



NSAIDs hypersensitivity: questions not resolved

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Purpose of review

NSAIDs are the drugs most frequently involved in hypersensitivity reactions (HSR). These are frequently prescribed at all ages. HSR are of great concern and can affect people at any age. These drugs can induce reactions by stimulating the adaptive immune system (IgE or T cell), known as selective responders or more frequently by abnormalities in biochemical pathways related with prostaglandin metabolism. These are known as cross-intolerant. With some exceptions, skin testing and in-vitro studies are of little value in selective responders.

Recent findings

In the last years, several classifications have been provided based on clinical symptoms, time interval between drug intake and appearance of symptoms, response to other nonchemically related NSAIDs and the underlying disease. Based on this classification, several well differentiated categories within each group of entities cross-intolerant and selective responders are now recognized. The most complex groups for evaluation are cross-intolerant in which three major groups exist: NSAIDs exacerbated respiratory disease, NSAIDs exacerbated cutaneous disease and NSAIDs-induced urticaria/angioedema in the absence of chronic spontaneous urticaria. Within the selective responders, there are two mechanisms involved: drug-specific IgE or T-cell effector responses. New entities have been added to this classification like mixed reactions within the cross-intolerant category, that must manifest as anaphylaxis and multiple immediate selective reactions.

Summary

The precise evaluation of patients with NSAIDs hypersensitivity following established guidelines will improve not only our understanding but also the management of these entities. As the number of patients affected with NSAIDs is important, further studies are warranted.

Keywords

cross-intolerants, NSAIDs hypersensitivity, questions, selective responders

INTRODUCTION AND CLASSIFICATION

Hypersensitivity to NSAIDs (HR-NSAIDs) is the most frequent type of hypersensitivity drug reactions [1]. Although antibiotics were considered the most important inducers of drug hypersensitivity [2], studies based on clinical histories and DPT confirm this point [3,4,5]. In the last years, significant progress has been made in the field of HR-NSAIDs, particularly in those with skin involvement [6]. For many years, Acetyl salicylic acid (ASA)-induced respiratory disease has been the best studied model with less attention paid to others entities [7–9].

In this review, we will follow the classification proposed by the European Academy of Allergy and Clinical Immunology (EAACI) Drug Allergy Interest Group (ENDA) [10,11] similar, although more complete than previous ones [12,13]. This is shown in Table 1 as first proposed, with their abbreviations [11–14]. Within the cross-intolerant category, the following entities exist:

- (1) *NSAIDs exacerbated respiratory disease (NERD)*. This is reserved for those patients that have upper and/or lower airways involvement. Patients usually have underlying asthma and or chronic rhinosinusitis, and the clinical course of the disease tends to get worse over the years [14].
- (2) *NSAIDs exacerbated cutaneous disease (NECD)*. This applies to those cases that having chronic spontaneous urticaria (CSU) have an increase or reappearance of the symptoms after NSAIDs

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KEY POINTS

- Hypersensitivity to NSAIDs includes a wide variety of clinical entities induced by immunological-specific mechanisms (IgE or T cell) as well as mechanisms based of abnormalities in biochemical pathways related with Leukotriene-Prostaglandin metabolism.
- Skin is the much more frequent organ involved, independently of the underlying mechanisms.
- Skin testing for IgE reactions and T-cell-dependent response are of limited value.
- For cross-intolerant reactions neither skin test nor in-vitro assays are recommended.
- Anaphylaxis can be part of the cross-intolerant reactions and included in NSAIDs-induced urticaria and angioedema.
- At early age, cross-intolerance predominates over selective response, although in some countries selective responders may be relevant depending of patterns of drug consumption.
- In children, combination of respiratory and skin symptoms occurs more frequently than in adults.

intake. The clinical course depends on the CSU activity. Other types of urticaria/angioedema may also be aggravated after NSAIDs intake [14].

- (3) *NSAIDs-induced urticaria and angioedema (NIUA)*. Defines those that in the absence of CSU, develop acute symptoms in the absence of any previous urticarial manifestations that disappear after drug withdrawal [14].

