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Endotypes in Immune Mediated Drug Reactions: Present and Future of Relevant Biomarkers. An EAACI Task Force Report

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ABSTRACT

Drug-induced immune reactions are an important burden for patients and health systems. They can be classified into immediate-drug hypersensitivity reactions (IDHRs) and delayed-DHRs (DDHRs) based on their phenotype. Drugs do not always behave as allergens and need to bind to proteins, forming adducts. Therefore, IDHRs can be classified as antigenic (IgE, and IgG mediated) and nonantigenic immune responses (complement activation-[CARPA], mas-related G-protein coupled receptor member X2 [MRGPRX2], cyclooxygenase [COX]-1 and cytokine release reactions [CRRs]). DDHRs are even more complex due to the different cell subsets and mechanisms involved, showing both antigenic and nonantigenic immune responses too. Since different endotypes result in similar phenotypes, the establishment of specific biomarkers is essential for an accurate diagnosis, with important relevance for the management of patients, as well as for risk stratification. The biomarkers of clinical utility are skin tests, specific IgE (sIgE), tryptase, and some HLA-DR genotyping. The diagnostic performance depends on the responsible drug. This review highlights that, unfortunately, most biomarkers have not gone beyond analytic or clinical validity. It is therefore important to set up multicentre translational studies to advance the validation process towards reaching a clinical utility phase.

1 | Introduction

The prevalence of drug hypersensitivity reactions (DHRs) is increasing in both adults and children, according to studies in populations from Europe and the United States [1], probably due to the higher consumption and heterogeneity of the pharmacological molecules for treating diseases. DHRs can be divided into immediate (IDHRs), when symptoms' onset (like urticaria, angioedema or anaphylaxis) occurs within the first hour after drug administration, and delayed DHRs (DDHRs), when symptoms (urticaria and maculopapular exanthema [MPE] or more severe ones like drug rash with eosinophilia and systemic symptoms [DRESS], acute generalized exanthematous pustulosis [AGEP], Stevens-Johnson Syndrome [SJS] or toxic epidermal necrolysis [TEN]) appear more than 1 h after drug administration [1]. Although useful in routine clinical practice, this classification has several

limitations. Thus, recently, the European Academy of Allergy and Clinical Immunology (EAACI) has updated the classification of allergic reactions [2]. However, concerning DHRs, this new nomenclature does not fit with all types of reactions. Drugs do not always behave as allergens and can interact with the immune system in different ways. Therefore, the pathogenesis of hypersensitivity reactions goes beyond Coombs and Gells classification and can be divided into antigenic (covalent binding) and nonantigenic (noncovalent binding) immune responses. Consequently, the most useful classification would be based on both phenotypes (drug exposure, timing, symptoms, and severity) and endotypes (mechanisms), including the particular biomarkers [3, 4]. On this basis, IDHRs can be further and endophenotypically classified into those driven by an antigenic-immune response, including both specific immunoglobulin E sIg-(E)- and/or –(G), and those induced by a nonantigenic-immune response, like complement activation-(CARPA), direct interaction with the mas-related G-protein coupled receptor member X2 (MRGPRX2), cyclooxygenase-1 (COX-1) inhibition, or cytokine release reactions (CRRs) [4]. DDHRs are even more complex due to the different cell subsets and mechanisms involved showing also both antigenic or nonantigenic immune responses [5].

Based on precision medicine, the establishment of specific biomarkers is essential for an accurate diagnosis, allowing endophenotyping of each DHR, with important relevance for the management of patients, as well as for risk stratification [6]. Therefore, the main aim of this review is to shed light on the mechanisms involved in DHRs, as well as on the most suitable biomarkers associated with each specific mechanism [7].

2 | Definition and Characteristics of Biomarkers

Lately, the interest in the identification, validation and qualification of biomarkers for unveiling mechanisms of disease, medicine assistance, or treatments has increased. The Biomarkers, EndpointS and other Tools (BEST) resource describes a biomarker as "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions" [7].

BOX 1 | An ideal biomarker should.

- Be reliable and easily quantifiable.
- Show quantitative demonstrable differences.
- Correlate with a relevant clinical outcome.
- Be consistent, fast, and economical.

An ideal biomarker should be used in clinical practice to select the accurate management to increase treatment success [7] and should have several characteristics (Box 1). Biomarkers can have different aims: susceptibility/risk, diagnostic, prognostic, and monitoring biomarkers, mostly used for patient selection/stratification, and/or enrichment, and efficacy measurement.

Successful implementation of new biomarkers will depend on their discovery and validation process by regulators that facilitates their harmonized use [7]. According to European and United States´ regulations (Regulation (EU) 2017/746 on in vitro diagnostic medical devices and European Union, 2012 FDA Safety and Innovation Act, 2016 21st Century Cures Act), after the discovery, the biomarker approval should be based on several phases [7] (Figure 1):

1. Analytical validity: the accuracy, precision, and reproducibility that permit a biomarker to measure what it is intended to.
2. Clinical validity: its ability to identify the feature of disease/treatment outcome with data about sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios.
3. Clinical utility: its ability to offer useful and safe information (high benefit/risk ratio) on diagnosis, treatment, management, or prevention of a disease [7]. It is required to determine how well a test balances benefits and harms when used in patient management.

Afterwards, the biomarker qualification process includes several steps (Box 2).

3 | Mechanism and Biomarkers in IDHRs Induced by Antigenic–Immune Response

IDHRs vary in the severity of the reactions, with urticaria with or without angioedema and drug-induced anaphylaxis being the most common ones in adults and less frequent in children.

The antigenic immune responses most frequently involved in IDHRs imply production of drug-sIgE with mast cells (MCs) and basophils as main effector cells involved. In antigenic-immune IDHRs, a prior phase of sensitization with the culprit drug is

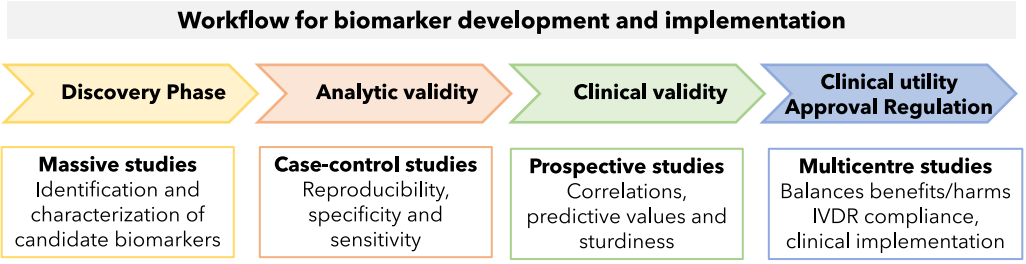

FIGURE 1 | Workflow for biomarker development and implementation.

BOX 2 | Biomarker qualification process.

- Potential benefits and risks associated with context of use (COU).
- Existing evidence supports the COU, as well as the scientific knowledge gaps and how they will be addressed.
- Description of the measurement method.
- Feasibility of and risks associated with their measurement.
- Relationship of the measurement to the disease/population area.
- Biological rationale for use of the biomarker (if known).
- Assay considerations (analytical validation and understanding of potential sources of variability in the measurement).

required [8], with subsequent production of sIgE that binds to high-affinity receptors (FCεRI) on basophils and MCs, with the capacity to recognize the drug on further exposures, triggering their activation and degranulation leading to the release of cytokine and proinflammatory mediators such as histamine, tryptase, cysteinyl leukotrienes, and prostaglandins, responsible for the clinical symptoms [6, 9]. In this case, multivalency of the drug/hapten-carrier complex is needed, although monovalent complexes have also been suggested to induce degranulation by mobilizing and redistributing FCεRI [10].

