Received: 12 November 2018 | Revised: 12 January 2019 | Accepted: 29 January 2019

DOI: 10.1111/all.13765

REVIEW ARTICLE

WILEY Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI

Immune pathomechanism and classification of drug hypersensitivity

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Abstract

Drug hypersensitivity reactions (DHR) are based on distinct mechanisms and are clinically heterogeneous. Taking into account that also off-target activities of drugs may lead to stimulations of immune or inflammatory cells, three forms of DHR were discriminated: the *allergic-immune* mechanism relies on the covalent binding of drugs/chemicals to proteins, which thereby form new antigens, to which a humoural and/or cellular immune response can develop. In IgE-mediated drug allergies, a possible tolerance mechanism to the drug during sensitization and the need of a covalent hapten-carrier link for initiation, but not for elicitation of IgE-mediated reactions is discussed. The *p-i* ("pharmacological interaction with immune receptor") concept represents an off-target activity of drugs with immune receptors (HLA or TCR), which can result in unorthodox, alloimmune-like stimulations of T cells. Some of these p-i stimulations occur only in carriers of certain HLA alleles and can result in clinically severe reactions. The third form of DHR ("pseudo-allergy") is represented by drug interactions with receptors or enzymes of inflammatory cells, which may lead to their direct activation or enhanced levels of inflammatory products. Specific IgE or T cells are not involved. This classification is based on the action of drugs and is clinically useful, as it can explain differences in sensitizations, unusual clinical symptoms, dependence on drug concentrations, predictability and immunological and pharmacological cross-reactivities in DHR.

KEYWORDS

allergic/immune hypersensitivity, classification, drug hypersensitivity, p-i concept, pseudo-allergic drug reactions

1 | INTRODUCTION

Adverse drug reactions (ADR) are due to different mechanisms and result in different clinical pictures. In 1977 and 1981, Rawlings and Thompson 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 dose, 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 may occur in every individual and are to a certain extent predictable. A typical example would be sleepiness caused by first-generation antihistamines.

Type B reactions are less well defined and comprise about 15% of all ADR. Originally, diseases like haemolysis after antimalarials, certain analgesics and antibiotics in patients with glucose-6-phosphate dehydrogenase deficiency[3] were included in type B reactions. It is debatable, whether such a defined enzyme deficiency with accumulation of reactive oxygen species and damage of red blood cells should be grouped in type B reaction: they are *not* due to an immune reaction and are *not* hypersensitivities.

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The vast majority of type B reactions involve the immune system and are drug hypersensitivity reactions (DHR). The term "drug allergy" refers to a specific immune response to a drug acting as hapten, which is actually directed against a hapten-carrier complex. This complex functions as allergen.[4,5] In contrast, the term drug hypersensitivity (DH) goes beyond drug allergy.[6] It includes—beside allergy—also reactions of immune or inflammatory cells, which are not due to the stimulation of the specific immune response by a hapten-protein antigen. This drug-dependent but not necessarily antigen-dependent stimulation of immune competent cells like T cells and/or inflammatory cells by drugs has been intensively studied in the last decades. An important conclusion was that drugs may bind *directly* to receptors on immune or inflammatory cells and stimulate them[7-9]: This activity of the drug with either immune receptors (pharmacological interaction with immune receptor [p-i] concept) or receptors/enzymes of inflammatory cells (pseudo-allergy) accounts for a substantial part of DHR. The old dogma that a drug needs to bind covalently to a protein to form a new antigen (hapten-carrier complex) is correct.[4-6] But the formation of a new antigen is not a prerequisite for *all* DHR and accounts for only part of the DHR (the allergic-immune reactions). Direct drug interactions with immune receptors (HLA, TCR) or enzymes or receptors of inflammatory cells can also lead to DHR. These distinct modes of immune or inflammatory cell stimulations are reflected in the new classification of DHR presented in this and previous reviews.[7,10] An emphasis is laid on certain IgE-mediated drug allergies: on one hand, on a possible role of antigen-specific tolerance during sensitization; and on the other hand, the necessity of covalent drug-protein links in the effector phase of IgE-mediated reactions is questioned. These and many of open questions of DH are summarized in "Future Research Perspectives" (Box 1).

1.1 | Classification of DHR based on timing or immune stimulation

Different attempts have been undertaken to sub-classify DHR, with the aim to better diagnose, manage and possibly avoid them. In clinical practice, these approaches are often combined to define a DHR (reviewed in [11]).

- The *time between start of treatment* until symptoms appear as follows: immediate reactions appear mostly *within 1 hour, occasionally later (<6 hours)*. Delayed reactions appear mostly after days (>3->12 days), but symptoms may already appear on day 1, for example in re-exposures.[10] AGEP may start on day 3, MPE appear mostly between day < 7-12 of treatment and most SCAR (severe cutaneous adverse reactions)-like SJS/TEN and DRESS appear often after >12—some even after >50 days.[12] Time of appearance is a simple and still very useful approach as it distinguishes the immediate reactions with mast cell degranulation from the IgG and common T-cell reactions (Figure 1).
- *Gell and Coombs* classification links the clinical phenotype to the immune mechanism.[13,14] The immediate appearing symptoms (urticaria, anaphylaxis) were classified as being due to IgE and mast cell degranulation. The delayed appearing symptoms (exanthems, hepatitis. SJS, DRESS, etc.) are dependent on activation of T cells with various functions.[10,13,14] Some reactions like haemolysis, thrombocytopaenia or arthralgia, vasculitis may be due to drug-induced IgG/IgM antibodies. This classification is needed to devise testing strategies, as the type of immune stimulation determines the procedures for skin testing (eg, prick or patch) or in vitro testing (BAT or T-stimulation assays) with the incriminated drug.
- Some reactions known to occur mainly with certain drugs were named accordingly, for example NSAID intolerance, anticonvulsant hypersensitivity syndrome and acute infusion reactions to biologicals.

2 | THE MODE OF ACTION OF DRUGS AS BASIS FOR SUB-CLASSIFYING DHR

The Gell and Coombs classification was developed with the background that DHR are hapten (antigen-)-driven events. The interactions of drugs with receptors or enzymes, which is the basis for pharmacological interaction with immune receptors (p-i) and pseudo-allergic reactions were not considered. Moreover, the p-i and pseudo-allergic reactions have features of pharmacologically mediated type A reactions and cannot be simply classified as type B.

To better understand the features of DHR, the *mode of action of drugs* was proposed as basis for a classification of DHR.[7,10] It seems to be conceptually straightforward and clinically useful, as it explains differences in sensitization, dose dependence, HLA restriction and cross-reactivity.

2.1 | The immune/allergic stimulation: hapten concept

The hapten mechanism is the classical explanation for DHR and is based on data generated in the early 20th century[4,5]: it 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).[15-17] A *distinctive feature of hapten-like drugs* is their ability to elicit *any type of the specific immune response (*all types of the Gell and Coombs classification). If a drug elicits both T- and B-cell responses, one may conclude that the drug is most likely acting as hapten (eg, amoxicillin, causing exanthems, or urticaria/anaphylaxis or even haemolytic anaemia). Some drugs are pro-haptens and gain the ability to bind covalently to proteins only after being metabolized.[18] The immune reaction may be directed to the metabolite/protein complex. Both antibody and T-cell reactions can be highly specific and can discriminate chemically similar haptens.[4-6]

Table 1 contains a list of drugs which are able to bind stably and covalently (=haptens) to larger molecules and can induce

Box 1 Future research perspectives

HAPTEN

Tolerance to hapten-carrier conjugates?

