



Role of T cells in non-immediate drug allergy reactions

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Purpose of review

Nonimmediate drug hypersensitivity reactions (NI-DHR) constitute the most complex group of drug allergy, with many drugs involved. Both parent drugs and their reactive metabolites can be implicated. Although with some drugs the number of metabolites is limited, with others it is quite extensive and many still remain to be identified. The diagnostic approaches are insufficient for the diagnosis and realistic approaches that reproduce the pathological response are lacking.

Recent findings

A wider view has now been considered, with the inclusion of several mechanisms that may contribute to drug hypersensitivity reactions (DHR): the classical hapten hypothesis, the danger signal and the pharmacological interaction. Monitoring the acute response provides relevant information about the mechanisms involved, with the identification of a large number of genes that can be over-expressed or under-expressed in the acute phase of the response. Assessment of risk of developing reactions can be verified by HLA associations.

Summary

Further knowledge of these NI-DHR, including molecular genetics and transcriptomic analysis, has enabled a better understanding and management of these reactions.

Keywords

allergy, drug, nonimmediate reactions, T cells

INTRODUCTION

Drug hypersensitivity reactions (DHR) are a problem of great concern contributing to significant morbidity and leading to fatal reactions [1]. Two major groups of mechanisms exist: immune-mediated, with the recognition of drugs by IgE or T cells, and those with mediators released by nonspecific immunological mechanisms; these are known as allergic and nonallergic hypersensitivity, respectively [2].

DHRs are increasing, though with variations in their frequency, clinical entities and drugs involved [3]. For example, NSAIDs can lead to a wide range of T-cell mediated reactions including the most severe [4].

The first drugs involved in allergic reactions were betalactams, contributing to IgE and T-cell reactions. With the improved production of betalactams, the number has decreased though they still remain one of the leading causes [3]. In many countries, the classical benzyl penicillin major and minor determinants (BPO and MDM) have given way to side-chain-specific involving amoxicillin or cephalosporins [5]. T-cell reactions are mainly attributed to aminopenicillins and amino-cephalosporins [6].

CLASSIFICATION OF T-CELL DRUG REACTIONS AND MAIN DRUGS INVOLVED

Nonimmediate DHR (NI-DHR) are diverse, ranging from mild-to-severe reactions that can be life-threatening. Although all of them share a common effector mechanism that implies T-cell activation, the way in which T cells induce the response differs. Table 1 shows some of the clinical entities including mild reactions, such as maculopapular exanthema (MPE), nonimmediate urticaria (NI-U) or fixed drug eruption (FDE), and severe reactions like acute

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KEY POINTS

- NI-DHR constitute a heterogeneous group of entities that involve mainly the skin, although systemic involvement or organ-specific reactions may occur.
- Drugs can interact with endogenous proteins by several mechanisms, implying both covalent and noncovalent binding.
- Most drugs, with the exception of betalactams, require a metabolic transformation to induce reactive metabolites that are recognized by T cells.
- The degree of cross-reactivity between parent drugs and their metabolites may vary, being extensive in some cases but in others quite stereo-selective.
- Skin testing and in-vitro testing lacks optimal sensitivity, and very often a DPT is needed, especially in mild reactions, to establish the diagnosis and assess the cross-reactivity.

generalized exanthematic pustulosis (AGEP), DRESS and bullous reactions [Stevens–Johnson syndrome and Toxic Epidermal Necrolysis (SJS)/TEN] (4). In addition to the skin, reactions can affect the liver, kidney, lung or other organs (Table 1) [7,8].

Within T-cell reactions, there are four major categories [7] now been extended to a fifth [9^{••}]. These are shown in Table 2 and reviewed in more detail in references [9^{••}] and [10].

Regarding drug involvements, culprit drugs in IgE-mediated reactions are limited [6], but in NI-DHR any can induce a nonimmediate reaction (NIR) [10]. Not only the parent drug but also the metabolites are potential allergens in the induction of NIR. In many drugs, there is a culprit metabolite but in others the metabolites vary extensively as shown below. Furthermore, some new metabolites may yet be identified. Table 3 shows some classical examples of drug/drug metabolites eliciting NI-DHR.