Besides, 10%–20% of patients with anaphylaxis do not present signs of IgE-dependent reactions, suggesting another potential mechanism [11]. Recently, a sIgG-mediated mechanism, mainly described in animal models but also in humans, has been proposed through the formation of sIgG-drug immune complexes interacting with IgG receptors (FCyR) on different cell populations, including MCs, basophils, neutrophils, and monocytes [9, 11]. Nevertheless, due to the lower affinity of FCyR, to elicit an IgG-mediated IDHR, a larger amount of the drug must be administered, typical of parenteral administration or treatments with biologics [9]. Moreover, both sIgE- and sIgG-mediated mechanisms can coexist, as well as the complement activation by drug-sIgG immunocomplexes and release of anaphylatoxins (C3a and C5a) that trigger MCs activation, increasing the reaction severity [11].

3.1 | Biomarkers in IgE-Mediated IDHRs

Determination of serum histamine and tryptase during the acute phase of the reaction has traditionally been used to assess basophil/MCs activation in IDHRs compared to baseline levels [6]. However, these biomarkers provide little information on the pathomechanism involved since, besides in IgE-mediated reactions, they can also be elevated in reactions induced by a nonantigenic immune response [12]. Moreover, sampling during the acute phase, lack of information on the drug involved, and the baseline heterogeneity levels between subjects make baseline level information necessary and routine clinical sampling difficult [3]. Similarly, other biomarkers released after basophil/MCs degranulation such as leukotrienes and prostaglandins also disappear shortly after the acute phase [3] and, although they persist longer in urine samples, their measurement in such samples makes their clinical use difficult (Figure 2A, Table 1) [6].

Immediate-reading skin test (ST), both skin prick test (SPT) and intradermal test (IDT) are good in vivo biomarkers for detecting sIgE-mediated reactions, in both adults and children, although with moderate results and with their sensitivity depending on the nature of the drug [9, 24, 43]. Interestingly, up to 15% of patients with IDHRs were negative for ST, suggesting an alternative mechanism responsible for MCs activation [9].

The most suitable biomarker for IgE-mediated IDHRs is the detection of serum sIgE, widely determined using immunoassays like the commercially available fluorometric enzyme immunoassays (FEIA), although only available for a limited number of drugs [9, 65, 72] such as betalactams (BLs), nonsteroidal anti-inflammatory drugs (NSAIDs), fluoroquinolones (FQs), chlorhexidine, or neuromuscular blocking agents (NMBAs) among others, with variable and moderate sensitivities but high specificities. When commercial FEIA is not possible, in-house radioimmunoassay (RIA) has been used for diverse drugs [65]. However, the lack of standardization and the use of radiolabelled antibodies make their inclusion in clinical routine difficult. Recent advances in nanotechnology open the doors to new materials with different physicochemical characteristics that can help reach standardization and more sensitive results [73, 74], as well as effective methods to remove serum IgG which, due to its high abundance compared to serum sIgE, could interfere in its detection (Table 1) [12].

The expression of CD63 and CD203c on basophils after the incubation with the culprit drugs/metabolites constitutes good in vitro biomarkers for the evaluation of sIgE-IDHRs in the basophil activation test (BAT) [25–27, 43, 75, 76]. Nevertheless, the determination of the most suitable activation marker is important to improve its sensitivity, although it seems to be highly dependent on the drug involved and the clinical entity studied [28, 29, 72]. Although relevant advances have been made in recent years to standardize procedures, there is still a limitation related to BAT sensitivity and heterogeneity [72, 77]. Moreover, CD63/CD203c expression does not exclude a non-IgE mediated mechanism, although anti-IgE biological agents (omalizumab), IgE-FCεRI disruptors (DARPins) [78], or protein Bruton's tyrosine kinase inhibitor (ibrutinib) [79] could be used to indirectly confirm the IgE-mediated. Therefore, despite its potential use in clinical diagnostic routine complementing ST, maintaining patients on first-line treatment or leading to delabelling and guiding the desensitization process in IDHRs to chemotherapeutics [3, 43], BAT has not been implemented in clinics [72, 77].

In recent years, mast cell activation test (MAT) has emerged as a promising technique that overcomes some limitations of BAT. Expression of CD63, CD203c, and CD107a as a consequence of drug exposure after MCs sensitization with patient serum is the most commonly used biomarkers [29]. Detection of externalized granule matrix formation using cationic

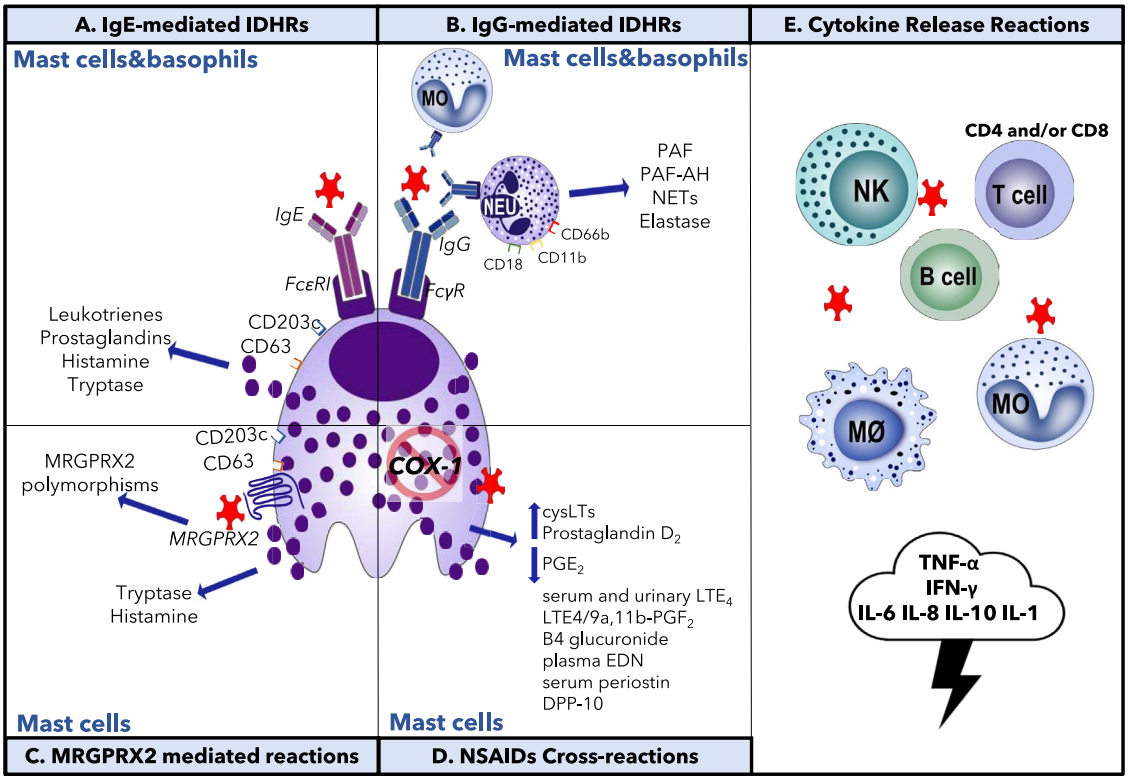

FIGURE 2 | Endotypes and biomarkers in immediate drug hypersensitivity reactions (IDHRs).

fluorescent avidin probes [29] or externalized histamine using fluorescent diamine oxidase (DAO), and the cytosolic Ca^{++} staining [29] is also used. For IgE-mediated reactions, MAT appears to be less sensitive than BAT [75], because MC lines show a reduced ability to bind to IgE after several weeks of culture, and it also requires serum with high sIgE titres, which are not frequent for IDHRs [75, 80]. To overcome these limitations, drug-conjugated nanoarchitectures are promising to determine the specific requirements for effective degranulation [35]. The combination of BAT and MAT results can provide important information regarding the mechanism involved, helping to differentiate between mechanisms induced by antigenic vs. nonantigenic immune responses [75].