Hapten-protein conjugates are formed regularly upon (high dose) beta-lactam therapy: when is it inducing an (asymptomatic) immune response, when a clinical hypersensitivity, when a symptomatic IgE, when a symptomatic T-cell response?

Covalent link only for induction, not for elicitation?

To *induce* an immune response, it is accepted that the drugs need to be covalently linked to a larger molecule/protein. But if the individuals are already sensitized and have produced drug-specific IgE, does the drug need to bind by covalent links to a larger molecule (like for sensitization) in order to cross-link IgE, or is a noncovalent link sufficient to cross-link IgE bound to Fc-IgE-RI?

IgE without prior sensitization to the elicitor?

Where and how are patients sensitized which react at *first* exposure to a drug with IgE (eg, ceftriaxone, radio contrast media, muscle relaxants, chlorhexidine)? Was it the same compound or another chemical/drug?

PI

Expand data on p-i HLA and p-i TCR

Many concepts of p-i are based on the analysis of a single/few drugs or a few patients. However, each drug seems to be "unique." To generalize *some* findings, one needs confirmation with other drugs and more patients.

p-i and SCAR

- Confirm concept of p-i stimulations in SJS/TEN and DRESS (ref [10]) and other manifestations;
- Why does a patient with a certain HLA-risk allele develop SJS, another a DRESS?

p-i HLA

- Where (inside cell/surface) are drugs loaded onto HLA-peptide: can loading of the drug on the cell surface and change of the peptide-drug HLA complex lead to allo-immunity?
- What are the conditions for drug binding on the cell surface: flexibility of bound peptides?; affinity of drug binding to HLA, location?
- Do endogenous small molecules also bind to HLA (example hypoxanthin, ref [42])? Role of small molecules in auto-inflammation?
- Missing link: the majority of individuals with the risk allele and drug exposure do NOT develop a DHR: which factors contribute to the manifestation of SCAR and whether DRESS or SJS/TEN develop?
- Clinic of p-i TCR vs clinic of p-i HLA; role of peptide in p-i HLA? Recognition of many peptides by T cells (polyspecificity?)
- Identification of TCR recognized peptide(s) presented ex vivo from affected tissue. Do the peptide specificity affect localization of immune response (liver, skin, kidney…)? Homing of p-i activated T cells

p-i TCR

- Investigate more drugs for p-i TCR
- p-i-TCR can lead to allo-recognition: mechanism?
- p-i interaction with HLA and TCR: oligoclonality, monoclonality, clinic
- Expanding the pharmacology of drug interaction with immune receptors (TCR, HLA): blocking of signalling (in drug, in allo- or peptide stimulations)
- Selective activation of drug reactive TCR/T cells: can it be exploited by stirring the immune response to a certain antigen?

Box 1 (Continued)

Risk assessment

- Incorporate p-i mechanism in risk assessment during preclinical testing
- Role of affinity of drug binding to immune receptors, relation of affinity of drug binding to individual drug concentration/symptoms causing DHR
- Expand computer modelling of drug – immune receptor interactions, establish screening models,
- Learn to discriminate between clinically relevant and non-relevant binding,
- Combine pharmacogenetics, immune-genetics for risk evaluation
- Establish in vitro confirmatory tests for modelling derived data

Animal model of p-i

Drug binding to other immune receptors: γδTCR or other HLA-molecules like HLA-Ib.
Role of cofactors in activating p-i-exposed T cells: viral, gvhd as cofactor, how does it work, clinical relevance?
Multiple drug hypersensitivity: a chronic DHR, like a chronic gvhd?

PSEUDOALLERGY

MRGPRX2/mast cell receptors

- Polymorphism of MRGPRX2: physiology and relation to acute drug reactions
- Involvement of other mast cell receptors in acute reactions (eg, opioid receptors?,..)

Mechanism of MRGPRX2/mast cell receptors in other drug reactions (eg, radio-contrast media).

NSAID intolerance

- What is the cause for differents clinical manifestations (N-ECD vs N-ERD)
- Investigate and define differences between affected patients and healthy controls in tolerating NSAID (genetic, epigenetic, cell activation…)

Risk assessment

- Cell lines with MRGPRX2 isoforms and establishment of solid functional assays
- Role of MRGPRX2 isoforms/SNP for drug reactions, role of affinity of drug-binding
- Computer models of drug MRGPRX2 interaction, confirmation of models with in vitro data

Risk assessment

- Incorporate p-i mechanism in risk assessment during preclinical testing
- Role of affinity of drug binding to immune receptors, relation of affinity of drug binding to individual drug concentration/symptoms causing DHR
- Expand computer modelling of drug-immune receptor interactions
- Establish in vitro confirmatory tests for modelling derived data and learn to discriminate between clinically relevant and nonrelevant drug binding

Animal model of p-i

Drug binding to other immune receptors: γδTCR or other HLA molecules like HLA-Ib.
Role of cofactors in activating p-i-exposed T cells: viral, gvhd as cofactor, how does it work, clinical relevance?
Multiple drug hypersensitivity: development of a chronic, persisting disease (like a chronic gvhd) after stopping drug therapy?(ref [85]).

Box 1 (Continued)

PSEUDOALLERGY

MRGPRX2/mast cell receptors

- Polymorphism of MRGPRX2: physiology and relation to acute drug reactions
- Involvement of other mast cell receptors in acute reactions (eg, opioid receptors?,..), mechanism of MRGPRX2/mast cell receptors in other drug reactions (eg, radiocontrast media)

NSAID intolerance

- Cause of different clinical manifestations (N-ECD vs N-ERD)
- Investigate and define differences between affected patients and healthy controls in tolerating NSAID (genetic, epigenetic, cell activation…)

Risk assessment

- Cell lines with MRGPRX2 isoforms and establishment of solid functional assays for drug-dependent activation
- Role of MRGPRX2 isoforms/SNP for drug reactions, role of affinity of drug-binding
- Computer models of drug MRGPRX2 interaction, confirmation of models with in vitro data