For the selective responders category, the following entities are identified:

- (4) *Single NSAIDs-induced urticaria, angioedema and/or anaphylaxis (SNIUAA)*. This usually occurs after taking any NSAID or analgesic independently of their capacity for inhibit Cyclooxygenase-1 (COX-1) enzymes. Entities like anaphylaxis, urticaria/angioedema (AE) (and in less instances rhinitis) and/or asthma or isolated angioedema may occur [14].
- (5) *Single NSAIDs-induced delayed hypersensitivity reactions (SNIDHR)*. This includes several and different clinical entities from mild reactions to very severe [15] (Table 2). They are considered by Type IV mediated by effector T cells [16]. Some of them like urticaria with or without angioedema and exanthema-like, because may have difficulties in differentiation with urticaria mediated by other mechanisms, will be considered in this review.

Several studies have claimed that the ENDA classification (Table 2) is not quiet appropriate and propose other alternatives [3,17,18]. For example, in the NIUA; often anaphylaxis may occur [3]; the combination of respiratory and cutaneous symptoms or vice versa was not included in the ENDA classification [3], and some differential characteristics in children were not considered [19²²,20,21,22²²]. Although the association of respiratory and cutaneous symptoms were not included within the cross-intolerant category or assumed to be part of NERD as originally described [3,7], this was published before the ENDA classification, and our view is that it must be considered as anaphylaxis following the criteria published elsewhere [23]. This is now shown in a modified classification (Table 2). Although the entities included are more extensive than in previous classifications, we will concentrate mainly in those who are within the category of cross-intolerant, in which most debate is generated when we are dealing with phenotype definitions.

MECHANISMS

NSAIDs exacerbated respiratory disease

This was the first defined model and the classical one to which the other entities within the cross-intolerant category are often compared [24²⁴]. Instead of naming this category as aspirin-induced asthma or aspirin exacerbated respiratory diseases it seems preferable to identify as NERD as ASA is not the drug most frequent involved. All NSAIDs with strong capacity for inhibiting the COX-1 are capable of inducing this entity and cross-intolerance exist between them [7]. In some instances, weak COX-1 or selective Cyclooxygenase-2 (COX-2) may induce symptoms. The mechanisms remain to be elucidated. According to Eastman *et al.*, inhibition of COX-1 in different cells shifts the arachidonic acid metabolism to lipo-oxygenase pathway with the production of sulfidopeptide leukotriene 12-hydroxyeicosatetraenoic from platelet that activate on leucocyte leukotrienes production [25²⁵]. A dynamic model has shown concomitant malfunctions of multiple enzymes of the araquidonic acid metabolic pathway that prolong the risk for bronchoconstriction [26].

NSAIDs exacerbated cutaneous disease

This occurs in the context of CSU that often can be mild or silent but reactivated after NSAID intake. A parallelism has been established between NERD based on the response to NSAIDs and the pattern of leukotrienes excretion [27]. However, this model

Table 1. Type of reactions induced by NSAIDs and example of drugs involved

Cat	Group	Mechanism	Entities	Drugs and references
CI	NERD	Inhibition PG-LEK pathways	Rhinitis, asthma, rhinosinusitis, nasal polyposis	NSAIDs in general [7]
CI	NECD	Unknown	CSU aggravated or reactivated by NSAIDs	NSAIDs in general [90]
CI	NIUA	Unknown	Urticaria and/or angioedema, anaphylaxis, mixed reactions	NSAIDs in general [3, 19 [■]]
SR	SNIUAA	IgE abs/others	Anaphylaxis, urticaria and/or angioedema, rhinitis, asthma	Aril-propionics [134 [■]]
SR	SNIDHR	T cells	CD	Diclofenac [81]
			Photosensitivity CD	Naproxen [68 [■]]; piroxicam [135]
			Isolated mucosal involvement	Etoricoxib [40]
			Bullous/or desquamative exanthema	Diclofenac [53, 136]
			DRESS	Ibuprofen [48]; phenylbutazone [49]
			TEN	Ibuprofen [50]; paracetamol [51]; celecoxib [52]
			AEP	Ibuprofen [45]; flurbiprofen [47]; piroxicam [46]
			FDE	Ibuprofen [41]; piroxicam [42]
			NI urticaria	Metamizol [37 [■]]
			Serum sickness like/accelerated urticaria	Diclofenac [43]; ibuprofen [44]
SR	Org. specif	Mechanism T cells/toxicological/both	Nicolau syndrome	Diclofenac [54]
			Hepatitis	Diclofenac [55]
			Bile duct syndrome	Ibuprofen [56]
SR	Skin/system ^a	Unknown	Meningitis	Ibuprofen [57]
			Vasculitis	Naproxen [58]; ibuprofen [59]