3.2 | Biomarkers in IgG-Mediated IDHRs

Different biomarkers have been proposed to assess these reactions (Figure 2B, Table 1). The interaction between drug-IgG complexes with FCyR on different immune cells triggers receptor internalization [81], and can be used as a biomarker. Besides, neutrophils seem to be relevant effector cells, mainly related to the most severe reactions. To assess neutrophil degranulation, the release of mediators such as neutrophil extracellular traps (NETs) and platelet-activating factor (PAF) [11] with or without histamine, or the quantification of PAF-acetyl hydrolase have emerged as useful biomarkers [3, 11]. Moreover, neutrophil activation markers such as CD18, CD11b, CD66b, or elastase can also be used, although other cell populations such as monocytes may also play an active role in IgG-mediated IDHRs.

4 | Mechanisms and Biomarkers in IDHRs Induced by Nonspecific Activation of the Immune System

4.1 | Mechanisms and Biomarkers in MRGPRX2-Mediated Reactions

Positively charged drugs (i.e., NMBAs, FQs, icatibant, ...) can induce IDHRs by nonantigenic immune response through the activation of the MRGPRX2 receptor that could happen within the first exposure to the drug [82]. This receptor is predominantly expressed in skin MCs, and its engagement requires sustained high plasma/tissue drug concentrations [83]. Although plausible, currently there is no irrefutable evidence that this receptor may play a role in human pathology. Importantly, the above-mentioned drugs are also able to induce IgE-mediated reactions, and the half-maximal effective concentration (EC50) required for MRGPRX2 activation often exceeds the peak plasma concentrations observed in vivo [82, 83].

At present, no specific biomarker has been identified for this mechanism. It is suspected after ruling out reactions induced by antigenic immune response combining clinical information and results of routine and research examinations [9, 41, 83]. Drug naivety, high dose, and presence of comorbidity (i.e., chronic urticaria) as prerequisite for their occurrence, and fast resolution of (cutaneous) symptoms represent possible *clinical* biomarkers. Recent in vitro [38] and in vivo [49] tests show that neither the increase of tryptase nor positive ST can be used as *diagnostic* biomarkers for distinguishing IgE vs. MRGPRX2 mediated reactions. Although it is tempting to speculate that in the case

TABLE 1 | Biomarkers in DHRs. Evidence level in different pheno/endotypes, technical validation and development stage.

Phenotype	Endotype	Biomarker & evidence Level	Assay performance	Results	Technical implementation and comments	Development stage
Immediate urticaria, anaphylaxis, angioedema	IgE-mediated	Serum tryptase [3, 6, 13–16]	SENS: 37.5%–78%; SPEC: 86%–94%	> 1.2× baseline+2 ng/mL > 1.68× baseline in HαT patient's	Only to be used retrospectively Short half-life (30′-2 h) and poor stability High interpatient variability then levels should be referenced to baseline data No information on drug or endotype of reaction.	Clinical utility
		Serum histamine [6, 14, 17–19]	SENS: 40%–70%; SPEC: 99%	> 1.2 ng/mL × baseline histamine	Only to be used retrospectively Short half-life (< 15′-1 h) and poor stability. High interpatient variability then levels should be referenced to baseline data No information on drug or endotype of reaction.	Analytic/ Clinical validity
		Skin test [9, 15, 17, 20–22]	SENS: 20%–95% SPEC: 80%–97%	> 3 mm wheal than that of the negative control with erythema	Relatively noninvasive, inexpensive, and rapid results. Useful for determining drug cross-reactivity Highly dependent of the drug. Need of trained personal and adequate place to reverse potential anaphylactic reactions. Need for using nonirritant drug concentrations. Lack of knowledge about the specific drug chemical structure IDT more sensitive than SPT, but higher risk	Clinical utility
		sIgE [9, 17, 23]	SENS: 0%–92% SPEC: 54%–100%	> 0.35KU/L > 0.10KU/L sIgE/tIgE > 0.002 (only BLs)	Serum can be stored for long time, easy transport and automation. Commercial immunoassay available for a limited number of drugs. Sensitivity highly dependent on the drug Sensitivity reduction over time High false positive results in BL and NMBA Complexity due to the need of drugs to bind to carriers. Different drug structures to be included. New solid phases to improve synthesis and reproducibility. Need of removing IgG that interfere IgE binding. Development stage is drug dependent	Clinical validity/ utility

(Continues)

TABLE 1 | (Continued)

Phenotype	Endotype	Biomarker & evidence Level	Assay performance	Results	Technical implementation and comments	Development stage
		BAT [24–34]	SENS:13%–90.91% SPEC: 73%–100%	% CD63/CD203c SI CD63/CD203c	Need for fresh blood Highly dependent on the drug and patient population Free drugs and metabolites can be included Sensitivity reduction over time Specific disruptive anti-IgE inhibitors could be used to confirm an IgE-endotype Inclusion of cofactors to improve sensitivity Development stage is drug dependent	Analytic/ Clinical validity
		MAT [25, 35–37]	No data available	Upregulation of CD63, CD203c and CD107a Detection of externalized granule matrix Cytosolic Ca^{++} staining	Lack of data for thresholds, reference values, techniques or biomarker validity Lack of case–control or prospective studies with different drugs Variety of mast cell lines with reduced and variable expression of FCεRI Need for inclusion of sera with high titres of sIgE	Analytic validity
	IgG-Mediated	sIgG [11, 30]	No data available	No data available	Lack of data for thresholds, reference values, techniques or biomarker validity Lack of case–control or prospective studies	Analytic validity
		Neutrophil activation [11, 30]			Although neutrophils appear to play a relevant role in these reactions, more data are needed.	Analytic validity
		Platelet activating factor [14, 30]			Human and animal studies link PAF to an IgE-independent mechanism and severity of anaphylaxis	Analytic validity
	MRGPRX2	Tryptase [38, 39]	No data available for all the biomarkers	> 1.2× baseline +2ng/mL	IgE- and MRGPRX2-mediated reactions result in a release of tryptase with similar magnitude Lack of confirmatory test specific for MRGPRX2	Implementation
		Skin tests [39]		> 3 mm wheal than that of the negative control with erythemal	In MRGPRX2 mediated reactions to rocuronium higher concentrations are needed for positive intradermal test Lack of confirmatory test specific for MRGPRX2	Analytic/ Clinical validity

(Continues)

TABLE 1 | (Continued)

Phenotype	Endotype	Biomarker & evidence Level	Assay performance	Results	Technical implementation and comments	Development stage
		cBAT [40]		Upregulation of CD63 in conditioned basophils	Prestimulation with anti-IgE (conditioning) can induce a synergistic effect on basophil degranulation in IgE-responsive subjects after incubation with moxifloxacin. Lack of case–control or prospective studies with different drugs	Analytic validity
		Genetics [41, 42]		Genetic polymorphism	Genetic polymorphisms might explain individual susceptibility to MRGPRX2 mediated reactions to NMBAs, icatibant, and opioids Lack of case–control or prospective studies	Discovery
	Cytokine release reactions	Skin test	SENS: 11%		Large series of case–control studies are not available.	Analytic validity
		IL-6 [3, 43–47]	SENS: 76.3%	> 17.4 pg/mL or > 1.8 pg/mL		Clinical validity
		TNF, IL1, Serum amiloids			Biomarkers are not specific for cytokine release reactions.	Discovery
		BAT			A negative BAT to could be related to CRRs	Analytic validity
	Mixed reaction	Skin test			Lack of standardized procedures, including drug concentrations Biomarkers can't differentiate between the endotype of the reaction	Analytic/ Clinical validity
		sIgE				Clinical validity
		IL-6		> 17.4 pg/mL or > 10 pg/mL		Clinical validity
		TNF, IL1, Serum amiloids				Discovery
		BAT	SENS: 54%–66.6% SPEC: 95%			Analytic validity
		Tryptase [3, 43, 44, 46, 47]		> 1.2× baseline +2 ng/mL		Clinical validity

(Continues)

TABLE 1 | (Continued)