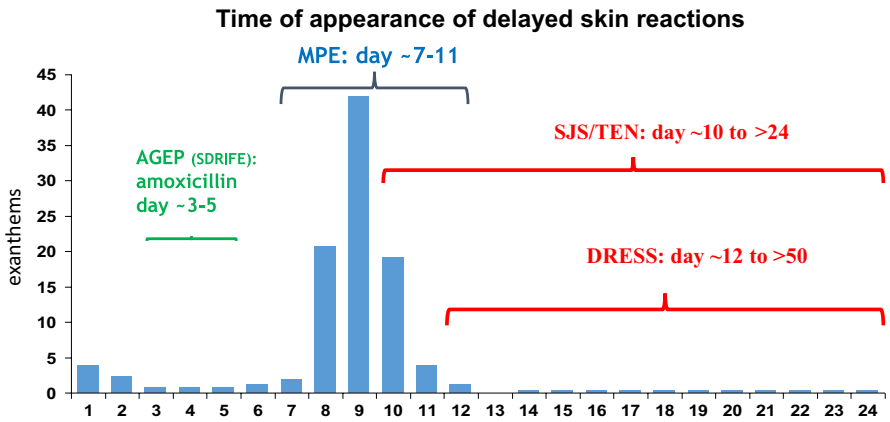

FIGURE 1 Manifestation of delayed appearing (T-cell-mediated) drug hypersensitivity reactions. The column shows the appearance of MPE after gemifloxacin therapy in females (www.accessdata.fda.gov/drugsatfda_docs/label/2008/021158s013lbl.pdf). The other manifestations of delayed type hypersensitivity appear earlier or later: AGEP can appear already after 3-4 d; MPE after < 7-12 d, not rarely after therapy was already stopped; SJS/TEN and DRESS appear mostly after a longer time interval; The reason for the differences is unclear, but might be related to a the precursor cell frequency of drug-reactive T cells or the affinity of drug-receptor interactions (p-i)

IgE-mediated anaphylaxis. Importantly, one should be aware that some drugs exert immune stimulation via hapten *and/or* via p-i *and/or* pseudo-allergic mechanism as well. Flucloxacillin, piperacillin and cephalosporins are examples of drugs acting via hapten and/or p-i mechanism, and chinolones and metamizole appear to be able to stimulate via hapten, p-i and pseudo-allergic mechanism.

2.1.1 | Antigenicity and immunogenicity

The ability to elicit a complete immune response is based on two features of haptens, antigenicity and immunogenicity:

The covalent binding by a drug alters the protein structure and can transform an autologous soluble (eg, albumin and transferrin) or cell-bound protein (integrins, selectins, etc.) to a novel drug-modified protein, to which no intrinsic tolerance exists and which may thus act as a new antigen (antigenicity). A broad *adaptive immune* response can be induced with the involvement of T and B cells, which react specifically with the whole or processed hapten-protein or hapten-peptide complexes.[15-20] Of note, the initial binding of the drug to a fitting site in the larger protein is fast and involves electrostatic interactions, hydrogen bonds, van der Waals forces. A covalent link of the reactive site within the drug

TABLE 1 Type of drugs eliciting drug hypersensitivity by hapten, p-i or pseudo-allergic mechanism[a]

Hapten	p-i[b]	Pseudo-allergy
Beta-lactam antibiotics: penicillins, amoxicillin, flucloxacillin, cephalosporins, carbapenem, monobactam; penicillamine	*Beta-lactam antibiotics*: flucloxacillin, amoxicillin, cephalosporins: monobactam	
Sulphanilamides: sulphamethoxazole-NO[c]	*Sulphanilamides* sulphamethoxazole, sulfapyrdine and other sulphanilamides	
		NSAID acetylsalicylic acid, diclofenac, mefenamic acid, ibuprofen, etc.
Metamizole	*Metamizole*	*Metamizole*
Chinolones[d] (ciprofloxacin, moxifloxacin, norfloxacin,..)	*Chinolones* (ciprofloxacin, moxifloxacin, norfloxacin,..)	*Chinolones*[d] (ciprofloxacin, moxifloxacin, norfloxacin,..)
RCM[d] iomeprol, iodihexol and other radiocontrast media	*RCM*: iomeprol, iodihexol and other radiocontrast media	*RCM*: Iomeprol[d], iodihexol[d] and other radiocontrast media
Muscle relaxants[d] (rocuronium, suxamethylcholin, etc....		*Muscle relaxants*[d] (rocuronium, suxamethylcholin, etc....
	Vancomycin	*Vancomycin*
	Antiepileptics[b]: carbamazepine lamotrigine, phenytoin	
	Local anaesthetics: lidocain, mepivacain etc.	
	Allopurinol[b]*/oxypurinol*[b]	

Not complete and only drugs where the mode of action has been documented are listed.
[a]Note that the action of a drug as a hapten does not exclude an action via p-i as well, or that drugs acting via pseudo-allergic mechanism may also act via IgE or even p-i (example are metamizole, chinolones, radiocontrast media or muscle relaxants).
[b]Note that most drugs involved in p-i-driven stimulations fail to elicit anaphylaxis (eg, abacavir, carbamazepine, lamotrigine...): these are drugs which are not acting via allergic/immune mechanism.
[c]Sulphamethoxazole-NO is available outside the liver; many other drugs may form reactive metabolites only locally in the liver, and the immune system does not react.
[d]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 (see text).

and the protein follows these initial noncovalent bonds and occurs mainly with a specific amino acid (eg, beta-lactams to lysine). A small drug will bind to multiple sites within the protein. For example, the lysins at position 190, 195, 199, 212, 351, 432, 541 and 525 in human serum albumin are accessible to beta-lactams and can be modified.[21] The covalent links persist—in contrast to noncovalent links—intracellular processing and allow the presentation of a battery of different hapten-peptide conjugates, which bind to *different* HLA molecules.[22] A polyclonal immune response to many hapten-modified peptides presented by different HLA molecules may arise.[21] It explains, that hapten reactions are *not* restricted to a single HLA molecule (in contrast to some p-i reactions, see below), as the modified peptides are presented by different HLA molecules.[22]

Providing antigenic determinants alone is not sufficient to elicit an immune response. Drugs acting as haptens can stimulate cells of *innate* immunity (eg, dendritic cells)[23,24] and thus provide the essential second signal for initiating T-cell immunity (immunogenicity): 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. Of note, this feature of drugs/chemicals is well established for contact dermatitis, where many of contact allergens are also skin irritants and a local inflammation can be observed. But where and how "danger signals" happen in systemic DHR is not well investigated (open questions). Actually, the second/danger signal may often be absent—and no immune response develops in spite of availability of new antigens.

2.1.2 | Time requirement for allergic-immune reactions

The generation of a hapten-protein or hapten-peptide specific immune response (T cells, IgG, IgE) *requires time*. It occurs in secondary lymphoid organs and is symptom-free. The time interval between initial exposure and appearance of clinical symptoms depends on various factors: time is needed (a) to form the hapten-protein complex; (b) to process the hapten-protein and present the hapten-peptides on HLA molecules; and (c) most time is needed for the expansion of drug-specific T and B cells. The more new antigenic determinants are provided, the more precursor cells may be stimulated and the faster do they reach an amount which is clinically relevant. The usual time period between start of drug therapy and MPE manifestation (eg,

