofenac and ASS in the frame of an NSAID intolerance.

- *Reaction type (Coombs and Gell)* and severity (clinical, laboratory tests) of symptoms (e.g. urticaria, anaphylaxis, mild or bullous exanthema, or involvement of internal organs).
- *Known chemical property* of the drug (namely to act as hapten/prohapten, via p-i or causing pseudo-allergic reactions like NSAID) and *prior experience* with the drug, namely what types of DHR are known.
- *Skin and in vitro tests*: immediate- and delayed-appearing skin tests as well as in vitro tests to define the type of immune mechanism and to pinpoint the eliciting drug and to define safe alternatives.

Timing and type of reaction/symptoms is usually not sufficient to dissect DHR, e.g. rapidly appearing urticaria can be due to allergy (IgE) and/or pseudo-allergy, whereas delayed-appearing exanthems may involve T-cell stimulations by allergic-immune or p-i mechanisms. Thus, additional information like known chemical properties of the drug, experience with the drug, and skin and in vitro tests complete the picture (Boxes 3, 4).

Discussion

Here we show that immune-mediated DHR develop based on three clearly distinct mechanisms: allergic-immune, p-i, and pseudo-allergic. Only allergic-immune DHR are due to the formation of a new antigen. p-i and pseudo-allergic reactions are pharmacological effects. While allergic and pseudo-allergic reactions have been recognized for many years now, the incorporation of p-i reactions as a distinct subform of DHR is novel. We con-

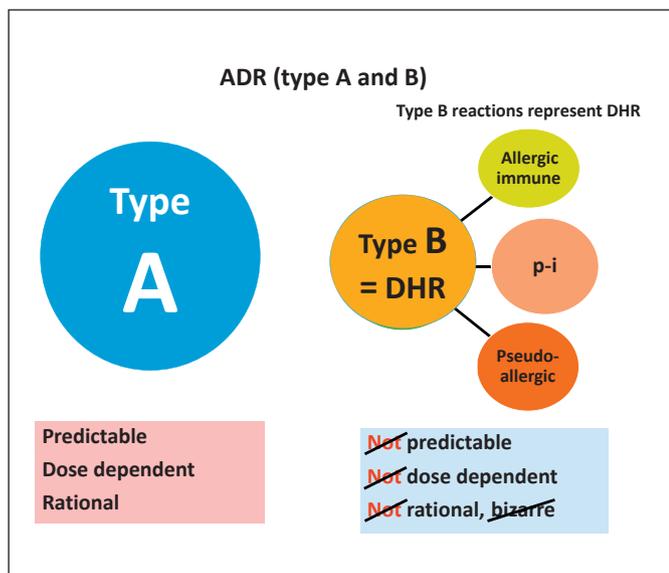


Fig. 2. ADR are subclassified as type A and B reactions. Type B reactions correspond to DHR, which can be classified as allergic/immune, p-i, and pseudo-allergic reactions. For details on predictability, dose dependence, and clinical pictures of the three subforms of DHR see text.

sider it justified, as p-i-mediated DHR are clearly distinct from allergic or pseudo-allergic reactions and follow different rules. They are not antigen-driven events and are exclusively T-cell mediated. They can be linked to certain HLA alleles or TCR-V β subgroups [24]. Importantly, they appear responsible for the most severe T-cell reactions (SJS/TEN/DRESS), but they are not involved in anaphylaxis. p-i-induced symptoms may depend on the presence of cofactors, and they do not need prior exposure, although a cell expansion is often required. They may also differ in desensitization, but this is still unclear. As subclassifying DHR as allergic, p-i, or pseudo-allergic has important implications for patient management and counseling, it is also clinically relevant (Table 4).