Phenotype	Endotype	Biomarker & evidence Level	Assay performance	Results	Technical implementation and comments	Development stage
NERD, NECD, NIUA	AA pathway	Urinary LTE_4 [48, 49]	SENS: 55%–81% SPEC: 77%–82% PPV: 65%–86% NPV: 66%–88%	Optimal thresholds 66–510 pg/mg Cr, according to methodology	Different odds ratio depends on the methodology. No standardized assessment. LTE4 and LTE4/$PGF_{2\alpha}$ could discriminate NERD from ATA.	Discovery
	AA pathway in MC activation	PGD2 and metabolite 9α,11β-PGF2 [48, 50]	No data available	No data available	Gas chromatography/mass spectrometry Methodology highly accurate and sensitive, not very efficient and expensive instrumentation NERD: Higher baseline plasma level than ATA 1.4× increase in plasma after ASA challenge	Discovery
NERD	Eosinophilic inflammation	Eosinophil Derived Neurotoxin [36]	SENS: 95% SPEC: 60%	Cut-off: 27.15 mg/mL	Genetic study ELISA assessment Biomarker to distinguish NERD from ATA	Discovery
	Epithelial cells	DPP10 [37] TGF-β1	No data available	Cut-off: 10.7 ng/mL	Cell culture, ELISA, Western Blot analysis DPP10 distinguish NERD vs. ATA	Discovery
	MCs activation	Serum or plasma tryptase [51]	No data available	> 10% × baseline	Variable results suggesting different endotypes of NERD Increased tryptase is directly related to uLTE4 levels and inversely related to FEV1 Increase less than 10%: higher basal level Increase more than 10%: higher level of LTE4 and PGD-M; lower level of FEV1 More studies are needed	Discovery
Delayed urticaria, MPE, DILIs, SCARs	T-cell mediated	Allele: HLA-B*57:01 [52, 53]	SENS: 45.5%–80% SPEC: 97.6%–99%	Presence	Hypersensitivity reactions to Abacavir PPV 55% Differences between ethnic's groups: Caucasian 82.8%, Black 12%	Clinical utility
		Allele: HLA-B*1502 [54, 55]	SENS: 75%–100% SPEC: 75%–100%	Presence	SJS to anticonvulsants Determined in Thai and Indian population	Clinical utility
		Allele: HLA-A31 [56]	SENS: 66.6% SPEC: 87.9%	Presence	Hypersensitivity reactions to Carbamazepine Determined in Japanese population	Clinical validity

(Continues)

TABLE 1 | (Continued)

Phenotype	Endotype	Biomarker & evidence Level	Assay performance	Results	Technical implementation and comments	Development stage
		Allele: HLA-B*5801 [57–61]	SENS: 55%–100% SPEC: 85%–98.5%	Presence	HSS, DRESS, SJS and TEN to allopurinol PPV 55% Determined in Han Chinese, Caucasian, Tai, Koreans population	Clinical validity
		Allele: HLA-B*13:01 [62]	SENS: 85.5% SPEC: 85.7%	Presence	Hypersensitivity syndrome to dapsone In Asia leprosy population	Clinical utility
		Skin test [52, 63, 64]	SENS:58%–64% in AGEP 32%–80% in DRESS < 25% in SJS	**PTs:** + to +++ **IDTs:** dWD > = iWD +3 mm	**PTs:** Drugs can be used as parenteral or capsules format Drug powder can be prepared at 10% in petrolatum A control PT with the vehicle (e.g., petrolatum, alcohol) is needed Higher drug concentrations **IDTs:** Need for injectable drugs Irritating reagent concentrations can induce false-positive results Contraindicated in SJS-TEN and GBFDE with the suspected drug	Clinical utility Clinical utility
		LTT [65–68]	SENS: 58%–89% SPEC: 85%–100% Mainly for BLs/ anticonvulsants	SI above 2–3	Difficulty with samples due to steroid treatment Difficulty with new drug modalities Difficulty to include specific drug metabolites responsible for the reaction Inclusion of DC as APC increase sensitivity Effector cells assessment increase sensitivity Different endpoints or multiplexed endpoints might increase sensitivity in certain reactions Complex laboratory facilities are required	Analytic/ Clinical validity
		ELISPOT [69–71]	SENS: 33%–91% SPEC: 83%–98%		Mainly for BLs and anticonvulsants Case–control studies are required with multiple drugs and analytes	Analytic validity

Note: Validation stage and assay performance depend on the responsible drug. Validation stages: discovery (not validated); Analytic validity (case–control studies); clinical validity (prospective studies); clinical utility (multicentric studies towards a IVD qualification).

Abbreviations: AA, arachidonic acid; AGEP, acute generalized exanthematous pustulosis; AntDCs, dendritic cells; APC, antigen presenting cells; ATA, aspirin tolerant asthma; BAT, basophil activation test; BLs, Betalactams; cBAT, conditioned BAT; CRRs, Cytokine release reactions; DPP10, dipeptidyl-peptidase; DRESS, drug reaction with eosinophilia and systemic symptoms; dWD, delayed wheal diameter; FEV1, forced expiratory volume in 1 s; GBFDE, Generalized bullous fixed drug reactions; HSS, drug hypersensitivity syndrome; HαT, Hereditary alpha tryptasemia; IDHRs, Immediate drug hypersensitivity reactions; IDTs, intradermal test; iWD, initial wheal diameter; LT, leukotrienes; LTT, lymphocyte transformation test; MRGPRX2, mas-related G-protein coupled receptor member X2; NECD, NSAID-Exacerbated Cutaneous Disease; NERD, NSAID-Exacerbated Respiratory Disease; NIUA, NSAID-induced urticaria/angioedema; NMBAs, neuromuscular blocking agent; NPV, negative predictive value; PG, prostaglandins; PPV, positive predictive value; PTs, patch tests; SENS, sensitivity; sIgE/G, specific IgE or IgG; SJS, Stevens-Johnson syndrome; SPEC, specificity; TEN, toxic epidermal necrolysis.

of the MRGPRX2 endotype, IDTs are expected to be positive at higher nonirritative concentrations and are not inhibited by bruton tyrosin kinase inhibitors (BTKi) [41], further studies are needed. Thus, although no in vivo or in vitro assay can be used in isolation for the diagnosis of MRGPRX2-mediated reactions (Figure 2C, Table 1), the positive direct MC activation test (d-MAT) and in vitro analysis of "conditioned" basophils (i.e., stimulated basophils that upregulated MRGPRX2) could be used as tests to prove MRGPRX2 agonism. Moreover, passive MAT (p-MAT) based on sensitization with serum sIgE, MRGPRX2-silenced MCs, negative BAT (resting basophils do not respond to MRPGRPX2 stimulation), and T-lymphocyte activation tests (TATs) can be used to document an IgE endotype. In this sense, a theoretical mechanistic algorithm using an exclusion decision tree has recently been published [83]. Finally, MRGPRX2 polymorphisms are candidates as *genetic* biomarkers due to their potential significant impact on the responsiveness of the receptor to specific agonists [49].

4.2 | Biomarkers in Cross-Reactive NSAIDs Reactions

Being one of the most consumed drugs, hypersensitivity reactions to NSAIDs are common worldwide. These reactions can be induced by both antigenic and nonantigenic immune responses. Then, two main clinical conditions, namely NSAIDs-exacerbated respiratory disease (NERD) and NSAIDs-exacerbated cutaneous disease (NECD) are driven by nonantigenic immune responses in a cross-reactive (CR) way [84]. CRs is a pharmacological mechanism in which patients develop reactions to different chemically nonrelated NSAIDs through cyclooxygenase (COX)-1 inhibition that causes dysregulation of arachidonic acid (AA) pathways with a decrease in prostaglandin (PG) E2, which is important for controlling overproduction of cysteinyl leukotrienes (cysLTs) through the lipoxygenase (LO) pathway [84]. However, the pathophysiology of NERD is heterogeneous and complex, with an additional T2 inflammation resulting in persistent eosinophilic inflammation both in the upper and lower airway mucosa. Recently, chronic MC activation, as well as the interaction of epithelial cells and platelets with immune cells, has been suggested to be other outstanding pathways underlying the clinical manifestation of NERD [85].