DRUG METABOLITES

Betalactams, in addition to immediate reactions, are also involved in NIR where some clinical entities

Table 1. Clinical entities and mechanisms involved in nonimmediate drug hypersensitivity reactions

Mechanism involved	Clinical entities
T cells	Maculopapular exanthema (MPE) Contact dermatitis (CD) Photosensitivity contact dermatitis Isolated mucosal involvement Bullous/or desquamative exanthema Drug reaction with eosinophilia and systemic symptoms (DRESS) Toxic epidermal necrolysis (TEN) Acute generalized exanthematic pustulosis (AGEP) Fixed drug eruption (FDE) Nonimmediate urticaria (NI-U) Serum sickness-like syndrome (SSLS)/accelerated urticaria Nicolau syndrome
T cells/ toxicological/both	Bile duct syndrome Hepatitis Meningitis Pneumonitis Nephritis Pancreatitis Other organ-specific clinical manifestations
Unknown	Vasculitis

may cause confusion-like accelerated urticaria [11]. In immediate reactions, the specificity of the antibody has been well defined, with a good correlation with clinical entities [5,12,13], but in NIR, the final structure recognized is more complex to define [14].

All betalactams bind spontaneously to proteins by nucleophilic attack of their amino groups. Amoxicillin forms penicilloyl adducts with lysine residues on human serum albumin (HSA) [15]. Other betalactams like flucloxacillin, benzyl penicillin, aztreonam and piperacillin bind to similar lysine residues [16]. This also occurs with clavulanic acid but the metabolites generated are quite different, and do not cross-react with classical betalactam structures [15]. However, whether differential binding occurs

Table 2. Immunological classification of nonimmediate drug hypersensitivity reactions

Classification	Cell type	Type of immune response	Pathologic characteristics
Type Iva	T cells	Th1 (IFN- γ)	Monocyte activation
Type IVb	T cells	Th2 (IL-4 and IL5)	Eosinophilic inflammation
Type IVc	T cells	CTL (perforin and granzyme B)	CD4 or CD8-mediated killing of cells
Type IVd	T cells	T cells (IL-8)	Neutrophil activation
Type IVe	T cells	Th2 cells	CD4 or CD8 cell activation

Table 3. Examples of drugs and/or drug metabolites involved in nonimmediate drug hypersensitivity reactions

Drug	Metabolites	References
Betalactamics	Not relevant with most of them	[5]
Fluorquinolones	Desetilenciprofloxacin, formilciprofloxacin, oxociprofloxacin, sulfociprofloxacin	[20,21,45]
Sulfonamides	sulfamethoxazole, sulfamethoxazole hydroxylamine, nitroso-sulfamethoxazole and other arylamines	[22,24]
Abacavir (ABC)	ABC-glucuronide, ABC-carboxylate	[25,26]
Carbamazepine	Carbamazepine-10,11-epoxide	[29]
Allopurinol	Oxypurinol	[27]
Hydantoin	Parahydroxyphenyl, fosphenytoin	[28]
Phenobarbital	P-hydroxyphenobarbital	[28]
Lamotrigine	lamotrigine-2-N-glucuronide, lamotrigine-2-N-methyl, lamotrigine-2-N-oxide	[31]
Corticoids	Prednisolone, 6- α -metilprednisolone-17-propionate, 5- α -THF, 5- β -THF, 21-OH-deflazacort	[36–42]
NSAIDs (ketoprofen, piroxicam)	2-(3-Benzoylphenyl)-propanoic acid, 2-[3-(3-hydroxybenzoyl)phenyl]-propanoic acid, 2-[3-(4-hydroxybenzoyl)phenyl]-propanoic acid, 2-[3-(hydroxy (phenyl)methyl)phenyl]-propanoic acid, piroxicam-hydroxymethylated, piroxicam-cyclodehydrated, piroxicam-carboxybenzothiazine	[45]

