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Journal of Dermatitis

Review Article

Update on Non-immediate Drug Allergy Reactions: State and New Aspects

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ABSTRACT

Purpose of the review: Among the Adverse Drug Reactions (ADR), around 10-15% are driven by an immunological mechanism and considered as allergic drug reactions. Within the Type IV of drug allergic reactions and in accordance with Gell and Coombs classification, the non-immediate drug hypersensitivity reactions (NI-DHR) relates to the most complex group of drug allergy, being cellular mediated responses and appearing from 1 hour to several weeks after drug/metabolites exposure. Current diagnosis protocols are limited and there is an unmet need to identify a diagnostic approach that mimic the pathological response and enhance the possibilities for a more accurate and realistic diagnosis.

Recent findings: Changes in gene patterns induced during the acute phase of the NI-DHR provide clues of the underlying immunological mechanisms, while the study and identification of specific HLA profiles in selected patients allows making inference about the risk of suffer a reaction.

Conclusion: Advances on the knowledge of NI-DHR, based on genetic and transcriptomic analysis, will provide better understanding of the biology behind, as well as more opportunities to diagnose and treat the patients

Keywords: Allergy; Drug; Non-immediate reactions; T-cells

Abbreviations: ADR: Adverse Drug Reactions; NI-DHR: Non-immediate Drug Hypersensitivity Reactions; NIR: Non-immediate Reactions; DHR: Drug Hypersensitivity Reactions; MPE: Maculopapular Exanthema; NI-U: Non-immediate Urticaria; AGEP: Acute Generalized Exanthematic Pustulosis; SJS: Stevens-Johnson Syndrome; TEN: Toxic Epidermal Necrolysis; DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms; ICM: Iodinated Contrast Media; BLs: Betalactams; CYP: Cytochrome P; NSAIDs: Non-Steroidal Anti-inflammatory Drugs; IR: Immediate Reactions; APC: Antigen-presenting Cells; FQ: Fluoroquinolones; IS: Immune System; CS: Corticosteroids; CLA: Cutaneous LymphocyteA; DPT: Drug Provocation Test; PT: Patch Tests; ST: Skin Testing; IDT: Intradermal Test; LTT: Lymphocyte Transformation Test; CR: Cross-reactivity.

INTRODUCTION

Among the Adverse Drug Reactions (ADR), around 10%-15% are driven by an immunological mechanism and considered as allergic drug reactions [1]. Categorized within Type IV of allergic drug reactions accordingly with Gel and Coombs classification [2], the Non-immediate Drug Hypersensitivity Reactions (NI-DHR) relates to the most complex group of drug allergy, being cellular mediated and with responses appearing more than 1 hour after drug/metabolites exposure. Current diagnosis protocols are limited and there is an unmet need to identify a diagnostic approach that mimic the pathological response and enhance the possibilities of an accurate diagnosis.

In this review, authors would like to update previous published work in this topic [3], include most recent discoveries on NI-DHR and providing their view on relevant aspects of the diagnosis.

CLASSIFICATION OF T-CELL DRUG REACTIONS

The NI-DHR is T-cell mediated reactions classified in four categories, although recently a fifth one has been proposed. The clinical manifestations are wide, affecting different organs, with severity ranging from mild reactions like Maculopapular Exanthema (MPE) or Non-immediate Urticaria (NI-U), to life-threatening reactions like Acute Generalized Exanthematic Pustulosis (AGEP), bullous reactions (Stevens-Johnson Syndrome (SJS)/TEN) or DRESS (Table 1) [4-8].

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Received: June 14, 2021; **Accepted:** June 28, 2021; **Published:** July 05, 2021

Citation: Gomez E, Lopez NB (2021) Update on Non-immediate Drug Allergy Reactions: State and New Aspects. J Dermatitis. 6: 133.

Table 1: More relevant clinical entities and mechanisms involved in NIR.

Type of reaction	Mechanism implied	Clinical manifestations
Non systemic reactions	a) T cell specific/Toxic metabolites	1. Maculopapular Exanthema (MPE) 2. Contact Dermatitis (CD) 3. Photosensitivity contact dermatitis 4. Isolated Mucosal Involvement 5. Bullous/Desquamative exanthema 6. Fix Drug Eruption (FDE) 7. Non-Immediate Urticaria (NI-U)
	b) Toxicological	1. Bile duct syndrome 2. Hepatitis 3. Meningitis 4. Pneumonitis 5. Nephritis 6. Pancreatitis 7. Other organ-specific clinical manifestations
Systemic reactions	a) T cell specific/ heterologous immunity/HLA haplotypes	1. Serum Sickness Like Syndrome (SSLS) / accelerated urticaria 2. Severe cutaneous adverse reactions 3. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) 4. Acute Generalized Exanthematic Pustulosis (AGEP) 5. Toxic Epidermal Necrolysis (TEN) 6. Stevens Johnson Syndrome (SJS)
	b) Unknown	Vasculitis
Located reactions	Vascular occlusion/T cell specific	Nicolau syndrome

DRUGS INVOLVED

Any drug or its reactive metabolites can induce a NI-DHR [9]. Classical drug/drug-metabolites eliciting this type of reactions are anticonvulsants, Iodinated Contrast Media (ICM), Betalactams (BLs) or Non-steroidal Anti-Inflammatory Drugs (NSAIDs). However, other chemical compounds have shown the capacity of triggering them [3].