So far, based on the underlying mechanisms of NERD and NECD, biomarkers related to the AA pathway, eosinophilic inflammation, MCs, epithelial cells, and platelets have been studied (Table 1). The most commonly studied biomarkers include serum and urinary LTE_4 [48] and the ratio $LTE_4/9a,11b\text{-}PGF_2$ [50], B4 glucuronide [86], plasma eosinophil-derived neurotoxin [36], serum periostin, and dipeptidyl-peptidase 10 [37] (Figure 2D). Among them, urinary $uLTE_4$ is considered the most available biomarker in NERD and NECD so far [49]. Suggestively, a recent meta-analysis showed that $uLTE_4$ is higher in NERD [49]. However, variations in measurement methods and unavailability in clinical practice limit its clinical utility. Increases in tryptase levels after MCs activation have been described in NERD and NECD [51] (Table 1), whereas platelet adherent leukocytes have also been related to NECD [87].

Although significant attempts have been performed for finding biomarkers in NSAIDs-induced reactions, they have not been incorporated into in vitro diagnosis since validation is deeply required. The identification of biomarkers in tissues other than peripheral blood would be of particular interest. Future studies should aim to standardize and increase the clinical significance and interpretability of the results.

4.3 | Biomarkers in Cytokine Release Reactions

CRRs phenotype can occur during first or after repeated exposures to a drug, mostly after the administration of biological or chemotherapeutic agents, such as platins [3]. The endotype underlying CRRs is not completely understood, but symptoms are hypothesized to be caused by the release of pro-inflammatory mediators, like IL-6, TNF-α, IFN-γ, IL-8, IL-10, and IL-1, from multiple cellular sources including monocytes, macrophages, endothelial cells, and T lymphocytes (mainly cytotoxic CD8 lymphocytes) (Figure 2E, Table 1) [44]. This could derive in a 'cytokine storm', an acute, severe, and potentially lethal reaction due to the release of large amounts of cytokines and chemokines, which could lead to systemic symptoms including multiple organ failure.

In vivo biomarkers, such as STs, are not useful to confirm a CRR phenotype [3, 43]. However, in vitro tests can show an increase in *TNF-α and IL-6 serum levels* during reaction compared to baseline values. IL-6 has been identified as an important biomarker that verifies this phenotype-endotype and correlates with thermal and hemodynamic changes accompanied by constitutional, cardiovascular, and neuromuscular symptoms [45]. Otherwise, BAT does not produce positive results in CRRs [43].

Additionally, patients suffering from CRRs can either switch into another phenotype or coexist along with IgE-mediated reactions, presenting a mixed phenotype [5]. Recently, a study has shown that patients allergic to oxaliplatin with initial IgE-mediated or mixed phenotype are more prone to switch to another phenotype compared to those with initial CRRs, who are more likely to continue in the same phenotype [5]. Moreover, although CRRs are considered IDHRs, they may appear more than 6 h after the infusion of the drug that elicited the reaction [46, 47].

5 | Mechanism and Biomarkers in DDHRs

The term DDHR covers a range of adverse events of varying severity and organ selectivity. Almost all marketed drugs are known to cause DDHRs, but reaction frequency varies greatly. T-cells are involved in the initiation, progression, and regulation of DDHR, bringing about tissue damage directly through the release of cytolytic molecules or indirectly through cytokine/chemokine release and the recruitment of different immune cells (e.g., macrophages, eosinophils, neutrophils...) (Figure 3). To initiate an immune response, the drug (metabolite or degradation product) forms a complex with HLA proteins, HLA embedded peptides, and/or the T-cell receptor [5]. The drug molecule essentially provides a molecular bridge

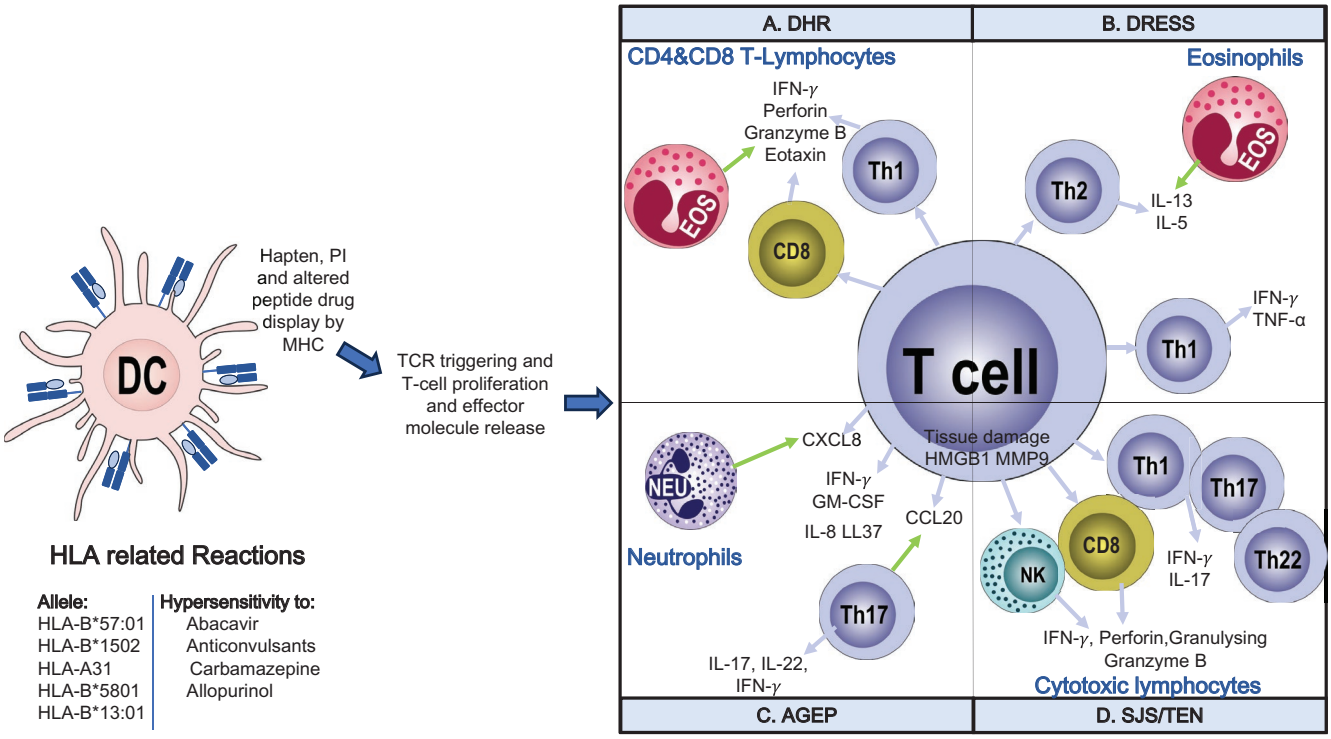

FIGURE 3 | Endotypes and biomarkers in delayed drug hypersensitivity reactions (DDHRs).

between the antigen-presenting cell (APCs), the T-cell, and the binding energy to initiate stimulatory T-cell signal transduction events. Three defining concepts explain the drug immune receptor interaction: hapten, pharmacological interaction (PI) and altered peptide repertoire that will determine how the drug is loaded on MHC and may initiate the same immune-mediated reactions.

5.1 | Hapten Hypothesis

For hapten recognition, the electrophilic drug (hapten), or a reactive metabolite, binds covalently to endogenous protein forming a hapten-protein adduct. The adduct is then processed within the APCs liberating hapten-modified peptides that bind to HLA proteins for presentation on their surface. The hapten structure is presumed to extend beyond the HLA peptide binding cleft and determine the specificity of T-cell binding interaction [88, 89]. This interaction will develop antigenic-immune IDHRs and DDHRs and requires a sensitization phase.

5.2 | Pharmacological Interaction

The PI concept states that drugs or metabolites bind directly, without APCs processing, to HLA proteins or HLA-associated peptides and cross-link T-cell receptors. Unlike hapten peptide binding, the interaction is labile and readily reversible; however, similarly, T-cell receives signals from the HLA protein, bound peptide, and drug [90]. These DDHRs are produced by a pharmacological interaction and can be named nonantigenic immune responses as covalent drug-adducts are not formed. This interaction can happen after the first drug exposure.