In daily clinical practice, the DHR subforms can be distinguished by a *combined approach* using (a) timing, (b) clinical phenotype/possible mechanisms of immune reactions, and (c) properties and experience with the drug (Table 4; Fig. 1). In addition, immunological tests (skin and in vitro tests) may be required to define the eliciting drug and to demonstrate involvement of specific immune reactions. This combined approach is already practiced in most drug allergy clinics to distinguish allergic from pseudo-allergic reactions. It can be easily extended to consider p-i-mediated reactions as well. Clues for a possible p-i reaction would be (a) the type of the reaction,

namely severe forms like SJS/TEN/DRESS, as these are mainly p-i mediated; (b) the property of the drug and history of prior DHR; an exanthema, for example, which is triggered by a known SJS/TEN/DRESS-eliciting drug like allopurinol should be judged differently than an exanthema due to a β -lactam; and (c) a known HLA association which is usually linked to p-i [25] (Fig. 1).

In view of the importance of p-i-mediated DHR for severe reactions, the pharmaceutical industry is challenged to develop tests to identify the risk for such reactions early in drug development. This may actually be advantageous, as p-i reactions may be linked to certain HLA alleles and are thus (partly) predictable [57, 60]. The identification of a risk allele may not terminate the development of the incriminated drug, it just limits its use by only excluding carriers of the risk allele. Overall, the drug application might therefore become even safer.

Last but not least, let us learn from our mistakes. The prior classification of DHR as type B reaction and thus “non-A” reaction is too restricted. Statements like “type B reactions are not pharmacologically mediated,” “are not predictable,” or “are dose independent” are misleading, as they do not apply to DHR in general. These statements can be challenged in some definable subforms of DHR, which have significant clinical consequences regarding dose adaptation or predictability (HLA screening).

In conclusion, one can still distinguish ADR type A and type B reactions. Type B reactions are ADR where the immune/inflammatory system is involved. Thus, *ADR type B = DHR*. DHR have to be further subclassified into allergic-immune, p-i, and pseudo-allergic reactions, which differ in various clinically relevant parameters (Fig. 2).

Funding Sources

The support of ADR-AC GmbH is appreciated.

Disclosure Statement

The authors have no conflict of interests to declare.