ANTICONVULSANTS

Anticonvulsants are among the most frequent drugs eliciting NI-DHR. It is well demonstrated that for these compounds the bioactive metabolites generated during the drug-metabolism by different enzymes belonging to the cytochrome P450 (CYP) are responsible of the induced reaction, where sub-families CYP2C and CYP2E are involved [10-15].

IODINATED CONTRAST MEDIA

ICM are widely involved in DHR, are inert chemical drugs that contain iodine atoms used for x-ray-based imaging. Based on their chemical structure, osmolarity, iodine content and ionization degree in solution they are classified in ionic or non- ionic, being the latest the most frequent eliciting NI-DHR [16-18]. Although most of reactions are specific to one CM compound, it has been shown an extensive cross-reactivity among them [19,20].

BETALACTAMS

BLs is also involved in NIR, with some clinical entities like accelerated urticaria causing confusion [21]. In IR the specificity of the antibodies has been well proven, existing good correlation with clinical entities [22-24], but in NIR the final structure recognized is more complex to define [25]. All BLs bind spontaneously to proteins by nucleophilic attack of their amino groups. Amoxicillin forms penicilloyl adducts with lysine residues on human serum albumin [26]. Other BLs like benzylpenicillin, aztreonam or piperacillin binds to similar lysine residues [27]. This also occurs with other BLs as clavulanic, although the metabolites generated are different and do not cross-react with classical BLs. Regarding cephalosporins, the lack of knowledge of the chemical structure of their antigenic determinants and the proteins involved in the sensitization makes difficult the understanding of the mechanisms involved [28]. However, whether differential binding occurs and if this influences the specificity of 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 BL protein conjugates. Both hapten and carrier contribute to the formation of the antigen [24,29]. In the case of T-cell mediated responses the BL is recognized after the formation of a BL-peptide complex formed after the processing of the adduct by the antigen-presenting cells (APC). BLs haptenizes extra and intracellular proteins. One study has found that heat shock protein 70 and enolase can be haptenized by amoxicillin [30]. These adducts can be incorporated into target cells transported by exosome.

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

NSAIDs can also induce NIR, which are including in the phenotype of single NSAIDs-induced delayed hypersensitivity reactions. This comprises a wide spectrum of pathologies that goes from mild to severe reactions. Concerning the different NSAIDs, although some entities like photo contact dermatitis are more likely to be induced aryl-propionics or oxicames, all of them can induce NIR [4,31-38].

Regarding the underlying mechanisms, drug-specific T-cell clones have not yet been developed. Concerning drug metabolites there have been identified for pyrazolones, although only few studies are focused on analysing their antigenicity [39,40].

QUINOLONES, PARTICULARLY FLUORQUINOLONES (FQ)

Quinolones, particularly fluorquinolones are one of the main drugs involved in DHR worldwide [41-43] inducing IgE- and T-cell reactions. FQ 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 (table), including photo-allergy, can be induced with differences depending on the FQ [44,45].

SULFONAMIDES

Sulfonamide were the first group of drugs involved in DHR, and nowadays continue eliciting reactions, being the most common clinical entity elicited MPE, although urticaria may also occur. NIR to sulfonamides are mainly caused by metabolites, particularly with nitro-sulphometoxazol. Around 45%-70% of sulfonamides are acetylated in the liver by N-acetyltransferase and approximately 15% glucuronidated. Moreover, 10% is hydroxylated by the cytochrome CYP2C9 to sulfamethoxazole hydroxylamine. The metabolite nitroso-sulfamethoxazole is a model for T-cell activation. More details about the generation of metabolites are shown in references [46-48].

MACROLIDS

Macrolids are other antibiotics that can be involved in NIR [49], but less is known about the metabolites generated and the recognition by the Immune System (IS) than with the antibiotics detailed above.

OTHER DRUGS

Abacavir

The elicits also NI-DHR, particularly associated with HIV infection [50]. The metabolism comprises 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) [51].