AEP, acute exanthematic pustulosis; CI, cross-intolerant; CSU, chronic spontaneous urticaria; DRESS, drug reaction with eosinophilia and systemic symptoms; FDE, fixed drug eruption; NI urticaria, Non-immediate urticaria, NECD, NSAIDs exacerbated cutaneous disease; NIUA, NSAIDs induced urticaria/angioedema; NERD, NSAIDs exacerbated respiratory disease; SNIUAA, NSAIDs-induced urticaria, angioedema and/or anaphylaxis; SNIDHR, single NSAIDs-induced delayed hypersensitivity reactions; SR, selective responder; TEN, toxic epidermal necrolysis.

^aSkin and in some instances systemic manifestations.

Table 2. Proposed guidelines for the differential diagnosis of clinical manifestation in which skin symptoms are the predominant

	NIUA	NECD	Mix reaction	SNIUA	SNIDHR
Category	CI	CI	CI	SR	SR
Urticaria	Yes	Yes	Yes	Yes	Yes
Angioedema	Yes/no	Yes/no	Yes/no	Yes/no	Yes/no
Anaphylaxis	+	+	++	+++	—
Time interval	1–6 h	Variable	2–24 h	≤ 1 h	6–24 h ^a
System symptoms	No	No	Yes/no	Yes/no	No ^b
ST	No value	No value	No value	Optional ^a	Optional ^a
Skin biopsy	Optional	Optional	Optional	Optional	Yes
Nature evolution	May disappear	Variable	Variable	May disappear	Unknown
Corticoids	Good	Variable		Good	Good

Anaphylaxis is graded in highly probable (+++), low probability (+), absence (—). CI, cross-intolerant; DRESS, drug reaction with eosinophilia and systemic symptoms; NECD, NSAIDs exacerbated cutaneous disease; NIUA, NSAIDs-induced urticaria and angioedema; SNIDHR, single NSAIDs-induced delayed hypersensitivity reactions; SR, selective responder.

^aThe interval can be shorter or in rarer instances longer than 24 h.

^bIf systemic symptoms appear, a DRESS must be ruled out.

has not been extensively studied, and the immunological abnormalities found in the skin biopsy of patients with CSU differ from the one of NERD [7].

NSAIDs-induced urticaria and angioedema

The entities within this group have been neglected for many years with the assumption that there were part of NECD [7,8]. Regarding LKT excretion, the evidence also suggest a shunting in the LKT as in the previous entities but basal level of leukotrienes in urine are normal in contrast to what is described in NERD [28]. However, further studies are needed to phenotype more precisely this group of entities [28,29].

Combinations of 1 and 3 are rather common and also combination of 1 and 2, although less frequently, have also been reported [1]. We will refer to this later on.

Within the selective responders, we will briefly detail the two most common groups of entities shown in Table 2.

Single NSAIDs-induced urticaria, angioedema and/or anaphylaxis

The clinical characteristics reflect those of immediate IgE reactions to betalactams (BLs) and other drugs [30,31]. Symptoms are often severe [30], sensitivity decreases over time and there are great differences from country to country according to patterns of drugs prescription [32,33] and infraclass cross-reactivity or selective responses may occurs [31,34,35]. It is assumed a Type I IgE mechanism although in few cases IgE antibodies have been shown [36].

Single NSAIDs-induced delayed hypersensitivity reactions

This includes a variety of clinical entities ranging from mild exanthema, nonimmediate urticaria [37], photo-contact dermatitis [38,39], isolated mucosal involvement [40], fixed drug eruption (FDE) [41,42] or serum sickness like syndrome [43,44], to life-threatening reactions including acute generalized exanthematic pustulosis [45–47], drug reaction with eosinophilia and systemic symptoms (DRESS) [48,49], bullous reactions such as Stevens–Johnson syndrome/toxic epidermal necrolysis (SJTEN) [50–53]. Single organ-specific reactions including hepatitis, nephritis, hypersensitivity pneumonitis and aseptic meningitis have been described [54–60]. Three models have been developed for drug recognition by specific T cells [61]. The development of T-cell clones specific for classical