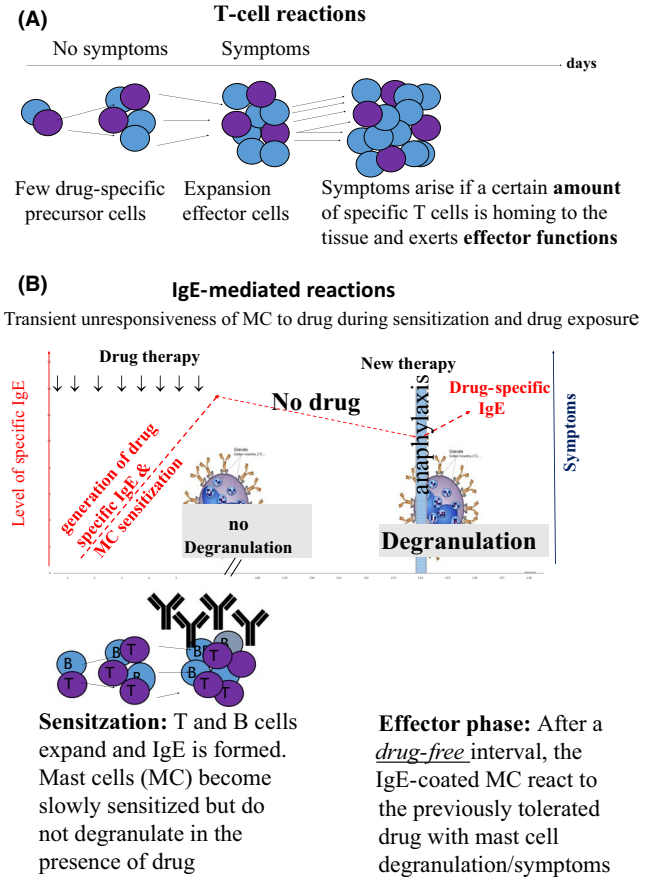

FIGURE 2 Delayed T-cell (A) and IgE-mediated, acute reactions (haptens, allergic-immune stimulation) (B): *T-cell reactions* (A) develop to hapten-modified peptides and with p-i stimulations; they develop upon antigen/drug exposure continuously and differentiate into effector cells with tissue orientation. Clinical symptoms appear, as soon as the cell expansion and tissue emigration by effector T cells reach a sufficient number. Not rarely, symptoms appear after drug therapy has been stopped (eg, on day 12 after a 10 d therapy with amoxicillin). *In IgE-mediated allergy* (B), the hapten-modified proteins and peptides stimulate T and B cells. This phase is symptom-free, although the newly formed IgE is already sensitizing mast cells and basophils and antigen (=drug) is constantly provided. This suggests that the development of IgE in the presence of constant drug supply goes along with a selective *nonresponsiveness* of IgE-coated mast cells/basophils for these specificities. Acute IgE-triggered symptoms appear after a drug-free interval, after which the mast cells are again responsive to the drug or if the drug dose is suddenly and strongly increased

amoxicillin) is ca. 7-12 days. The appearance of SJS or DRESS symptoms, which are considered to represent mainly p-i stimulations,[10] occurs later: Probably, the amount of precursor cells able to react to p-i stimulations is low. Alternatively, the stimulatory complex (peptide-drug-HLA or TCR-drug-HLA) is rather labile, which may reduce T-cell reactivity: the in vitro induction of T-cell reactivity to abacavir, which binds with rather high affinity to B*57:01, needed ca. 14 days in healthy B*57:01+ individuals.[25] In contrast, the in vitro induction of flucloxacillin-specific T cells in drug-naive donors needed 28-35 days[26] (Figure 1).

2.1.3 | Change of cells in IgE-mediated reactions with possible transient unresponsiveness of effector cells

There is an important difference between symptom *appearance of delayed (T cell) and acute reactions (IgE/mast cell)*: In both instances, a silent sensitization takes place for some days (Figure 2A/B): The symptoms of *delayed reactions* occur after a *constant* (eg, daily) drug exposure and are dose-dependent. The cytotoxic and cytokine-secreting effector T cells are *not paralysed* by the constant drug exposure, and symptoms (eg, exanthema) are simply a consequence of amount of drug, number of drug-reactive T cells and their migration to the tissue, and affinity of the drug-specific TCR for the peptide/hapten/drug complexes. Whether a desensitization in delayed DHR is possible is still unclear.

The immune reactions leading to IgE-related symptoms differ: importantly, it involves the *change of effector cells* (from T-B cell axis to IgE/mast cells): The drug-specific T and B cells expand without causing symptoms. After 5-6 days, secreted IgE sensitize mast cells, however, do *not* react to the continued drug application (Figure 2). Sensitization seems to go along with a transient and selective *unresponsiveness of mast cells* to the drug given. Mast cell degranulation and corresponding symptoms (urticaria/anaphylaxis) appear actually to a normal drug dose *after a drug-free* (or at least strongly reduced) *interval*. This mast cell "unresponsiveness" to normal drug doses during sensitization is drug-specific. It seems to be a normal process in IgE/mast cell reactions to proteins and is probably the basis for so-called "desensitization," which is practiced to induce transient unresponsiveness in acute DHR.[27] It is also well documented in bee venom allergic bee keepers, which react in spring to the first bee stings,[28] but tolerate the stings soon again without symptoms in spite of the presence of specific IgE. Experience with desensitization procedures suggests that a sudden high drug concentration may also overcome this transient mast cells unresponsiveness.

Hapten formation and generation of hapten-carrier complexes occur during each penicillin therapy. Why some persons develop a B-, others mainly a T-cell reaction to the drug and why the vast majority do not react[29] is still unclear. It is also a puzzle why—if an immune response develops—the clinical symptoms are based on IgE- or T-cell-mediated reactions. Probably, the amount and type of modified antigen play a role: if hapten modification occurs mainly on soluble proteins, then an IgG/IgE B-cell response may dominate. On the other hand, a modification of cell-bound proteins may give rise to a T-cell reaction, which always involves some cytotoxic reaction as well (see open questions).

2.1.4 | Dissociation between covalent and noncovalent drug-protein binding in IgE initiation and effector phase

While it is well accepted that the *induction* of the IgE immune response to a hapten requires a covalent link to a protein (hapten-carrier

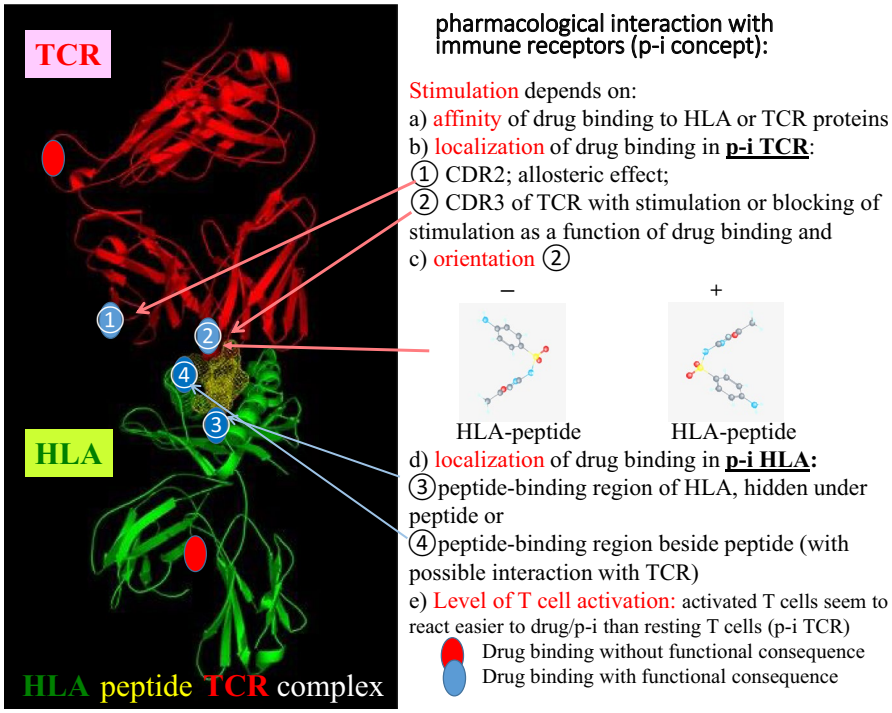

FIGURE 3 Drug binding to TCR and/or HLA (p-i concept). Drugs can bind directly to TCR and HLA molecules. Some of this interaction may result in functional consequences (blue ●, numbered), some not (red ●). The consequences depend on *affinity* of drug binding, *location* of drug binding, *orientation* of drug binding, ability to *transmit signals* when this site is triggered (only TCR), *blocking* of signalling and elicitation of *allosteric* effects. The consequences are complex and all are T-cell-mediated. For *full* activation of T cells, an additional interaction of the TCR with peptide/HLA protein is required, but some signals are transmitted even without peptide/HLA interaction. Details see text and ref[7,33,34]