and if this influences the specificity of the adducts is not well known. It has been shown that the hapten-specific IgG antibodies found in piperacillin hypersensitive patients do not bind to other betalactam protein conjugates [16]. Both hapten and carrier contribute to the formation of the antigen [13,17]. In the case of T-cell mediated responses, the betalactam is recognized after the formation of a betalactam–peptide complex formed after the processing of the adduct by the antigen-presenting cells (APC). Other possibilities will be discussed below. Betalactams haptenize extracellular and intracellular proteins. One study has found heat shock protein 70 and enolase, that can be haptenized by amoxicillin [18]. These adducts can be incorporated into target cells transported by exosomes [17].

Quinolones, particularly fluorquinolones are the second group of drugs involved in DHR in many countries [3,19] inducing IgE-cell and T-cell reactions [20]. Fluorquinolones have one pyridone and another aromatic ring. The structural differences within this group are derived from the number and position of nitrogen and fluoride atoms and the side chains. All types of reactions described in Table 1, including photo-allergy and phototoxicity, can be induced with differences depending on the fluorquinolones [19,20].

Sulfonamides, the first drugs involved in DHR in the past, continue eliciting reactions. The most common being MPE, although urticaria may occur.

NIR to sulphonamides are mainly caused by metabolites particularly with nitro-sulphomethoxazol [21]. About 45–70% of sulfonamides are acetylated in the liver by *N*-acetyltransferase and approximately 15% glucuronidated. In addition, 10% is hydroxylated by the cytochrome CYP2C9 to sulfamethoxazole hydroxylamine. The metabolite nitroso-sulfamethoxazole (SMX-NO) is a model for T-cell activation [22]. For more details, about the generation of metabolites and the position in which each reaction occurs we recommend references cited [21,23].

Abacavir elicits also NI-DHR, particularly in persons with HIV infection [24]. The metabolism constitutes Phase II glucuronidation mediated by uridine diphosphate glucanosyltransferase, which yields an inactive glucuronide metabolite (abacavir-glucuronide), and Phase I oxidation that yields a carboxylate (abacavir-carboxylate) [25].

Oxypurinol is the main metabolite of allopurinol after transformation by xanthine oxidase [26]. Excess production of this drug is assumed to lead to tissue damage, evoking an immunological response with the development of antibodies against tissue components.

Anticonvulsants were also amongst the first drugs eliciting DHR, particularly NI-DHR and idiosyncratic toxic reactions [27]. Carbamazepine can trigger NI-DHR by the original drug or by its metabolite, carbamazepine-10,11-epoxide [28], although other metabolites can also be involved. Structure-

activity studies using 29-carbamazepine metabolite specific T-cell clones revealed four patterns of drug recognition, which could be explained by the generation of preferred three-dimensional structural conformations. T cells stimulated by carbamazepine (metabolites) bound directly to the MHC in the absence of processing. Some patients with a history of NI-DHR to carbamazepine have T cells that cross-react with oxcarbazepine [29].

Hydantoins contribute to NI-DHR by the generation of bioactive metabolites that are recognized by T cells [30]. Regarding phenytoin, 95% of the drug is metabolized by CYP2C9 and to a lesser extent by CYP2C19, with the principal metabolite being a para-hydroxyphenyl compound. Phenytoin administered by intravenous route generates fosphenytoin, a water-soluble drug, by phosphatase enzymes [27].

Phenobarbital is metabolized mainly by CYP2C9, and lesser by CYP2C19 and CYP2E1 [27], probably generating metabolites implicated in NI-DHR. Other drugs like lamotrigine and felbamate involve similar processes: bioactivation, detoxification, covalent adduct formation, processing and presentation of antigen to the immune system [30].