References

- Rawlins MD, Thompson JW: Pathogenesis of adverse drug reactions; in Davies DM (ed): *Textbook of Adverse Drug Reactions*. Oxford, Oxford University Press, 1977, p 10.
- Rawlins MD: Clinical pharmacology: adverse reactions to drugs. *BMJ* 1981;282:974–976.
- Edwards IR, Aronson JK: Adverse drug reactions: definition, diagnosis and management. *Lancet* 2000;356:1255–1259.
- Warny M, Klausen TW, Petersen J, Birgens H: Prevalence of glucose-6-phosphate dehydrogenase deficiency and diagnostic challenges in 1,500 immigrants in Denmark examined for haemoglobinopathies. *Scand J Clin Lab Invest* 2015;75:390–397.
- Pichler WJ: Pharmacological interaction of drugs with antigen-specific immune receptors: the p-i concept. *Curr Opin Allergy Clin Immunol* 2002;2:301–305.
- Pichler WJ, Beeler A, Keller M, Lerch M, Posadas S, Schmid D, Spanou Z, Zawodniak A, Gerber B: Pharmacological interaction of drugs with immune receptors: the p-i concept. *Allergol Int* 2006;55:17–25.
- Pichler WJ, Adam J, Watkins S, Wullemmin N, Yun J, Yerly D: Drug hypersensitivity: how drugs stimulate T cells via pharmacological interaction with immune receptors. *Int Arch Allergy Clin Immunol* 2015;168:13–24.
- McNeil BD, Pundir P, Meeker S, Han L, Undem BJ, Kulka M, Dong X: Identification of a mast-cell-specific receptor crucial for pseudo-allergic drug reactions. *Nature* 2015;519:237–241.
- Kowalski ML, Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Bochenek G, Brockow K, Campo P, Celik G, Cernadas J, Cortellini G, Gomes E, Niżankowska-Mogilnicka E, Romano A, Szczeklik A, Testi S, Torres MJ, Wöhrl S, Makowska J: Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy* 2013;68:1219–1232.
- Pichler WJ: Adverse side-effects to biological agents. *Allergy* 2006;61:912–920.
- Boutros C, Tarhini A, Routier E, Lambotte O, Ladurie FL, Carbonnel F, Izzeddine H, Marabelle A, Champiat S, Berdelou A, Lanoy E, Texier M, Libercic C, Eggermont AM, Soria JC, Mateus C, Robert C: Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Clin Oncol* 2016;13:473–486.
- Johansson SG, Hourihane JO, Bousquet J, Brujnzeel-Koomen C, Dreborg S, Haahtela T, Kowalski ML, Mygind N, Ring J, van Cauwenberge P, van Hage-Hamsten M, Wüthrich B; EAACI (the European Academy of Allergy and Clinical Immunology) Nomenclature Task Force: A revised nomenclature for allergy. An EAACI position statement from the EAACI Nomenclature Task Force. *Allergy* 2001;56:813–824.
- Coombs RR, Gell PG: Classification of allergic reactions responsible for clinical hypersensitivity and disease; in Gell PG (ed): *Clinical Aspects of Immunology*. New York, Oxford University Press, 1976, p 575.
- Pichler WJ: Delayed drug hypersensitivity reactions. *Ann Intern Med* 2003;139:683–693.
- Landsteiner K, Jacobs J: Studies on the sensitization of animals with simple chemical compounds. *J Exp Med* 1936;64:625–639.
- Whitaker P, Meng X, Lavergne SN, El-Ghaiesh S, Monshi M, Earnshaw C, Peckham D, Gooi J, Conway S, Pirmohamed M, Jenkins RE, Naisbitt DJ, Park BK: Mass spectrometric characterization of circulating and functional antigens derived from piperacillin in patients with cystic fibrosis. *J Immunol* 2011;187:200–211.
- Naisbitt DJ, Farrell J, Gordon SF, Maggs JL, Burkhard C, Pichler WJ, Pirmohamed M, Park BK: Covalent binding of the nitroso metabolite of sulfamethoxazole leads to toxicity and major histocompatibility complex-restricted antigen presentation. *Mol Pharmacol* 2002;62:628–637.
- Martin SF: Contact dermatitis: from pathomechanisms to immunotoxicology. *Exp Dermatol* 2012;21:382–389.