Oxipurinol

It is the main metabolite of allopurinol after transformation by xanthine oxidase. Excess production of this drug is assumed to lead to tissue damage, evoking an immunological response with development of antibodies against tissue-components [52].

Corticosteroids

Inhibit the allergic response by suppressing the transcription of a variety of pro-inflammatory cytokines like IL-12 and IFN-γ. However, they are more common involved in NIR than in IR. Although contact dermatitis has been the most frequently reported, reactions to parenterally administered drugs have also been published. The more frequently involved are betamethasone, dexamethasone and triamcinolone, although other like prednisone and metilprednisolone are also implicated. Though anecdotic, severe reactions like SJS/TEN or AGEP are published [53-60].

DRUG-RECOGNITION AND IMMUNE RESPONSE

Drugs are molecules under 1Kda that are not visible to the IS, evolved to recognize antigens with a molecular weight above 1Kda.

There are 3 hypothesis explaining the molecular events behind the recognition of drugs by the IS [61].

I The hapten model: drug binds to a peptide/protein forming an adduct recognizable.

II. The danger hypothesis focuses on danger-signals released as consequence of a tissue damage created by the drug. These signals would activate APCs and eventually trigger the immune response [62].

III. The pharmacological interaction (p-i) model proposes interaction drug-immune receptors like drug-specific T-cell receptors or HLA molecules present on APCs. The reversible interaction drug: MHC–TCR complexes would induce structural changes leading the response. However, this model was ineffective in mounting a primary response; therefore it is considered as complementary to the hapten model [63].

NI-DHR can be associated to certain HLA-I alleles. This modifies the antigen clef location allowing the recognition of new peptides otherwise not recognized. In the case of abacavir, the binding to HLA-B*57:01 is able to re-shape the antigen-binding location and inducing CD8-mediated responses. Several alleles have been proposed for carbamazepine, with the strongest association reported with HLA-B*15:02 and HLA-A*31:01. Phenytoin have shown a genomic association with HLA-B*15:02 HLA-B*56:02, and HLA-B*51:01, while lamotrigine is associated to HLA-A*38:01, HLA-A*24:02 or HLA-B*15:02. Many other DHR have been associated with HLA-responses [64-72].

MONITORING THE ACUTE RESPONSE

Monitoring acute phase of the reaction allows for instance the Identification of increased levels of circulating T-cells expressing the Cutaneous Lymphocyte Antigen (CLA) or the presence of skin chemokines like CTACK/CCL27, involved in the recruitment of CCR10+ lymphocytes [73-77], provides valuable information about the mechanisms involved. Comparison between subjects developing IR versus NI-DHR shows a polarized immune response, with high expression of IL-12 and IFN-γ and down-regulation of IL-4 (Th1 pattern), opposite to subjects with IR (Th2 pattern) [78]. Similarly, gene expression analysis of lymphocytes from NI-DHR patients showed high expression of TNF-α, perforin, Granzyme B and Fas-L, with higher levels in more severe responses [79], using microarray technology, demonstrated a differential expression of 85 genes during the acute phase, with overexpression of alarmins, suggesting that in severe reactions drugs can trigger this proteins [80].

DIAGNOSTIC APPROACHES

Although for NIR the diagnosis relies mainly in the clinical history or in a DPT when indicated, positive intradermal, photocontact or Patch Tests (PT) have been reported [81]. *In vitro* tests, although useful, do not have appropriate sensitivity nor verified specificity [24,82].

The clinical history is always the first step; the more precise it is the more accurate will be the diagnosis. Important data to be collected are: Drugs involved, dose administered, duration of treatment, detailed description of symptoms presented, time interval between drug/drugs administration and reaction, treatment received and time to recovery after it. Important cofactors to be considered are underlying infections. Nevertheless, frequently data recorded are retrospective and imprecise, the clinical history is not always reliable. The European Academy Allergy Clinical Immunology-Drug Allergy interest Group/European Network for Drug Allergy (EAACI-DAIG/ENDA) has provided a detailed questionnaire useful for diagnosing DHR [83].

Concerning ST, the most used approaches are Intradermal Test (IDT) and/or PT with delayed readings. Details of how to perform them can be found elsewhere. The PT, applicable with non-soluble drugs, consists of the dilution of the drug in a vehicle for adequate skin absorption, being the photo-patch a modification recommended for photoallergic reactions. The IDT, recommended for soluble drugs, have higher sensitivity than PT, though in most studies published it is no higher than 50%-60%. Indications are available for BLs, CM, heparins and CS, amongst others. Recommendations for readings as well as the precautions to be taken to avoid risks are detailed elsewhere [84-94].