Contrast media are not used as therapeutic drugs; however, these stable and inert chemical compounds are widely used and involved in DHR [31,32]. Nonionic dimers are implicated more often than nonionic monomers in NIR, as opposed to what occurs with immune system [31]. Iodinated contrast media are classified into four groups depending on their chemical structure, osmolarity, iodine content and ionization degree in solution [31,33]. Some NI-DHR respond selectively to one contrast media compound but in other instances, there is extensive cross-reactivity.

Corticosteroids inhibit the allergic response by suppressing the transcription of a variety of proinflammatory cytokines like IL-12 and IFN- γ [34]. However, they are involved in NIR, and less commonly in immediate reactions [35]. Although contact dermatitis has been the most frequently reported, reactions to parenterally administered drugs have also been published, including anaphylaxis [35,36]. The more frequently involved are betamethasone, dexamethasone and triamcinolone [37], although prednisone, beclomethasone, budesonide and deflazacort are implicated [38–40]. Severe reactions like SJS, TEN or AGEP have been published, though they are anecdotal [41].

In photoallergic reactions, the drug binds to protein-forming adducts that are captured by skin dendritic transforming naïve T cells into effector memory cells responsible for the lesions [42]. Common drugs involved in photoallergic reactions are ketoprofen and oxicams, and fluorquinolones [43].

INTERACTION BETWEEN DRUG AND T CELLS

Several hypotheses have been proposed to explain how low-molecular-weight drugs are able to interact with the immune system and trigger the allergic response.

In the hapten model relies a low-molecular-weight substance or its metabolites ($<10^3$ Da) bind to a larger peptide/protein forming an adduct that is recognized by the immune system eliciting an immune response. This explains betalactam sensitivity [6] or sulfamethoxazole immune reactions [44]. The danger hypothesis [45] proposes that the drug induces the damaged tissue to release immunostimulating signals that activate the immune system, transmitting the danger signal, or directly binds to toll-like receptors (TLRs) present on the APC [46]. The pharmacological interaction (p-i) model [47] proposes an interaction between the drug and immune receptors like drug-specific T-cell receptors or HLA molecules present on APC. The reversible interaction between the drug and the MHC complex–TCR complex would induce a structural change that initiates the response.

NI-DHR can be associated with the expression of certain HLA alleles, presenting higher binding affinity for specific drugs that are also presented to specific TCRs on T cells. This modifies the antigen cleft location allowing the recognition of new peptides otherwise not recognized. For example, in the case of abacavir, its binding to HLA-B*57:01 is able to re-shape the antigen-binding location and induce the activation of T cells, driving a CD8-mediated response [48]. With carbamazepine, several alleles have been proposed as biomarkers, with the strongest associations reported with HLA-B*15:02 [28,49] and HLA-A*31:01 [50–53]. Like carbamazepine, phenytoin DHR have shown a genomic association with HLA-B*15:02 [49] HLA-B*56:02, and HLA-B*51:01 [52], whereas lamotrigine have shown an association with HLA-A*38:01, HLA-A*24:02 [50] or HLA-B*15:02 [51]. Many other drugs have been associated with a HLA-response and this is reviewed elsewhere [54–56].

MONITORING THE ACUTE RESPONSE

Monitoring the response at the acute phase provides relevant information concerning the mechanism involved. This has been applied to atopic dermatitis asthma and other allergies [57–60].

Increasing levels of circulating T cells express the cutaneous lymphocyte antigen (CLA), a marker that enables skin homing [60]. Monitoring the acute response has been used for discriminating not only the skin-homing process but also the mechanism.

Comparison between patients that developed IR versus NI-DHR showed a polarized immune response, with a high expression of IL-12 and IFN- γ and down-regulation of IL-4 (TH1 pattern), with the opposite in subjects with IR (TH2 pattern) [61]. Gene expression analysis in lymphocytes of peripheral blood (PBMC) in NI-DHR showed a high expression of TNF- α , perforin, Granzyme B and Fas L, with higher levels in more severe responses [62]. Another study showed that there was involvement of the skin chemokine CTACK/CCL27 with the recruitment of CCR10+ lymphocytes to the skin not only in cases with SJS/TEN but also in less severe drug reactions [63].