drugs inducing these reactions has played a pivotal role in the understanding of the physiopathology as well as genetic studies identifying HLA molecules involved in drug presentation. Regarding NSAIDs, drug-specific T-cell clones have not yet been developed, and this precludes the analysis of specific mechanisms involved. Drug metabolites have been identified for ibuprofen and pyrazolones [62], but few studies have analysed their antigenicity. Among them, lymphocyte transformation test (LTT) assays performed with the parent drug metamizole and several metabolites in a patient with a systemic hypersensitivity reaction were able to detect in-vitro T-cell proliferation, with the more robust responses to several concentrations of 4-methylaminoantipyrine [63] which is the first of metabolites formed and constituting 40% of the metabolites found in peripheral blood [64]. The authors propose that the positive T-cell responses to the parent drug as well as to the metabolites detected by LTT may be due to cross-reactivity [63]. It is therefore tempting to speculate that drug-responsive T cells might be specific of the different metabolites and that low amounts of them might be generated during the in-vitro cell culture allowing the stimulation of specific T cells. Further research would be needed to confirm this hypothesis. Similar situation may occur with other NSAIDs including weak and selective COX-2 inhibitors.

EPIDEMIOLOGY AND DRUGS INVOLVED

Epidemiology of NSAID hypersensitivity very often focus on drug adverse reactions without entering in too much detail of drug hypersensitivity reactions (DHR) and no information of the different entities according to recent classifications [1,65]. The information on DHR is incomplete or fragmented, and in many instances, data on prevalence/incidences must be retrieved after a careful reading when possible. In retrospectives studies, many data are lacking, incomplete or not taken in all cases evaluated [66]. Even in recent studies, the symptoms are not clearly described or if does, it cannot be classified as tolerance to other NSAID has not been assessed [67]. Despite that, recent studies show relevant information in this respect.

In a retrospective study carried out by Blumenthal *et al.*, 60 000 patients were analysed in the context of adverse drug reactions (ADR) for NSAID. From the total ADR to NSAIDs, one out of five were hypersensitivity reactions (HSR) [68]. In another study carried out in an Allergy and Clinical Immunologic, from more than 50 000 cases included, 1000 had drug hypersensitivity (DH) with NSAIDs being the most important drugs involved [66].

Focusing only on cutaneous adverse reactions, a study reported by Kasemsarn *et al.* showed that urticaria associated or not with angioedema was the most frequent entity (54%) followed by maculopapular exanthema. Ibuprofen was the most important drug involved followed by COX-2 inhibitors. Clinical entities included within SNIDHR like FDE, DRESS and SJS were reported in a much lower proportion [65]. Messaad *et al.* [4[•]] evaluated a large group of subjects with suspected DH in a wide age range, and NSAIDs were the drugs more commonly involved in reactions after confirmation by challenge. However, in this study, the type of reactions to NSAIDs following the ENDA classification could not be established as ASA was not given for discriminating cross-intolerants from selective responders.

Regarding the NERD, different studies have provided information concerning prevalence of NERD with variable results according to the criteria for patient selection. A recent survey conducted in 22 centres in 15 European countries random samples of cases aged 15–74 years old were selected by a questionnaire, with a total number of more than 62 000 participants. The mean prevalence of dyspnoea induced by NSAIDs was 1.9% with the highest values in Polish centres (4.9–6%). The prevalence of NERD was higher in participants with chronic rhinosinusitis symptoms, asthma symptoms in the last 12 months, hospitalization due to asthma, and adults vs. children, but was not associated with allergic rhinitis [69^{••}].

Concerning both respiratory and cutaneous reactions according to ENDA classification (Table 2) in a large study that evaluated more than 600 cases confirmed as DH, the 76% had cross-intolerance and the 54% were selective responders. The most relevant drug for cross-intolerants was ibuprofen and for selective responders pyrazolones [3]. In this study, the frequency of the different entities following the ENDA classification is the highest for NIUA followed by, SNIUA and NERD [3]. As in these studies, subjects with any type of chronic urticaria including CSU were excluded the frequency of NECD was not known. Although anaphylaxis to NSAIDs is mainly reported in SNIUAA with a significant difference compared with NIUA, this entity has been also observed in the cross-intolerant group [3].

NSAIDs are, in the absence of urticaria, the first cause of isolated AE being ibuprofen and diclofenac the most common triggers, as well as other NSAIDs strong COX-1 inhibitors [70]. However, as these cases were not challenges by either ASA or an alternative strong COX-1 inhibitor, we cannot correctly classify the cases [29].