- Arrighi JF, Rebsamen M, Rousset F, Kindler V, Hauser C: A critical role for p38 mitogen-activated protein kinase in the maturation of human blood-derived dendritic cells induced by lipopolysaccharide, TNF-alpha, and contact sensitizers. *J Immunol* 2001;166:3837–3845.
- Ariza A, Mayorga C, Fernandez TD, Barbero N, Martín-Serrano A, Pérez-Sala D, Sánchez-Gómez FJ, Blanca M, Torres MJ, Montanez MI: Hypersensitivity reactions to β -lactams: relevance of hapten-protein conjugates. *J Invest Allergol Clin Immunol* 2015;25:12–25.
- Gefen T, Vaya J, Khatib S, Rapoport I, Lupo M, Barnea E, Admon A, Heller ED, Aizenshteyn E, Pitcovski J: The effect of haptens on protein-carrier immunogenicity. *Immunology* 2015;144:116–126.
- Yun J, Adam J, Yerly D, Pichler WJ: Human leukocyte antigens (HLA) associated drug hypersensitivity: consequences of drug binding to HLA. *Allergy* 2012;67:1338–1346.
- Watkins S, Pichler WJ: Activating interactions of sulfanilamides with T cell receptors. *Open J Immunol* 2013;3:139–157.
- Watkins S, Pichler WJ: Sulfamethoxazole induces a switch mechanism in T cell receptors containing TCRV β 20-1, altering pHLA recognition. *PLoS One* 2013;8:e76211.
- Pavlos R, Mallal S, Ostrov D, Buus S, Metushi I, Peters B, Phillips E: T cell-mediated hypersensitivity reactions to drugs. *Annu Rev Med* 2015;66:439–454.
- Adam J, Wullemmin N, Watkins S, Jamin H, Eriksson K, Villiger P, Fontana S, Pichler WJ, Yerly D: Abacavir induced T cell reactivity from drug naïve individuals shares features of allo-immune responses. *PLoS One* 2014;9:e95339.
- Illing P, Vivian JP, Dudek NL, Kostenko L, Chen Z, Bharadwaj M, Miles JJ, Kjer-Nielsen L, Gras S, Williamson NA, Burrows SR, Purcell AW, Rossjohn J, McCluskey J: Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. *Nature* 2012;486:554–558.
- Ostrov DA, Grant BJ, Pompeu YA, Sidney J, Harndahl M, Southwood S, Oseroff C, Lu S, Jakoncic J, de Oliveira CA, Yang L, Mei H, Shi L, Shabanowitz J, English AM, Wriston A, Lucas A, Phillips E, Mallal S, Grey HM, Sette A, Hunt DF, Buus S, Peters B: Drug hypersensitivity caused by alteration of the MHC-presented self-peptide repertoire. *Proc Natl Acad Sci USA* 2012;109:9959–9964.
- Norcross MA, Luo S, Lu L, Boyne MT, Gomar-teli M, Rennels AD, Woodcock J, Margulies DH, McMurtrey C, Vernon S, Hildebrand WH, Buchli R: Abacavir induces loading of novel self-peptides into HLA-B*57:01: an autoimmune model for HLA-associated drug hypersensitivity. *AIDS* 2012;26:F21–F29.
- Zanni MP, von Greyerz S, Schnyder B, Brander KA, Frutig K, Hari Y, Valitutti S, Pichler WJ: HLA-restricted, processing- and metabolism-independent pathway of drug recognition by human alpha beta T lymphocytes. *J Clin Invest* 1998;102:1591–1598.
- Britschgi M, Steiner UC, Schmid S, Depta JPH, Senti G, Bircher A, Burkhart C, Yawalkar N, Pichler WJ: T-cell involvement in drug-induced acute generalized exanthematous pustulosis. *J Clin Invest* 2001;107:1433–1441.
- Wullemmin N, Adam J, Fontana S, Krahenbuhl S, Pichler WJ, Yerly D: HLA haplotype determines hapten or p-i T cell reactivity to flucloxacillin. *J Immunol* 2013;190:4956–4964.
- Yang CW, Hung SI, Juo CG, Lin YP, Fang WH, Lu IH, Chen ST, Chen YT: HLA-B*1502-bound peptides: implications for the pathogenesis of carbamazepine-induced Stevens-Johnson syndrome. *J Allergy Clin Immunol* 2007;120:870–877.
- Wei CY, Chung WH, Huang HW, Chen YT, Hung SI: Direct interaction between HLA-B and carbamazepine activates T cells in patients with Stevens-Johnson syndrome. *J Allergy Clin Immunol* 2012;129:1562–1569.
- Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, Lin YL, Lan JL, Yang LC, Hong HS, Chen MJ, Lai PC, Wu MS, Chu CY, Wang KH, Chen CH, Fann CS, Wu JY, Chen YT: HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc Natl Acad Sci USA* 2005;102:4134–4139.