The microarray technology has enabled a deeper analysis of the NI-DHR mechanisms. One study has shown that 85 genes were differentially expressed during the acute phase, with an overexpression of alarmins, suggesting that in severe reactions, drugs can trigger this family of proteins [64]. Monitoring acute NIR to other drugs like contrast media has also been done [65].

DIAGNOSTIC APPROACHES

The in-vivo diagnosis involves a detailed clinical history, skin testing and drug provocation test (DPT) when indicated [66]. In-vitro tests, although useful, do not have appropriate sensitivity, in many cases the specificity has not been verified, and they are not always available [13].

The clinical history is the first step. Important data to be collected are: drug/s involved, dose administered, duration of treatment, detailed description of signs and symptoms presented, time interval between drug/s administration and reaction, treatment received and time to recovery after it. Bacterial or viral infections are important cofactors that must be taken into account. The clinical history is not always reliable, data provided are retrospective and not sufficient. The EAACI-DAIG/ENDA group (European Academy Allergy Clinical Immunology-Drug Allergy Interest Group/European Network for Drug Allergy) has provided a detailed questionnaire that can be used for diagnosing DHR and adapted to each centre [67]. The clinical history of a NI-DHR can overlap with immediate reaction-like urticaria [68[■]].

Concerning skin testing for NI-DHR, the most used approaches are intradermal and/or patch tests with delayed readings at 24, 48 and 96 h. Details of how to do this can be found elsewhere [69,70]. Patch testing, applicable with nonsoluble drugs, consists of the dilution of the drug in a vehicle for adequate skin absorption [71,72]. The photo-patch test is a modification recommended for photoallergic or

phototoxic reactions [73]. Intradermal tests with delayed reading have higher sensitivity than patch tests, although in most studies reported so far it is no higher than 50–60% [73,74]. Information is available especially for betalactams [69], contrast media [75], heparins [76] and corticosteroids [74], amongst others. Recommendations for readings as well as the precautions to be taken to avoid risks are detailed in the literature [77,78].

In-vitro tests are considered complementary to in-vivo tests for the diagnosis of NI-DHR. They enable the identification not only of the culprit drug but also the mechanism [79]. The lymphocyte transformation test (LTT) is based on the capacity to detect specific T-cell proliferation that can now be measured by flow cytometry [80]. Formerly, LTT used H³-labelled thymidine but with flow cytometry the response in lymphocyte subpopulations can be measured. Its sensitivity is variable, from low values up to 100%. In one study, it was 62% [80], lower than the 74% is reported by another group [81]. When different penicillins are used, some patients may respond only to amoxicillin or BP, whereas other to both. This cannot necessarily be extrapolated to the response *in vivo* and subjects with a positive response to BP and negative to amoxicillin can tolerate BP and develop a reaction to amoxicillin [80]. The sensitivity can improve by stimulating T cells with amoxicillin-driven dendritic cells from the same patient [82,83]; however, it is costly, time consuming, and only available to a few laboratories.

DPT is the gold standard but usually indicated only in mild reactions [84,85]. Most of its indications are to exclude drug allergy or to de-label cases diagnosed as drug allergy. If DPT is not performed, a large number of cases can be overdiagnosed. It is particularly useful in children where the most frequent reactions are MPE [86]. In fact, in many series, the number of cases finally confirmed after DPT is below 10% [84]. Several groups have recently proposed directly doing DPT after undertaking a clinical history in those cases with mild reactions [85,87,88[■]].

The dosages and time intervals recommended depend on the drug, the route of administration and the severity of the reaction. Other conditions to take into account are comorbidities and comedications [77]. DPT is contraindicated in severe reactions like Drug reaction with eosinophilia and systemic symptoms (DRESS), AGEP or SJS/NET [85].