The cellular *in vitro* tests are considered for supporting the diagnosis of NI-DHR. The Lymphocyte Transformation Test (LTT) is based on flow cytometry technology that not only helps in measuring the proliferative capacity of drug-specific T-cells, but to identify which subpopulations are involved in the reaction, providing clues of the underlying mechanism. Conveniently, the LTT allows the evaluation in one single experiment of several compounds from the same drug-family/drug-metabolites that could induce cross-reactions [95-100]. A limitation of the test is its variable sensitivity, as demonstrated in studies with BLs with values from 62% to 74.4%. However, it must be kept in mind its complementary nature, since some results could lead to misdiagnosis. This is the case with penicilins, where has been published how some patients may respond exclusively to amoxicillin or BP, while others react to both compounds, which cannot be extrapolated to the response *in vivo*, where subjects with positive response to BP and negative to amoxicillin, can tolerate BP and react to amoxicillin. A 2nd generation of LTT has shown improvement of the sensitivity, based on the co-cultivation of T-cells with autologous monocyte-derive dentritic cells from patients in presence of the culprit drug [101-103]. However, the increased complexity limits its applicability.

DPT is the gold standard for the diagnosis, although it is only indicated in mild reactions. It is used 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. In fact, the number of cases finally confirmed after DPT is below 10%. Therefore, according to recent studies, it has been proposed to perform directly DPT without ST in cases with mild NIR [104-108].

Regarding the dosages and time intervals recommended, they depend on the drug, the route of administration and the severity of the reaction. Other conditions to consider are comorbidities and co-medications [93]. For children doses are adjusted to weight and age. The procedure consist in administering escalating doses of the drug till reaching the full therapeutic dose, followed in negative cases by a prolonged challenge [96, 109-112].

ASSESSMENT OF CROSS-REACTIVITY (CR)

A lot of information is available concerning CR with IgE antibodies between penicillins and cephalosporins, and within the penicillin group. Assessment is based on the knowledge of the chemical structure and no information has been provided concerning the protein carrier. Data published show high degree of CR between amoxicillin and ampicillin, although some cases are also positive to benzylpenicillin [109]. Regarding FQ three patterns of CR have been proposed: 1) T-cells reacting to the eliciting drug, 2) limited CR and 3) broad CR. Published studies conclude that CR is quite frequent.

Concerning sulfonamides, the structure of the functional group is unknown being the assessment of CR difficult. All these antibiotics contain structural characteristics that are absent from non-antibiotic ones. The CR appears to be due to a predisposition to allergic reactions rather than CR with sulfonamide-based drugs [111]. The metabolism of sulfonamide is specific to certain molecular substituents and stereospecific. Since it involves structures contained only in the sulfonamides, similar metabolites are not formed and CR must be regarded as highly unlikely.

Evaluation of CR among corticoids is also difficult. Frequently, individuals do not remember whether they have received CS previously. Within this group, it is difficult to confirm if we are dealing with CR or co-sensitization. Based on PT results and their chemical structure, classified CS in four groups: A (hydrocortisone type), B (triamcinolone acetonide type), C (betamethasone type), and D (hydrocortisone-17-butyrate type), with subdivision into groups (D1, D2) depending on the presence/absence of a C16-methyl substitution and/or halogenation on the C9 of the B-ring. It is known that high CR exists within each group as well as between groups D2, A and B, being CR with D1 quite low. This classification is especially useful with topically CS, although not accepted worldwide. Furthermore, other rings can be relevant for determining CR, showing substitutions at C6/9 and C16/17 sites important in inducing NI-DHR [113-116]. Regarding systemic reactions it is even more difficult to define patterns of CR. Succinate-ester seems to have more immunogenicity, probably because its capacity to bind to arginine groups from proteins similar to glyoxal derivatives.

DISCUSSION AND CONCLUSION

NI-DHR comprises a heterogeneous group of clinical entities potentially induced by any drug. More studies are needed to decipher the interaction between immune and skin cells in NI-DHR. Likewise, it is important to delve into the discovery of the drug metabolites and the mechanisms behind their generation on the skin, most likely by keratinocytes, with demonstrated expression of CYP-proteins that could act as APC.

There is an unmet for models to characterize the haptenome in cases of sensitization by the oral/parenteral route, as for contact dermatitis.

The LTT demonstrated its value in studying NI-DHR and a 3rd variation, integrating skin cells, would be desirable.

The monitorization of the acute phase and the integration of transcriptomics have proved its value in deciphering the underlying mechanisms in DHRs. The application of high-density expression platforms represents a more integrative way for providing a complete view of gene expression.

However, the lack of replication studies and the heterogeneity of the clinical entities have led to dispersed results and difficulties to stable genetic biomarkers related to DHRs. Further investigations are needed to identify genes and polymorphisms related to these disorders that could be useful for an accurate diagnosis

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