complex), it is less clear whether a covalent bond between the drug/hapten and the carrier/protein is also required for *cross-linking* already formed, drug-specific IgE on Fc-IgE-RI on mast cells or basophils. Various data would support that *noncovalent* links between drug and carrier protein are sufficient for the effector phase:

- Most data on the hapten-protein model derive from animal experiments, where the covalently bound hapten-protein conjugates were used for both sensitization and effector phase of allergic reactions. However, in drug-induced anaphylactic reactions in humans, the eliciting drug/hapten-protein conjugate may not be identical to the conjugate causing symptoms in the re-exposure phase (degranulation).
- One should bear in mind that the noncovalent association of the drug occurs to the same site within a larger protein where the subsequent covalent association occurs. It is faster and may or may not proceed to a covalent bond. Indeed, beta-lactams like benzylpenicillin or amoxicillin bind to lysin groups at pH 10.2, and only poorly at physiological pH 7.4, and it takes hours to form covalent links. The often quasi-immediate (minutes) reactivity in beta-lactam allergy is hard to explain by this slow formation of a covalent bond.
- Moreover, a drug bound either via covalent or via noncovalent bonds may look the same for a drug-specific IgE. Some noncovalent bonds of the drug to a carrier protein (eg, albumin) may be rather affine and the complex may be sufficiently stable to cross-link drug-specific IgE on Fc-IgE-RI.

This widely neglected distinction between covalently and noncovalently bound drugs to (same) proteins and reactivity of drug-specific IgE with both covalently and noncovalently bound drug may be an important cause for acute, often unexpected IgE-mediated DHR: it is more than just intellectual gadget. It would explain the following:

1. Immediate mast cell degranulation in skin tests or immediate basophil degranulation in vitro with drugs, which are not (yet) able to form covalent hapten-carrier complexes or which require metabolism to become ready for covalent links to protein carriers (eg, SMX).These drugs are, however, well able to bind to proteins via noncovalent bonds;
2. The extremely fast reactions (anaphylaxis, often <1 minute) to some i.v. given drugs, which occur before the drug acquires hapten characteristics or is able to bind covalently; and
3. The anaphylaxis to some drugs at *first* exposure: the IgE-mediated sensitization might have occurred to a drug/chemical type A acting as hapten. The acute anaphylaxis occurs due to the presence of IgE, which cross-reacts with drug A*, which has no or low capacity to bind covalently to proteins, but as noncovalent [A*-protein] complex is still able to cross-link IgE. Such a reaction may be facilitated by the sudden high concentrations of the drug A* following i.v. bolus injections (see open questions, Box 1).

In conclusion, a drug with hapten-like features can elicit both T- and B-cell reactions simultaneously. Examples for haptens are beta-lactam antibiotics or the nitroso-metabolite of sulphamethoxazole (SMX-NO) (Table 1). This immune response 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 able to activate inflammatory cells.[14] They appear rapidly, if the person is already sensitized and has developed IgE (in minutes) or has a high frequency of reactive T cells (in 1-3/4 days). In T-cell reactions, the sensitization goes directly over into the effector phase with cytotoxic

TABLE 2 p-i concept: pharmacology leads to immune stimulation

p-i concept	
Pharmacology → *Immunology*	
Ligand protein binding • Drug-protein interaction with sufficient affinity • Orientation of drug in p-i TCR • Stimulation of signalling in T cells (p-i TCR) • Blocking of stimulation (p-i TCR) • Allosteric effect on TCR and increased binding of the TCR to HLA/peptide	T-cell activation • Direct drug-specific activation (TCR-CDR3) • Alloimmune-like stimulation of memory *and* naive T cells • Bypassing control mechanism of immune stimulation as no second signal is required (like in direct allo-recognition) • Autoimmune stimulation (altered peptide) • Oligo- and monoclonal T-cell expansion • Costimulation/preactivation of reactive T cells to enable reactivity to low intensity signal

and cytokine-secreting T cells orchestrating the inflammatory cells (T cells, PMN, eosinophils). In IgE reactions, the sensitization is silent and is accompanied by a transient mast cell unresponsiveness to the drug, when given initially. Symptoms appear after a *drug-free interval*, due to the activation and degranulation of mast cells/basophils. While for the induction of an IgE response to a drug, the drug must have been bound by covalent links to a protein, a noncovalent link seems often to be sufficient to cross-link IgE-Fc-IgE-RI on mast cell or basophils.

2.2 | The pharmacological interaction with immune receptors: p-i concept

Detailed functional analysis of the drug stimulation of drug-specific T-cell clones and TCR transfected cell lines lead to the generation of the p-i concept (*pharmacological interaction with immune receptors* concept).[7,30-32] It postulates that some drugs bind via *noncovalent* bonds (van der Waals forces, hydrogen bonds and electrostatic interactions) directly to immune receptor proteins (HLA and TCR) and that this interaction leads to a *T-cell-mediated reaction*, which has features of hypersensitivity, and/or alloimmune and/or autoimmune reactions. One can differentiate binding of drug to HLA (*p-i HLA*) or binding to TCR (*p-i TCR*).[7] Some drugs can interact with both HLA and TCR.

The p-i concept actually *bridges pharmacology with immunology*. The pharmacological part is due to a *typical off-target effect* of the drug on immune receptors. For example, a drug designed and developed to block an ion channel protein happens to bind to a certain HLA protein or a certain TCR as well. This "off-target" drug-immune receptor interaction follows the normal rules of pharmacological ligand/protein interactions, namely a certain dose dependence and, in case the off-target receptor is identified, it may be predictable. The functional consequence of this drug-immune receptor interaction is dependent on the *location* of the drug binding site on the immune receptor protein, on the *affinity* of drug binding, on the *orientation* of the drug binding and on the state of T-cell activation (Figure 3).[7,33-37]

The immunological part of this p-i concept results in a rather *unorthodox T-cell stimulation*. It can involve both CD4+ and/or CD8+ cells and occasionally even double-positive, CD4+/CD8+ T cells.[38,39] Importantly, according to the alloimmune model for DHR, no second signal is needed to develop a strong T-cell reaction.[40,41] As discussed, the origin of danger/second signals in DHR is an open issue.[7,40]

The clinical consequence of this interference with the HLA-peptide-TCR axis is complex (Table 2). It may depend whether the drug stimulated TCR interact with the *drug* (eg, in SMX, CBZ), with the *peptide/HLA* (in altered peptide [abacavir],[33-35]) or in the allosteric effect model induced by SMX[34] or with an allo-*HLA/peptide* complex (as in the alloimmune model[7,40]), which implies a rather uncontrolled T-cell activation. Like in hapten-dependent reactions, in vitro (cytokine, cytotoxic and proliferative responses) and in vivo tests (patch/i.d.) with the drug can be positive in p-i stimulations—even if the drug is not directly recognized by T cells (eg, abacavir model).