ASSESSMENT OF CROSS-REACTIVITY

A lot of information is available concerning cross-reactivity at the IgE level between penicillins and cephalosporins as well as within the penicillin group

[89]. Assessment for NI-DHR is based on the knowledge of the chemical structure of the drug and its metabolites [90]. Data regarding cross-reactivity within penicillin show that both amoxicillin and ampicillin share a high degree of cross-reactivity, although some cases are also skin testing-positive to benzyl penicillin [89]. Regarding fluorquinolones, three patterns of cross-reactivity have been proposed: T cells reacting only to the eliciting drug, others with limited cross-reactivity and thirdly those with broad cross-reactivity. The study concludes that cross-reactivity amongst fluorquinolones is quite frequent [20].

Concerning sulfonamides, the structure of the functional group is not known and assessment of cross-reactivity is difficult [21]. Sulfonamide-containing drugs can be divided into antibiotics and nonantibiotics. All sulfonamide antibiotics contain structural characteristics that are absent from nonantibiotic [21]. The association of cross-reactivity between both appears to be because of a predisposition to allergic reactions rather than cross-reactivity with sulfonamide-based drugs [91]. The metabolism of sulfonamide is specific to certain molecular substituents and stereospecific. As it involves structures contained only in the sulfonamide antibiotics and not in other sulfonamide-containing agents, similar metabolites are not formed and cross-reactivity must be regarded as highly unlikely.

Assessment of cross-reactivity to corticoids is also difficult because most individuals that have received cross-reactivity do not remember very often whether they received them or not previously. It is difficult to confirm if we are dealing with cross-reactivity or co-sensitization. On the basis of the corticosteroid patch test results and their chemical structure, Coopman *et al.* [92] classified these drugs in four groups: A (hydrocortisone type), B (triamcinolone acetonide type), C (betamethasone type), and D (hydrocortisone-17-butyrate type). Group D was later subdivided into two groups (D1 and D2) depending on the presence/absence of a C16 methyl substitution and/or halogenation on the C9 of the B-ring. High cross-reactivity exists between corticosteroids in each group as well as between Group D2 and Groups A and B, with Group D1 exhibiting quite low cross-reactivity with the others. This classification is useful in reactions to topically corticosteroids, although it is not accepted worldwide. It has been suggested that other rings can be relevant for determining cross-reactivity, showing that substitutions at the C6/9 and C16/17 sites are important in inducing NI-DHR [93]. In systemic allergic reactions to corticosteroids, it is more difficult to define patterns of cross-reactivity.

Succinate ester seems to have more immunological potential, probably because it has the capacity to bind to arginine groups from proteins similar to glyoxal derivatives [37].

FURTHER NEEDS AND CONCLUSION

NI-DHR constitute a very heterogeneous group of allergic reactions with any drugs potentially being involved. Interaction of keratinocytes as well as other skin cells with lymphocytes and APC should be studied to understand the skin involvement.

The metabolism of drugs is critical for the development of DHR and very often both drugs and their metabolites are involved. As the skin is the most important organ involved, we must assume that some erratic metabolism can occur in the skin keratinocytes that may act as APC inducing proliferation of T cells [94]. Although there are models of contact dermatitis that have characterized the haptenome for different sensitizers [95], similar studies have not been made in cases taking the drugs by the oral or parenteral route.

The development of realistic assays with the involvement of all the key players in skin reactions needs further study. In this sense, the use of dendritic cells plus lymphocytes has been shown to be a good model for evaluating NI-DHR [82,83].

Monitoring the acute phase should be undertaken. A tremendous impact has been made with transcriptomic analysis. Transcriptomic approaches have also been used to investigate DHRs by identifying genes that show different patterns of expression in a number of clinical entities. This information can be of value for further elucidation of mechanisms involved. Although the initial studies were performed using RT-PCR analysis to monitor the acute phase, nowadays high-density expression platforms represent a more integrative way for providing a complete view of gene expression [96].

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Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

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