- 36 Yun J, Marcaida MJ, Eriksson KK, Jamin H, Fontana S, Pichler WJ, Yerly D: Oxypurinol directly and immediately activates the drug-specific T cells via the preferential use of HLA-B*58:01. *J Immunol* 2014;192:2984–2993.
- 37 Mauri-Hellweg D, Bettens F, Mauri D, Brandner C, Hunziker T, Pichler WJ: Activation of drug-specific CD4+ and CD8+ T cells in individuals allergic to sulfonamides, phenytoin and carbamazepine. *J Immunol* 1995;155:462–472.
- 38 Naisbitt DJ, Britschgi M, Wong G, Farrell J, Depta JPH, Chadwick DW, Pichler WJ, Pirmohamed M, Park BK: Hypersensitivity reactions to carbamazepine: characterization of the specificity, phenotype and cytokine profile of drug-specific T-cell clones. *Mol Pharmacol* 2003;63:732–741.
- 39 Naisbitt DJ, Britschgi M, Wong G, Farrell J, Depta JPH, Chadwick DW, Pichler WJ, Pirmohamed M, Park BK: Characterization of drug-specific T cells in lamotrigine hypersensitivity. *J Allergy Clin Immunol* 2003;111:1393–1403.
- 40 Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, Khan DA, Lang DM, Park HS, Pichler WJ, Sanchez-Borges M, Shiohara T, Thong BY: International consensus on drug allergy. *Allergy* 2014;69:420–437.
- 41 Choi JH, Kim MA, Park HS: An update on the pathogenesis of the upper airways in aspirin-exacerbated respiratory disease. *Curr Opin Allergy Clin Immunol* 2014;14:1–6.
- 42 Fujisawa D, Kashiwakura J, Kita H, Kikukawa Y, Fujitani Y, Sasaki-Sakamoto T, Kuroda K, Nunomura S, Hayama K, Terui T, Ra C, Okayama Y: Expression of Mas-related gene X2 on mast cells is upregulated in the skin of patients with severe chronic urticaria. *J Allergy Clin Immunol* 2014;134:622–633.
- 43 Sánchez-Borges M, Caballero-Fonseca F, Capriles-Hulett A, González-Aveledo L: Aspirin-exacerbated cutaneous disease (AECD) is a distinct subphenotype of chronic spontaneous urticaria. *J Eur Acad Dermatol Venerol* 2015;29:698–701.
- 44 Szczeklik A: Aspirin-induced asthma: new insights into pathogenesis and clinical presentation of drug intolerance. *Int Arch Allergy Appl Immunol* 1989;90(suppl 1):70–75.
- 45 Morales DR, Guthrie B, Lipworth BJ, Jackson C, Donnan PT, Santiago VH: NSAID-exacerbated respiratory disease: a meta-analysis evaluating prevalence, mean provocative dose of aspirin and increased asthma morbidity. *Allergy* 2015;70:828–835.
- 46 Blanca-López N, Ariza A, Doña I, Mayorga C, Montañez MI, García-Campos J, Gomez F, Rondón C, Blanca M, Torres MJ: Hypersensitivity reactions to fluoroquinolones: analysis of the factors involved. *Clin Exp Allergy* 2013;43:560–567.
- 47 Levy M, Koren G, Dupuis L, Read SE: Vancomycin-induced red man syndrome. *Pediatrics* 1990;86:572–580.
- 48 Kim BS, Park SM, Uhm TG, Kang JH, Park JS, Jang AS, Uh ST, Kim MK, Choi IS, Cho SH, Hong CS, Lee YW, Lee JY, Choi BW, Park HS, Park BL, Shin HD, Chung IY, Park CS: Effect of single nucleotide polymorphisms within the interleukin-4 promoter on aspirin intolerance in asthmatics and interleukin-4 promoter activity. *Pharmacogenet Genomics* 2010;20:748–758.
- 49 Kim JM, Park BL, Park SM, Lee SH, Kim MO, Jung S, Lee EH, Uh ST, Park JS, Choi JS, Kim YH, Kim MK, Choi IS, Cho SH, Choi BW, Park HS, Chang HS, Shin HD, Park CS: Association analysis of N-acetyl transferase-2 polymorphisms with aspirin intolerance among asthmatics. *Pharmacogenomics* 2010;11:951–958.
- 50 Adam J, Eriksson KK, Schnyder B, Fontana S, Pichler WJ, Yerly D: Avidity determines T-cell reactivity in abacavir hypersensitivity. *Eur J Immunol* 2012;42:1–11.