A further enhancing factor for clinical manifestations of p-i seems to be the *state of activation of the reactive T cells*: some rather weak drug stimulations by p-i may result in clinical manifestations only if the cells are pre-activated. The conditions for this assumed need for costimulation[7] have not yet been investigated (see open questions).

In conclusion, the p-i reactions (drug binding to TCR/HLA) do also start with an off-target activity of the drug. But the subsequent events of p-i stimulations are complex immune reactions and go far beyond a normal off-target activity of a drug: In contrast to "normal" off-target reactions where the effect is restricted to the affected molecule and/or cell (eg, modification of HLA molecules by a drug would lead to a reaction of the HLA-expressing APC), the off-target effect of drugs on the immune receptors TCR and HLA does *always* result in rather unorthodox T-cell reaction *which has* features of hypersensitivity and/or alloimmunity and/or autoimmunity. (Table 2)

2.2.1 | p-i HLA

In p-i HLA, the drug binds directly by noncovalent means to the HLA molecule. The functional consequence of this binding is influenced by various factors:

- Does the binding of the drug to the HLA molecule take place inside the ER or on the cell surface (or both)?
- To which region of the HLA molecule does the drug bind and is the drug still able to interact with the reactive T cell/TCR as well?
- Does the drug binding to HLA-peptide complex transform the self-HLA to an allo-HLA, which make it stimulatory like an allo-allele? The direct allo-stimulation represents an (unorthodox) T-cell stimulation, which does not need costimulation.

It is possible that various possibilities occur together. Figure 3 summarizes conditions of drug binding to HLA and TCR (p-i HLA and p-i TCR) needed for functional consequences (Table 2) (see also ref [7]).

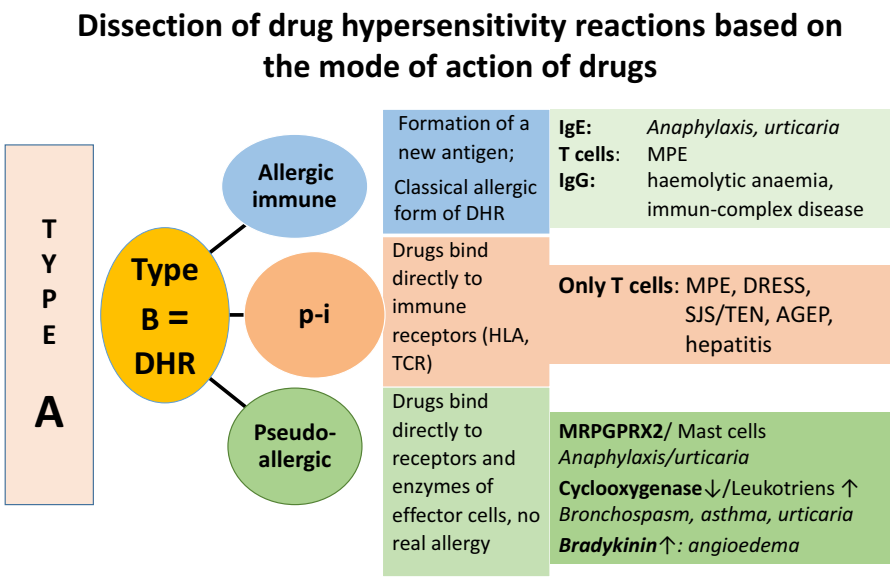

FIGURE 4 Classification of type B reactions (modified from 10): Adverse drug reaction are sub-classified as type A and B reactions.[1,2] Type B reactions correspond to DHR, which can be classified as *allergic/immune, p-i and pseudo-allergic reactions*.[10] Allergic/immune reactions are due to antigen formation and can lead to all types of Gell and Coombs-mediated immune reactions; p-i stimulations lead exclusively to T-cell reactions, which are unorthodox and sometimes severe. So-called pseudo-allergic reactions are heterogeneous and due to stimulation of inflammatory mechanism. They include MRGPRX2 stimulation of mast cells, inhibition of cyclooxygenase due to NSAID and of bradykinin metabolism in ACE therapy. *details see text

Where does the drug bind to HLA?

The best studied model for this drug-HLA interaction is the antiviral drug abacavir: Two possibilities of abacavir loading onto HLA are well documented: abacavir may be loaded with rather high affinity to the F pocket of HLA-B*57:01 in the *endoplasmic reticulum* (ER).[35-37] This binding of abacavir to the F pocket of the HLA-B*57:01 make the pocket smaller and hampers the binding of peptides normally presented. In vitro it occurs with rather low abacavir concentrations (in vitro 1-10 microg/mL) and takes hours until an (HLA-drug-peptide) complex, which may contain other peptides than usual, is presented on the surface.[25] Mainly peptides with a smaller amino acid at F pocket position (eg, valin instead of tryptophan) are chosen for presentation. This phenomenon is termed *altered peptide repertoire* and may lead to autoimmunity.[35-37] One criticism for this actually beautiful and well-documented model is that the "costimulatory" signal for inducing an autoimmune response has not been deciphered, and it also has been shown only for abacavir.

Abacavir can also bind to B*57:01 on the *cell surface*: this is shown by the immediate reactivity (Ca++ influx < 10 minutes) of abacavir reactive T-cell clones and TCR transfectants, when abacavir is added to a mixture of B*57:01+ antigen-presenting cells and specific T-cell clones or TCR transfectants.[25,40] This surface presentation requires higher drug concentrations than in intracellular loading—probably because the surface HLA molecules are already occupied by peptides and the access to the F pocket in the HLA peptide-binding groove is hampered.[25] Such an outside loading leads to a Ca++ influx of those T cells which bear a rather affine TCR for the altered (MHC-drug-peptide) complex. A similar fast reactivity and presentation was also seen in flucloxacillin and allopurinol (oxypurinol) hypersensitivity, where no intracellular loading could be observed.[26,42]

In B*15:02-linked carbamazepine (CBZ)-induced T-cell reactions, the drug is so positioned in the HLA-B*15:02 peptide-binding groove that an additional interaction with the TCR can take place.[43,44] This ability of CBZ to interact with public or private region of the TCR may explain why oligoclonal or even monoclonal T-cell reactions are observed in some of the severe clinical manifestations (SJS/TEN). An interaction with both, HLA and TCR, may also occur in other forms of p-i reactions (eg, against radiocontrast media).[45]