Although within the NSAID-HR, the contribution of a T-cell mechanism in SNIDHR is lower than 20% the number of clinical entities is quite diverse

as shown in Table 2. Only nonimmediate urticaria, serum-like syndrome (SLS) and exanthema can pose problems in the identification whether they are cross-intolerants or selective responders. Many studies focus in SNIDHR in the context of ADR with cutaneous involvement but focusing only on those entities mentioned above; there are no data available on prevalence [71–74].

Concerning drug involved for cross-intolerant in most series propionic acid derivatives, particularly ibuprofen and other drugs of the same group are the most frequent NSAIDs involved followed by diclofenac and the other NSAIDs that are strong COX-1 inhibitor. For immediate selective responders, dipirone is the most frequent but propionic acid derivatives are also gaining relevance in this [1,3]. For selective responders of nonimmediate type, any drug can induce a reaction, and some propionic are quite relevant in photo-contact dermatitis and oxicams and COX-2 inhibitors in severe reactions [38,39]. Groups, structures and specific drug names of NSAIDs are shown in (Fig. 1).

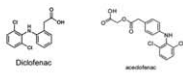
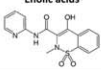
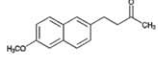
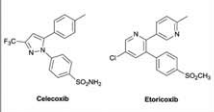
Single NSAIDs-induced delayed hypersensitivity reactions

Among NSAIDs, pyrazolones are the drugs most frequently involved in cutaneous exanthemas. Etoricoxib, metamizol and oxicams are frequently reported as the cause of FDE and generalized bullous FDE [71,75,76], and NSAIDs of the oxicams group have been associated with high risk to develop SJS/TEN [77]. Although antipyretics and analgesic NSAIDs are held responsible for inducing SJS/TEN, in some published case reports, case–control studies did not find an association [77].

CLINICAL ENTITIES

NSAIDs exacerbated respiratory disease

Patients develop nasal symptoms usually after the 3rd decade of age consisting on nasal discharge, rhinorrhoea, sneezing and more constantly nasal blockage usually appear several years later. The sequence of symptoms is described elsewhere [7,78,79], although this is not always the rule. Skin rash and erythema may appear in some cases, and in severe cases, an anaphylaxis may occur, but these are not the first symptoms appearing and follow the respiratory ones [80–83]. Isolated upper respiratory and/or conjunctival symptoms can also occur [84]. The Sampter's triad occurs exceptionally in children [21,22^{••}], although cases of bronchospasm have been reported [19^{••}]. However in these studies, whether cases were cross-intolerant or selective

Salicylic acids 	Acetyl salicylic acid (ASA), Salicylic acid, Diflunisal, Salisalates.
Carbo and heterocyclic acetic acids 	Indomethacin, Sulindac, Ketorolac, Etodolac, Tolmetin.
Propionic acids 	Ibuprofen, Loxoprofen, Naproxen, Ketoprofen, Desketoprofen, Fenoprofen, Flurbiprofen, Indoprofen, Tiaprofenic acid, Oxaprozin.
Phenylacetic acids 	Diclofenac, Aceclofenac.
Enolic acids 	Meloxicam, Piroxicam, Tenoxicam.
Fenamic acids 	Mefenamic acid, Flufenamic acid, Meclofenamate.
Para-aminophenol derivative 	Acetaminophen
Pyridinic sulfonamide 	Nimesulide
Naphthyl alkanone 	Nabumetone
Pyrazolone derivatives 	Dipyrone, Propifenazone, Phenylbutazone, Oxyphenylbutazone, Acetaminophen.
Diaryl heterocyclic acids 	Celecoxib, Valdecoxib, Etoricoxib, Rofecoxib, Paracetamol, Lumiracoxib
Benzothiazoline 	Tiamide*

*Tiamide is considered a NSAIDs that does not inhibit the COX enzymes.

FIGURE 1. Groups, structures and specific drug names of NSAIDs.

responder is not always clarified. In a recent study carried out in children from the total subjects confirmed as cross-intolerant, only the 3.3% developed isolated respiratory symptoms [19^{***}]. Severe respiratory has been found in children [85,86[†]].