- 51 Castells Guitart MC: Rapid drug desensitization for hypersensitivity reactions to chemotherapy and monoclonal antibodies in the 21st century. *J Investig Allergol Clin Immunol* 2014;24:72–79.
- 52 Yang CY, Chen CH, Deng ST, Huang CS, Lin YJ, Chen YJ, Wu CY, Hung SI, Chung WH: Allopurinol use and risk of fatal hypersensitivity reactions: a nationwide population-based study in Taiwan. *JAMA Intern Med* 2015;175:1550–1557.
- 53 Chung WH, Chang WC, Lee YS, Wu YY, Yang CH, Ho HC, Chen MJ, Lin JY, Hui RC, Ho JC, Wu WM, Chen TJ, Wu T, Wu YR, Hsieh MS, Tu PH, Chang CN, Hsu CN, Wu TL, Choon SE, Hsu CK, Chen DY, Liu CS, Lin CY, Kaniwa N, Saito Y, Takahashi Y, Nakamura R, Azukizawa H, Shi Y, Wang TH, Chuang SS, Tsai SF, Chang CJ, Chang YS, Hung SI: Taiwan Severe Cutaneous Adverse Reaction Consortium; Japan Pharmacogenomics Data Science Consortium: Genetic variants associated with phenytoin-related severe cutaneous adverse reactions. *JAMA* 2014;312:525–534.
- 54 Fruth K, Pogorzelski B, Schmidtman I, et al: Low-dose aspirin desensitization in individuals with aspirin-exacerbated respiratory disease. *Allergy* 2013;68:659–665.
- 55 Fajt ML, Petrov AA: Outpatient aspirin desensitization for patients with aspirin hypersensitivity and cardiac disease. *Crit Pathw Cardiol* 2011;10:17–21.
- 56 Kim S, Choi IS, Kim YJ, et al: Airway responsiveness to inhaled aspirin is influenced by airway hyperresponsiveness in asthmatic patients. *Korean J Intern Med* 2010;25:309–316.
- 57 Mallal S, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, Jägel-Guedes E, Rugina S, Kozyrev O, Cid JF, Hay P, Nolan D, Hughes S, Hughes A, Ryan S, Fitch N, Thorborn D, Benbow A; PREDICT-1 Study Team: HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008;358:568–579.
- 58 Singer JB, Lewitzky S, Leroy E, et al: A genome-wide study identifies HLA alleles associated with lumiracoxib-related liver injury. *Nat Genet* 2010;42:711–714.
- 59 Vitezica ZG, Milpied B, Lonjou C, et al: HLA-DRB1*01 associated with cutaneous hypersensitivity induced by nevirapine and efavirenz. *AIDS* 2008;22:540–541.
- 60 Chen P, Lin JJ, Lu CS, et al., Taiwan SJS Consortium: Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. *N Engl J Med* 2011;364:1126–1133.
- 61 Ko TM, Chung WH, Wei CY, Shih HY, Chen JK, Lin CH, Chen YT, Hung SI: Shared and restricted T-cell receptor use is crucial for carbamazepine-induced Stevens-Johnson syndrome. *J Allergy Clin Immunol* 2011;128:1266–1276.
- 62 Naisbitt DJ, Yang EL, Alhaidari M, Berry NG, Lawrenson AS, Farrell J, Martin P, Strebel K, Owen A, Pye M, French N, Clarke SE, O'Neill PM, Park BK: Towards depersonalized abacavir therapy: chemical modification eliminates HLA-B*57:01-restricted CD8+ T-cell activation. *AIDS* 2015;29:2385–2395.
- 63 Hung SI, Chung WH, Liu ZS, Chen CH, Hsieh MS, Hui RC, Chu CY, Chen YT: Common risk allele in aromatic antiepileptic-drug induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Han Chinese. *Pharmacogenomics* 2010;11:349–356.
- 64 Friedman HZ, Arias AM, Catchatourian R, Fretzin DF: Toxic epidermal necrolysis following bone marrow transplantation. *Cutis* 1984;34:158–162.
- 65 Jeanmonod P, Hubbuch M, Grünhage F, Meiser A, Rass K, Schilling MK, Kollmar O: Graft-versus-host disease or toxic epidermal necrolysis: diagnostic dilemma after liver transplantation. *Transpl Infect Dis* 2012;14:422–426.
- 66 Azukizawa H, Itami S: Animal models of toxic epidermal necrolysis; in Pichler WJ (ed): *Drug Hypersensitivity*. Basel, Karger, 2007, pp 129–139.
- 67 Aronson JK, Ferner RE: Joining the DoTS: new approach to classifying adverse drug reactions. *BMJ* 2003;327:1222–1225.