5.3 | Altered Peptide Repertoire

The altered peptide repertoire concept has been described for abacavir, which specifically binds to an HLA variant (HLA-B*57:01) deep within the HLA peptide binding cleft. Binding alters the binding cleft surface area, and when proteins are naturally processed, peptides with different amino acid sequences bind. T-cells are stimulated by this repertoire of novel peptides displayed on the cell surface, with little or no interaction between the T-cell receptor and drug [91]. These reactions are also nonantigenic immune responses.

5.4 | Biomarkers for DDHRs

Some drugs are mainly associated with specific forms of DDHRs; for example, flucloxacillin causes very frequent liver injury compared to other β-lactam antibiotics. However, flucloxacillin exposure is also associated with mild and serious skin reactions. These varied clinical presentations illustrate that a structural alert within a given drug moiety impacts whether a DDHR develops and the nature of the adverse event; however, as most individuals tolerate drugs with no noticeable adverse event, the primary determinant of susceptibility must lie within the individual's immune handling and perception of the drug. In this respect, the expression of single HLA molecules is strongly associated with antigenic and nonantigenic immune DDHR [52]. The sensitivity and specificity of a handful of drug *HLA DDHR associations* have resulted in HLA prescreening of patients before drug use, effectively eradicating the development of the adverse event (table 1, Figure 3) [53, 92]. However, as most individuals expressing an HLA protein associated with a specific DDHR tolerate the drug safely, additional factors must

determine susceptibility. Researchers have worked extensively to explore whether the expression of a specific T-cell receptor is key to developing a DDHR. However, it seems that different T-cell receptor clonotypes are activated in patients who develop a DHRs [93].

Alongside effector immune pathways, there is a complex network of regulatory pathways (cytokines, receptors, and cells) that work together to prevent effector T-cell responses to inadvertent antigens and to restrict the duration and impact of effector T-cells once activated [94]. The presence and activity of these immune regulatory pathways vary across individuals and within individuals throughout their life as they are impacted by environmental, disease-related, and genetic factors. This interindividual variation and lack of knowledge relating to drug-specific T-cell activation regulation pathways make it impossible to predict a DDHR currently. The use of checkpoint inhibitor therapy for cancer treatment, which is associated with an increased frequency of DDHRs [95], provides an ideal opportunity to dissect the importance of individual regulatory pathways in patient susceptibility.

Diverse in vivo (*STs*) and in vitro assays (*TAT*) have been developed and are widely used in specialist centers to diagnose both antigenic and nonantigenic immune DDHRs and to determine whether reactions might develop to closely related drug structures. The testing strategies available are the subject of extensive review [63, 66, 96]. ST is widely available in clinics but is restricted by the absence of test materials for many drugs and reduced sensitivity, which may relate to the drug not reaching the site of immune activation after application to the skin. In this regard, patch tests (PTs) and IDTs with delayed readings are the most valuable methods. IDTs are not recommended as first-line in severe DDHRs, but some centers perform it in patients with negative PT, circumventing its use to look for alternative drugs [63].

TATs (e.g., lymphocyte transformation test, multi cytokine ELIspot, molecule expression or cytokine release) display good sensitivity and specificity for many drugs (Figure 3, Table 1) [66, 69, 96, 97]; however, problems arise with (i) drugs that suppress T-cell responses due to their pharmacology (e.g., kinase inhibitors); (ii) specific clinical entities and severity of DDHR such as SJS-TEN or DRESS; and (iii) unexpectedly negative testing with the parent drug as the only testing reagent when stable or reactive metabolites are unavailable. Due to this heterogeneity, despite the good sensitivity/specificity balance, in vitro diagnostic testing is not always widely used in clinical use.

Several soluble secreted proteins (e.g., TNF-α, IFN-γ, perforin, granzyme B, granulising, HMGB1) from different cell sources and cell surface receptors (e.g., CCL27, CCR6, CCR10) are elevated in plasma or blister fluid of patients with the different severe DDHRs (Figure 3, Table 1) [98]. Most of these proteins have a direct role in the pathogenesis and measurement of their over-expression and may be useful as biomarkers. However, these proteins are unlikely to be specific, which might require a biomarker panel to differentiate between different forms of DDHRs. Progress in this area will benefit from the increased accessibility to single-cell sequencing methods for comparison of drug-tolerant and hypersensitivity patients expressing similar genetic risk factors and patients that develop different forms of adverse events. These methods will also identify functional subsets of immune cells that interact to initiate DDHRs.

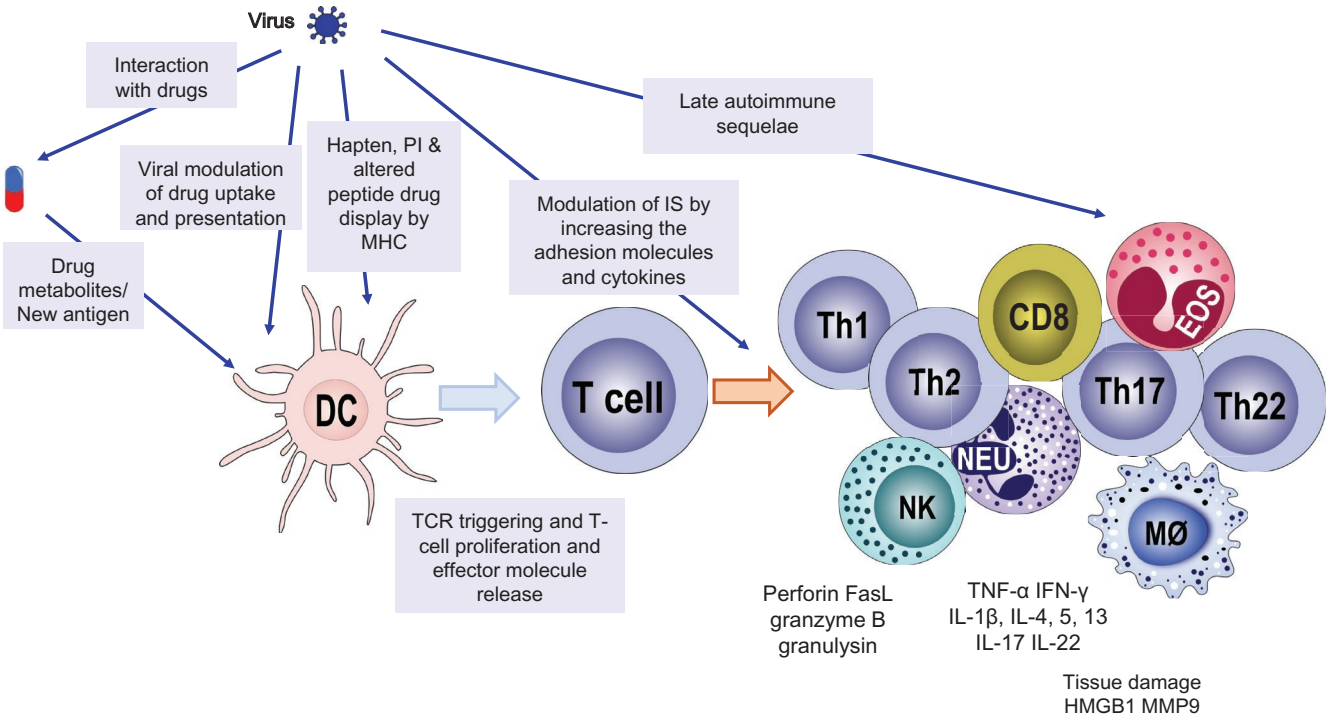

FIGURE 4 | Different mechanisms of infectious disease interactions with DHRs.