NSAIDs exacerbated cutaneous disease

This entity appears in the context of a CSU that may aggravate or reactivate and can be associated with angioedema [7]. In the more severe cases, anaphylaxis may occur [87]. The percentage of subjects with CSU that develop NECD after strong COX-1 administration varies from 5 to 20% [7], but we cannot identify a specific profile for establishing the risk. Time interval of symptoms appearance can vary between 15 and 20 min to several hours or even longer. The natural course and the evolution depend on the CSU activity. It is suspected that after resolution, subjects may tolerate NSAIDs [7].

NSAIDs-induced urticaria and angioedema

As stated above, it is in fact the most common entity evaluated in allergy centres, being also the higher confirmed by challenge [3]. This statement is now been confirmed by many Allergy Services who deal with HDR elsewhere. More than 50% of patients develop symptoms in 1 h or less, with the remaining between 1 and 6 h and less likely after 6–24 h after NSAID intake [3,19^{***}]. The most common clinical entity is urticaria, but in a low percentage of cases anaphylaxis may appear. There is a good agreement between symptoms reported by the patients and the results of the challenge [3,88]. Often cases developed several episodes alternating with good tolerance to other NSAID. In these cases, multiple selective response to NSAID may occur [89], as will be detailed below.

Whether NIUA can evolve to NECD in the natural course has been proposed by some [90]. But in one study published by our group, these patients do not develop CSU after a long period of follow-up [91]. Furthermore, in a series of patients re-evaluated in a period longer than 6 years, the possibility of becoming tolerant exists [92].

Mixed reactions

Although some authors define cases with respiratory and cutaneous involvement as blended reactions [12], we prefer to define them as mixed reactions. In mixed reactions, symptoms do not follow the acute episode of bronchospasm induced by NSAIDs, rather, we found at the same time combination of skin and airways or even skin symptoms precede the respiratory ones. In one study, these mixed reactions were much more frequent than NERD [3]. According to actual classifications, when two different organs are involved after the release of histamine and other vasoactive mediator, we can classify it as anaphylaxis [23].

Single NSAIDs-induced urticaria, angioedema and/or anaphylaxis

There are significant differences in the time interval of reaction appearance after NSAIDs intake and appearance of symptoms between this entity and NIUA, although we must consider 1 h as a cut-off point for both. Symptoms may appear at several hours up to 24-h time interval. Although it is difficult to establish a cut-off point, for BL it is considered than more than 1 h we must classify as nonimmediate reactions and exclude IgE mechanisms [93]. In case of some NSAIDs, this separation can be arbitrary as the IgE response can be due to a drug metabolite requiring a time for generation. Other alternative is that we must consider them as accelerated reactions, and therefore, they will be classified as SNIDHR.

The most common frequent clinical entity is anaphylaxis often severe like occur with dypirone and diclofenac, appearing in more than 50% of the cases. We must also include in this section selective respiratory responders. Recently, our group has reported a series of 10 cases with nasal and/or lower airways involvement symptoms after the intake of paracetamol or other NSAID, but with good tolerance to ASA confirmed by challenge [94^{***}]. If these cases are supported by other groups, we have to reconsider the current classification. Another entity identified by us is multiple selective responders to NSAIDs with good tolerance to ASA [89]. In those cases of proven hypersensitivity to two or more NSAIDs, not chemically related, they must not be considered as cross-intolerant until a positive response to ASA is verified.

Single NSAIDs-induced delayed hypersensitivity reactions

Within this category, the number of entities is diverse and heterogeneous as shown in Table 2. We will not enter in detail and only consider relevant those that may cause confusion with cross-intolerant. These are nonimmediate urticaria and serum sickness like syndrome (SSLS). Only when pass events are recorded in some cases due to the inaccuracy of the patients reports doubt may occur between exanthema and urticaria but not with the other outlined above [37^{*}].

SSLS is characterized by urticarial rash accompanied by polyarthritis and fever have been reported with naproxen with good tolerance to ASA and ibuprofen [44]. Other cases have also been reported and attributed to immunocomplex diseases (serum skinless reaction) without providing further detail supporting these mechanisms [43]. A series of cases with accelerated urticaria due to amoxicillin point

out that this was a T-cell-dependent mechanisms with participation of CD4 and CVD8 lymphocytes with increased expression of homing and cell activation markers [95]. From these data, we may extrapolate the same mechanism in SSLS induced by NSAIDs. In a large series of 137 cases who developed a selective response to metamizol, 16.7% of the cases developed symptoms in a time interval of more than 1 h [37^{*}]. However, the mechanisms have not been studied.