Alloreactivity

Already early studies on T-cell reactions to drugs via the p-i mechanism revealed a frequent alloreactivity of drug-reactive T cells: An analysis of >100 lidocaine and SMX reactive TCC showed that 30% react to self-HLA plus drug or allo-alleles directly (without drug).[46,47] The implication of this "cross-reactivity" of drug-reactive T cells became clear as Adam J et al[40] described that ca 5% of >100 abacavir-induced T-cell clones from three B*57:01+ blood donors did react to (B*57:01+ abacavir + peptide) and (B*58:01+ peptide). This cross-reactivity is due to a structural similarity between (B*57:01+ abacavir + peptide) and (B*58:01+ peptide) without drug, which differ only by 8 amino acids and can present the same peptides; importantly, this finding implies *more than just simple cross-reactivity*. In the same study,[40] it was found that abacavir reactive T cells, which were generated from drug naïve donors, could be induced in the absence of dendritic cells—no second signal was required. Both naïve *and* memory T cells were activated, and the reaction was polyclonal, cytotoxic and even polyspecific (reacting with many peptides): Such

Box 2 Milestone findings in DHR[+]

Year	Initial description/finding	Reference[+]
1902	Aspirin intolerance	72
1904	Hapten mechanism (serum)	4
1905	Serum sickness	73
1922	Stevens-Johnson syndrome (SJS)	74
1935	Hapten mechanism (delayed type hypersensitivity)	5
1938, 1950	severe drug hypersensitivity (DHS, later named DRESS/DiHS)	75, 76
1956	Lyell syndrome (later named TEN)	77
1949–2018	anaphylaxis to penicillins	***
1965–1969:	Hapten feature of penicillins, skin testing	78, 79,
1966	discovery of IgE	80, 81
1967	Classification of allergic reactions (Gell & Coombs)	12
1975	Protaglandin-synthesis and aspirin intolerance	82
1977	ADR-classification	1, 2
1980	AGEP	83
1983	fine specificity of IgE to drugs	84
1985–2018	fundamental work on haptens (TNP, penicillins) & Nickel, second signals (in vitro)	*group of Weltzien HU* & *S Martin et al (Freiburg /Germany*
1992–2018	Clinic, definition, genetic and immune-mechanism of SCAR (SJS/TEN; DRESS/DiHS; AGEP)	*group of Roujeau JC et al (Paris, France); Euro-SCAR and RegiSCAR; group of Chung WH/Hung SI, Taiwan*
1995–2018	T cell reactivity to drugs in DHR, subclassification of Type IV reactions	*groups of Pichler WJ, Bern, Switzerland & of Naisbitt D, Liverpool/GB*
1999–2018	basophil activation tests with drugs	*** *group of Ebo D, et al, Antwerp, Belgium*
1997–2018	establishment & development of p-i concept	*group of Pichler WJ in Bern, Switzerland group of Chung WH/Hung SI, Taiwan*
2002–2018	HLA and DHR	48-53
2000–2018	biologicals: new, expected & unexpected ADR to biologicals	***
2011	crystallographic data of HLA-drug binding & altered peptide concept	35-37
2014	MRGPRX2: mast cell receptor able to bind drugs	8
2015–2018	Checkpoint inhibitors and adverse side effects	***

[+] list is incomplete; *** various groups contributed over a longer time period.

unorthodox reactions are known to occur in direct alloreactivity[7,41] and suggest that the complex [B*57:01-abacavir-peptide] is stimulatory like an allo-allele.

Since allo-stimulations were also observed in lidocaine, sulphamethoxazole, chinolone, iohexol reactive T-cell clones,[46,47] this allo-like stimulation is not unique for abacavir and seems to take place in various drug-induced p-i stimulations, including some reactions due to p-i TCR (mechanism unclear). The *alloimmune concept of p-i DHR* implies that the drug binding alters the HLA-peptide complex and thereby alters the self-HLA, to which the own immune system reacts ([40], reviewed in [7]). Severe p-i stimulations and resulting DHR-like SJS/TEN have indeed features of a gvhd.[7,10,41] This concept of allo-like and not well-controlled stimulation in severe DHR would explain how a small, "innocuous" drug is able to elicit a sometimes deadly immune reaction without classical danger signals.

HLA restriction of DHR

In the p-i concept, the drug binds directly to HLA molecules, which represents one of the most polymorphic protein systems of humans.

The polymorphism of the HLA system occurs in the population with >14.000 HLA alleles (www.allelefrequencies.net), while the individual itself carries only ca. 14->20 HLA alleles. This polymorphism in the population but selective expression in the individual explains also one of the key finding of DHR research of the last 15 years, namely the link of some severe DHR to the presence of a certain HLA allele: only the involved HLA allele, for example B*57:01 is able to bind abacavir with high affinity (ca 5% of Caucasians carry this allele), the other and even the similar HLA-B*58:01 do not bind abacavir.[48] Similarly, carbamazepine (CBZ) binds to the allele B*15:02, which is rather common in Southeast Asia (ca 13%-15%), and to A*31:01 in Caucasians.[49,50] Other relevant examples are B*57:01 and flucloxacillin, allopurinol/oxypurinol and B*58:01, and dapsone and B*13:01 ([1], reviewed in [53]). By HLA typing before abacavir or CBZ therapy starts and excluding the carriers of the risk allele, the incidence of SCAR could be dramatically reduced.[54,55] An ADR, assumed to be nonpredictable, became predictable.

2.2.2 | p-i TCR

The primary off-target activity of drugs leading to p-i reactions does also include the TCR, which is present in a very high variability (ca 10^{11}TCR/individual) and thus offers endless opportunities for binding sites of a drug. There are only very few studies addressing this topic.[33,34,43-47,56,57]

The best studied example of p-i TCR is the sulphamethoxazole (SMX)-specific T-cell response, which was investigated in great detail using T-cell clones and TCR transfected cell lines.[33,34,56,57] It was found that SMX binds directly to the TCR and that this drug-TCR interaction results in different ways of T-cell activation. Other drugs like lidocaine and chinolones may also bind primarily to the TCR, followed by interactions with HLA peptide.[56,57]

Direct drug recognition; stimulatory and blocking actions

The SMX reactive T-cell clone "1.3" produced cytokines and proliferated if exposed to SMX and autologous APC.[33] But 11 other sulphanilamides (sulfapyridine, sulfadoxine, etc.) failed to elicit a reaction. Combining in vitro stimulation assays with 12 sulphanilamides and computer modelling revealed that the drug SMX binds directly into a rather large loop in the CDR3 region of the TCRVα (TCR "1.3"), which usually interacts with the peptide-HLA complex.[22] Binding of SMX resulted in TCR-triggered cytokine secretion, proliferation upon interaction with HLA peptides presented by the antigen-presenting cell (APC). Interestingly, 11/12 sulphanilamide compounds did not stimulate. They were, however, able to *block* the stimulation by SMX itself. Modelling revealed that the nonstimulatory sulphanilamides had their NH2 ends directed towards the TCR, and that only the stimulatory SMX can bind to the CDR3/Vα in an inverse *orientation*, with its NH2 group pointing to the peptide-binding groove (Figure 3). The SMX reactive TCC 1.3 did also react with the hapten SMX-NO, which is covalently binding via the amide ending to the HLA-presented peptide. This explains the rare but well-documented cross-reactivity between p-i (SMX) and hapten (SMX-NO) reactions.[7,33,47]