6 | Molecular Mechanisms of Viral Infections in DHRs

Viral infections and DHRs manifestations can influence each other since they can exacerbate or trigger DHRs through several molecular mechanisms, which often coexist (Figure 4). These mechanisms include viral-induced immune activation (activation of APCs, increased expression of costimulatory molecules, cytokine storm), molecular mimicry, viral modulation of drug metabolism, immune response, or enhanced drug uptake by infected cells. DHRs can also lead to viral reactivation via some of these immunological phenomena [99]. The topic can be complex due to the variety of viral infections, the number of culprit drugs, and the clinical manifestations.

More often, DHRs during viral infections are driven either by costimulation of T cells or increased expression of TCR/HLA. In homeostatic conditions, neo-antigens do not induce immune reactions. However, during viral infections, which are often systemic, they can be presented by APCs in an immune-stimulatory environment, characterized by high expression of adhesion molecules and cytokines (IFN-γ, TNF, IL-1, IL-6, etc.) promoting the reactions [100].

Moreover, DHRs during viral infections could happen through a p-i mechanism [101]. Since during viral infections, immune receptors are widely expressed, thus increasing the p-i avidity and subsequently allows more frequent immune interactions through the formation of an "*allo-HLA-peptide-TCR complex*" that may be sufficient for eliciting DHRs. These reactions occur in patients who have restricted TCRs or HLA that can be activated by the drug. P-i stimulation, with activation and expansion of many polyclonal cytotoxic $CD4^+$ and $CD8^+$ T cells, underlies severe DHRs like DRESS [101]. Moreover, the p-i-activation of T cells in DRESS has also been associated with the occurrence of late autoimmune sequelae, with a switch to a cytotoxic effector pathway in autoreactive T cells [101].

Sometimes the virus-DHR sequence of events is inverted: within a DRESS, a DHR can precede reactivation and herpes viraemia. This phenomenon may be partially explained through the massive immune stimulation during the acute phase within the p-i activated T-lymphocyte specific for endogenous herpes viruses [99] that can control viral replication, likely through IFN-γ release [102]. Virus-specific T-cells become cytotoxic due to the p-i stimulation, and when they encounter their target stimulus (i.e., HHV6, CMV, EBV) in the peripheral tissue, they attack the herpes-infected cells [103] and the intracellular herpes viruses are released, leading to viral reactivation. Some authors have correlated systemic cytokine storm with viral replication, as shown for TNFα and HHV6 [101], and severe, potentially fatal complications.

Special attention should be given to patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) who have been registered for DHRs, especially those documented during the first wave of the pandemic in 2020 and in cases of severe disease. These DHRs were characterized by important cutaneous involvement, eosinophilia, slow clinical improvement, and poor responsiveness to high-dose systemic corticosteroids in subjects with DRESS. Preliminary studies suggest that SARS-CoV-2 could induce DHRs indirectly by triggering a cytokine storm. Massive SARS-CoV-2 infection in airway epithelial cells or many other infected cell types via ACE2 and other potential receptors [104] lead to a cytokine storm [105], followed by hyperactivation of APCs [106] and T cell response to drugs. This is in line with the clinical findings that these DHRs mostly occurred during the later stages of SARS-CoV-2 infections and that almost only patients with severe infections were affected [107, 108].

7 | Conclusions

The mechanisms underlying DHRs are complex and diagnosis requires a detailed in vivo and in vitro assessment on an individual basis. Although recent developments provided more clues for biomarkers, most of them are still on analytic or clinical validity. The biomarkers of clinical utility are STs, sIgE, tryptase, and some HLA-DR genotyping. The diagnostic performance depends on the responsible drug. Major limiting factors in the identification of specific biomarkers are: (i) different endotypes result in similar clinical features; (ii) to date, some endotypes with different mechanisms are diagnosed by an exclusion process; (iii) the same drug might be associated with different endotypes which could coexist. Moreover, some already identified biomarkers (e.g., tryptase) are not widely available.

Therefore, it is important to set up multicentee translational studies in order to advance the process of validation toward achieving a clinical utility phase.

Author Contributions

Mayorga C and Sabato V should be considered joint senior author, Mayorga C, designed the position paper, and wrote the section "Definition and characteristics of Biomarkers" and the different versions to be discussed; Fernandez-Santamaria R and Mayorga C were in charge of the *Mechanism and biomarkers in IDHRs induced by antigenic-immune response section*; Sabato V wrote the section *Mechanisms and biomarkers in MRGPRX2-mediated reactions*; Çelik GE was involved in writing the *Biomarkers in Cross-Reactive NSAIDs Reactions*; Labella M was in charge of writing *Biomarkers in Cytokine Release Reactions*; Naisbitt D wrote *Mechanism and biomarkers in DDHRs* and Murdaca G and Sokolowska M were incharge of writing Molecular mechanisms of viral infections in DHRs. All authors have reviewed and agree on the final version.

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Conflicts of Interest

D.N. and G.M., declare no conflicts of interest. C.M. holds a contract from Nicolas Monardes Program (RC-0004-2021) from Andalusian Regional Ministry of Health. M.L. holds a contract from "Juan Rodes" program (JR23/0039) and R.F.S. from "Sara Borrell" program (CD23/00118) from the Institute of Health "Carlos III" of he Ministry of Economy and Competitiveness [grants co-funded by European Social Fund (ESF)]. M.S. has received research grants from the

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Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

References

1. C. Mayorga, T. D. Fernandez, M. I. Montañez, E. Moreno, and M. J. Torres, "Recent Developments and Highlights in Drug Hypersensitivity," *Allergy* 74, no. 12 (2019): 2368–2381.

2. M. Jutel, I. Agache, M. Zemelka-Wiacek, et al., "Nomenclature of Allergic Diseases and Hypersensitivity Reactions: Adapted to Modern Needs: An EAACI Position Paper," *Allergy* 78, no. 11 (2023): 2851–2874.

3. B. D. Jakubovic, L. L. Vecillas, T. W. Jimenez-Rodriguez, S. Sanchez-Sanchez, and M. Castells, "Drug Hypersensitivity in the Fast Lane: What Clinicians Should Know About Phenotypes, Endotypes, and Biomarkers," *Annals of Allergy, Asthma & Immunology* 124, no. 6 (2020): 566–572, https://doi.org/10.1016/j.anai.2020.04.005.

4. I. Dona, M. J. Torres, G. Celik, E. Phillips, L. K. Tanno, and M. Castells, "Changing Patterns in the Epidemiology of Drug Allergy," *Allergy* 79, no. 3 (2024): 613–628.

5. W. J. Pichler, "Immune Pathomechanism and Classification of Drug Hypersensitivity," *Allergy* 74, no. 8 (2019): 1457–1471.

6. A. Akarsu, O. Soyer, and B. E. Sekerel, "Hypersensitivity Reactions to Biologicals: From Bench to Bedside," *Current Treatment Options in Allergy* 7, no. 1 (2020): 71–83.

7. E. Bakker, N. M. Hendrikse, F. Ehmann, et al., "Biomarker Qualification at the European Medicines Agency: A Review of Biomarker Qualification Procedures From 2008 to 2020," *Clinical Pharmacology and Therapeutics* 112, no. 1 (2022): 69–80.

8. R. Fernandez-Santamaria, G. Bogas, M. I. Montanez, et al., "Synthetic Antigenic Determinants of Clavulanic Acid Induce Dendritic Cell Maturation and Specific T Cell Proliferation in Patients With Immediate Hypersensitivity Reactions," *Allergy* 77 (2022): 3070–3083.

9. C. Mayorga, A. Ariza, R. Munoz-Cano, V. Sabato, I. Dona, and M. J. Torres, "Biomarkers of Immediate Drug Hypersensitivity," *Allergy* 79, no. 3 (2024): 601–612.

10. N. Molina, A. Martin-Serrano, T. D. Fernandez, et al., "Dendrimeric Antigens for Drug Allergy Diagnosis: A New Approach for Basophil Activation Tests," *Molecules* 23, no. 5 (2018): 997.