DIAGNOSIS DIFFICULTIES

Diagnostics procedures (*in vivo* and/or *in vitro*) aimed to the diagnosis of SNIUAA are based on the detection of IgE antibodies. Skin testing is only valid for pyrazolones, with a sensitivity not higher than 50% [96]. For the rest of NSAIDs, no validated series are provided, although there are single individual cases. Immunoassays have been developed with ASA [97], propifenazone [98] and paracetamol [99] without further validation by other groups. BAT assays have been tried with good results for pyrazolones [96,100] but are not recommended for cases with cross-intolerance [101,102].

Although for SNIDHR the diagnosis relies mainly in clinical evaluation of the reaction or drug challenge in non-severe cases, positive intradermal and/or epicutaneous test to NSAIDs has been reported [103]. Concerning accelerated urticaria or SSLS, no studies have been carried out, but the same procedure use for the other T-cell responses can be used. As in cross-intolerant responses, diagnostic tests are not useful, we need to rely upon clinical history and DPT for assessing the diagnosis.

The most common organ involved in HR-NSAID is the skin, although severe T-cell reactions can be easily differentiated with the clinical course, in which patients developed exanthema and/or urticaria often accompanied by systemic symptoms and the clinicians faced with a number of problems for taking a decision. The most common example is urticarial or urticaria-like reactions. In Table 2 are shown the mechanisms and clinical characteristics as well as other criteria useful to validate urticaria accompanied or not by systemic symptoms.

PHARMACOGENETICS

Due to the different underlying mechanisms associated with HR-NSAID [6,36], the target genes in these studies vary depending on the type of reaction. In this section, we are focusing in cross-intolerant, in which NERD is the most studied model [29]. It has been associated with variants in genes involved in arachidonic acid pathway [104–106], in cytokines

[107], in antigen presentation (HLA) [108–111] and in other genes as *CEP68* [112]. Concerning NECD, associations with arachidonic acid pathway have been also found [113]. In relation to NIUA, significant relationship with variants involved in arachidonic acid pathway has been found once again [114–116], together with variants in cytokines [117–119], genes involved in mast cell activation [120], genes related to Ca^{2+} , cyclic AMP (cAMP) or p53 signalling pathways [121] and others like *CEP68* [122]. Furthermore, Kim *et al.* [123,124] conducted several studies in a group of patients with NECD and NIUA, all together, in which associations with variants in *IL18* and *ADORA3* genes were found.

Concerning histamine homeostasis [125], several studies have been done in cross-intolerant, finding a SNP in diamine oxidase which is significantly related to all the clinical entities, but mostly associated with NERD [126]. Ayuso *et al.* [127] conducted a study trying to relate cross-reactions and their clinical presentations with histamine receptors, without conclusive results.

Although great efforts have been done to elucidate the genetic and molecular basis of NSAIDs hypersensitivity [128,129,130–132], lack of replication studies together with the complex phenotyping of these reactions [9,89] has led to inconclusive results that do not allow to establish robust genetic biomarkers for these disorders. Hence, further investigation in this field is necessary to identify genes and polymorphisms involved in these disorders and to be able to translate these biomarkers as putative tools in clinical practice.

CONCLUSION

As NSAIDs hypersensitivity reactions are the most common causes of HDR, sufficient number of patients is warranted in many centres that are actually working in this line of research. In Spain as a consequence of the networking on drug allergy carried out by the Network for the Study of Adverse Reaction to Drugs, significant progress has been made that will continue in the coming years. This includes not only a detailed phenotyping but on set-up close collaborations with pharmacologists and organic chemists for identifying the metabolites and the protein targets to which these drugs are bound. New technologies like Next Generation Sequencing, which allow us to carry out an exhaustive analysis of candidate genes, hold great promise in this field, as these procedures have been successfully used to identify biomarkers in other diseases [133]. In addition monitoring of the acute phase, as has been carried out in others studies of drug allergy like the monitoring of the acute phase [135], the

transcriptomic analysis of peripheral blood and the skin [137] and the contribution of how histamine and other vasoactive mediators are metabolized [138] can be relevant for understanding the mechanisms involved in these reactions (Fig. 1).

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Conflicts of interest

There are no conflicts of interest.

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