Allosteric configuration

A drug binding to TCR can enhance the interaction of the TCR with fitting peptides/HLA: This is shown for the SMX reactive TCC ("H13"), which expressed CDR2-Vβ20.[34] The drug (SMX and 5 other sulphanilamides) causes proliferation in the presence of APC. Six of 12 other sulphanilamides could not bind and did not cause proliferation. Molecular modelling revealed that only SMX and the 5 stimulatory sulphanilamides bound to the CDR2-Vβ20, the other 6 sulphanilamides did not bind. The binding of SMX altered the configuration of the TCR-Vβ, and the altered TCR shows a 7-fold more affine interaction with the HLA-peptide complex (in the model, the peptide stemmed from laminin presented by the autologous HLA-DR-B1*10:01).[34]

Costimulation

The binding site for SMX on "H13" was in the public region of TCR-vβ CDR2, which is present on ca. 3% of circulating T cells. Actually, all persons should have the potential to react to SMX, but an adverse drug effect is observed only in some exposed. Why this difference? One of many hypotheses is that SMX-induced stimulations and clinical manifestations occur only, if the drug-reactive T cells are already pre-activated by, for example, viral infections and thus have a lower activation threshold than resting T cells. Without this infection and pre-activation of T cells, the drug binding to TCR may not result in activation and symptoms. Indeed, the experience with early AIDS therapy and use of SMX to reduce nosocomial infections showed that the incidence of SMX-related DHR increased from ca. 3% to ca. 50% during active HIV infection.[58]

2.3 | Pseudo-allergy (non-immune-mediated drug hypersensitivity)

There is a third possibility to cause DHR, namely that drugs directly activate effector mechanism of inflammation without the involvement of adaptive immune mechanism. These are a group of quite heterogeneous forms of ADR, which can be summarized as *nonallergic drug hypersensitivity*, *drug intolerance* or *pseudo-allergy*, as the clinical symptoms imitate symptoms of allergy (urticaria, anaphylaxis, bronchoconstriction, angioedema).[8,9,59,60] The terminology for these reactions is controversial, as "nonallergic hypersensitivities" would also include the T-cell reactions via p-i, "drug intolerance" is too general and "pseudo-allergy" implies a "fake" reaction, which in reality can be very real and dangerous. Optimal would be to call these DHR by their eliciting drug class (eg, NSAID intolerance or NSAID-exacerbated respiratory disease [N-ERD] or NSAID-exacerbated cutaneous disease [N-ECD]) or Mas-receptor (MRGPRX2)-mediated mast cell degranulation or bradykinin-related drug-induced angioedema.

The so-called "pseudo-allergic" reactions (which is at least a short name) are actually type A reactions involving inflammation. They are based on a pharmacological off-target activity of certain drugs on receptors on effector cells of inflammation (MRGPRX2)

[8] or blocking of enzymes like cyclooxygenase[9,61] (Figure 4): This can result in an enhanced level of inflammatory mediators (higher leukotrienes upon NSAID therapy) or longer persistence of bradykinin by blocking its peptide degradation in therapy with angiotensin-converting enzyme inhibitors (ACE) and eventually dipeptidyl peptidase-4 Inhibitors.[62,63] No specific immune response occurs. Pseudo-allergic reactions are elicited by a limited number of drugs (Table 1), and they are clearly dose-dependent. Indeed, they usually require substantially higher doses to elicit clinical symptoms than IgE-mediated 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-allergic reactions occur in a minority of patients only, although the mechanism is linked to a general feature of the drug/drug class. The distinction between individuals with or without reaction in NSAID intolerance or MRGPRX2G triggered mast cell activation and angioedema after ACE is not yet deciphered, but is intensively studied and some cofactors or polymorphism of the, for example MRGPRX2G receptor has already been described ([63,64]; see also Box 1 for research perspectives). In NSAID-exacerbated respiratory diseases, some link to interleukin-4 promoter polymorphism and N-acetyl transferase-2 polymorphism have been described in Korean patients.[65,66]

3 | DISCUSSION/COMMENTARY

The area of drug hypersensitivity is a special area of medicine: it deals with man-made, iatrogenic diseases, which overall occur often, but for a single drug are still rare (exception are DHR to beta-lactams). Animal models were not available, and if hypersensitivity reactions occurred during the development of a drug in preclinical research of pharmaceutical companies, it was not pursued. To investigate milder or severe reactions in affected patients required a lot of logistics, ethical approval for an unplanned event and collaboration of patients. DHR was not seen as an attractive area of research.

In spite of these hurdles, some academic groups (with some occasional support by the pharmaceutical industry, who realized how expensive the lacking knowledge on DHR can be) investigated the immunology of these diseases with the available human material and could contribute to a better understanding of the underlying pathomechanism—which was more complex than anticipated (Box 2).

Soon some "dogma" of type B reactions were found to be wrong.[10,67] The generation of drug-specific T-cell lines and T-cell clones and their functional analysis led to the p-i concept, the study of risk factors and genetic predisposition made some of these DHR to preventable diseases.[68] Understanding the DHR also allowed to improve the diagnosis of DHR, which helped to pinpoint the relevant drug, during a time when polytherapy is the rule and not the exception. Another big step forward was the development of drug-specific T-cell lines from healthy individuals in vitro.[25,26,40,42,69] This made research more independent on patients and make the area open to research in academia and pharmaceutical companies. Some of the important older and newer progresses are summarized in Box 2.

One of the purposes of this review is to highlight the many open questions which have arisen due to new insights of DHR pathomechanism (Box 1).

An important area of DHR research will be *tolerance mechanism*. Exposure to beta-lactam leads often to hapten-carrier formation, but some persons develop no immune reaction, others a harmless IgG response, others T cells with or without symptoms (exanthems) and some even a potentially dangerous IgE response.[29,70] There is normal tolerance mechanism present—and we should know its rules.

In the abacavir model, all B*57:01+ individuals can develop an immune response to abacavir in vitro, but the development of a clinical DHR occurs in only ca. 50%.[54,71] The clinical manifestation in risk groups is even lower with other drugs (in flucloxacillin-induced hepatitis only ca 0.01%).[52] The "missing link" between risk and clinical manifestation is still not clarified. This is a big and still unresolved challenge for risk assessment.

It is high time to implement the p-i concept as well as an evaluation of drug binding to MRGPRX2G into *preclinical risk assessment* strategies. But the p-i concept is not just relevant for understanding DHR and for risk assessments of drugs. The finding that drugs can directly bind and stimulate T cells without antigen formation, that drugs can block activation and elicit autoimmune and allo-reactions without second/danger signals opens a new area of immunology. If a drug can elicit a strong, sometimes even deadly immune reaction (SJS, TEN, DRESS), the control of such a drug-induced immune response has a great potential, if the specificity of the immune reaction can be controlled. "Immunology of small molecules" will become a new area of medicine, far beyond allergy. The good aspect of DHR is that one can learn from them.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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How to cite this article: Pichler WJ. Immune pathomechanism and classification of drug hypersensitivity. *Allergy*. 2019;74:1457-1471. https://doi.org/10.1111/all.13765