11. F. Jonsson, L. de Chaisemartin, V. Granger, et al., "An IgG-Induced Neutrophil Activation Pathway Contributes to Human Drug-Induced Anaphylaxis," *Science Translational Medicine* 11, no. 500 (2019): eaat1479.

12. J. L. Paris, C. Monio, A. M. Perez-Moreno, et al., "Influence of Pore Size in Protein G'-Grafted Mesoporous Silica Nanoparticles as a Serum Pretreatment System for In Vitro Allergy Diagnosis," *Advanced Healthcare Materials* 12, no. 15 (2023): e2203321.

13. R. L. Baretto, S. Beck, J. Heslegrave, et al., "Validation of International Consensus Equation for Acute Serum Total Tryptase in Mast Cell Activation: A Perioperative Perspective," *Allergy* 72, no. 12 (2017): 2031–2034.

14. C. M. Sullivan, N. S. Paul, and M. J. Rieder, "Bridging the Gap Between Bench and Clinic: The Importance of Understanding the Mechanism of Iodinated Contrast Media Hypersensitivity," *British Journal of Radiology* 96, no. 1141 (2023): 20220494.

15. M. M. R. Felix, M. V. Aun, U. P. Menezes, et al., "Allergy to Penicillin and Betalactam Antibiotics," *Einstein (Sao Paulo)* 19 (2021): eMD5703, https://doi.org/10.31744/einstein_journal/2021MD5703.

16. J. Vitte, L. Amadei, M. Gouitaa, et al., "Paired Acute-Baseline Serum Tryptase Levels in Perioperative Anaphylaxis: An Observational Study," *Allergy* 74, no. 6 (2019): 1157–1165.

17. M. S. Opstrup, G. B. E. Jemec, and L. H. Garvey, "Chlorhexidine Allergy: On the Rise and Often Overlooked," *Current Allergy and Asthma Reports* 19, no. 5 (2019): 23.

18. S. F. Stone, C. Cotterell, G. K. Isbister, A. Holdgate, and S. G. Brown, "Elevated Serum Cytokines During Human Anaphylaxis: Identification of Potential Mediators of Acute Allergic Reactions," *Journal of Allergy and Clinical Immunology* 124, no. 4 (2009): 786–792.e784.

19. P. Vadas, B. Perelman, and G. Liss, "Platelet-Activating Factor, Histamine, and Tryptase Levels in Human Anaphylaxis," *Journal of Allergy and Clinical Immunology* 131, no. 1 (2013): 144–149.

20. I. Torres-Rojas, D. Perez-Alzate, M. L. Somoza, et al., "Patterns of Response and Drugs Involved in Hypersensitivity Reactions to Beta-Lactams in Children," *Pediatric Allergy and Immunology* 32, no. 8 (2021): 1788–1795.

21. B. Sousa-Pinto, I. Tarrio, K. G. Blumenthal, et al., "Accuracy of Penicillin Allergy Diagnostic Tests: A Systematic Review and Meta-Analysis," *Journal of Allergy and Clinical Immunology* 147, no. 1 (2021): 296–308.

22. G. E. Fouda and S. Bavbek, "Rituximab Hypersensitivity: From Clinical Presentation to Management," *Frontiers in Pharmacology* 11 (2020): 572863.

23. A. Ariza, C. Mayorga, G. Bogas, et al., "Detection of Serum-Specific IgE by Fluoro-Enzyme Immunoassay for Diagnosing Type I Hypersensitivity Reactions to Penicillins," *International Journal of Molecular Sciences* 23, no. 13 (2022): 6992.

24. G. Bogas, I. Dona, J. Dionicio, et al., "Diagnostic Approach of Hypersensitivity Reactions to Cefazolin in a Large Prospective Cohort," *Journal of Allergy and Clinical Immunology. In Practice* 9, no. 12 (2021): 4421–4430.e4424.

25. A. Ariza, E. Garcia-Martin, M. Salas, et al., "Pyrazolones Metabolites Are Relevant for Identifying Selective Anaphylaxis to Metamizole," *Scientific Reports* 6 (2016): 23845.

26. N. Barbero, R. Fernandez-Santamaria, C. Mayorga, et al., "Identification of an Antigenic Determinant of Clavulanic Acid Responsible for IgE-Mediated Reactions," *Allergy* 74, no. 8 (2019): 1490–1501.

27. T. D. Fernandez, M. J. Torres, N. Blanca-Lopez, et al., "Negativization Rates of IgE Radioimmunoassay and Basophil Activation Test in Immediate Reactions to Penicillins," *Allergy* 64, no. 2 (2009): 242–248.

28. J. A. Cespedes, R. Fernandez-Santamaria, A. Ariza, et al., "Diagnosis of Immediate Reactions to Amoxicillin: Comparison of Basophil Activation Markers CD63 and CD203c in a Prospective Study," *Allergy* 78, no. 10 (2023): 2745–2755.

29. K. Heremans, A. Toscano, J. Elst, et al., "Basophil Activation Test Shows Poor Sensitivity in Immediate Amoxicillin Allergy," *Journal of Allergy and Clinical Immunology. In Practice* 11, no. 2 (2023): 500–505.

30. M. La Sorda, M. Fossati, R. Graffeo, et al., "A Modified Basophil Activation Test for the Clinical Management of Immediate Hypersensitivity Reactions to Paclitaxel: A Proof-Of-Concept Study," *Cancers (Basel)* 15, no. 24 (2023): 5818.

31. J. J. Laguna, G. Bogas, M. Salas, et al., "The Basophil Activation Test Can be of Value for Diagnosing Immediate Allergic Reactions to Omeprazole," *Journal of Allergy and Clinical Immunology: In Practice* 6, no. 5 (2018): 1628–1636.

32. S. Beyaz, N. Akdeniz, A. Yilmaz, et al., "Diagnostic Workup Including CD203c-Based Basophil Activation Test in Immediate Hypersensitivity due to Metronidazole and Ornidazole and Evaluation of Cross-Reactivity in Between," *Allergy* 76, no. 3 (2021): 842–852.

33. T. D. Fernandez, A. Ariza, F. Palomares, et al., "Hypersensitivity to Fluoroquinolones: The Expression of Basophil Activation Markers Depends on the Clinical Entity and the Culprit Fluoroquinolone," *Medicine (Baltimore)* 95, no. 23 (2016): e3679.

34. J. A. Céspedes, R. Fernández-Santamaría, G. Bogas, et al., "Lipopolysaccharides in Combination With Amoxicillin Increases Basophil Activation Test Sensitivity to Amoxicillin IgE-Mediated Hypersensitivity," *Allergy* 79, no. 9 (2024): 2537–2542, https://doi.org/10.1111/all.16133.

35. A. Tesfaye, A. Rodriguez-Nogales, S. Benede, et al., "Nanoarchitectures for Efficient IgE Cross-Linking on Effector Cells to Study Amoxicillin Allergy," *Allergy* 76, no. 10 (2021): 3183–3193.

36. S. W. Shin, J. S. Park, and C. S. Park, "Elevation of Eosinophil-Derived Neurotoxin in Plasma of the Subjects With Aspirin-Exacerbated Respiratory Disease: A Possible Peripheral Blood Protein Biomarker," *PLoS One* 8, no. 6 (2013): e66644.

37. S. Sim, Y. Choi, D. H. Lee, H. R. Lee, Y. Seob Shin, and H. S. Park, "Contribution of Dipeptidyl Peptidase 10 to Airway Dysfunction in Patients With NSAID-Exacerbated Respiratory Disease," *Clinical and Experimental Allergy* 52, no. 1 (2022): 115–126.

38. J. Elst, M. M. van der Poorten, A. L. Van Gasse, et al., "Tryptase Release Does Not Discriminate Between IgE-And MRGPRX2-Mediated Activation in Human Mast Cells," *Clinical and Experimental Allergy* 52, no. 6 (2022): 797–800.

39. D. G. Ebo, M. L. Van der Poorten, J. Elst, et al., "Immunoglobulin E Cross-Linking or MRGPRX2 Activation: Clinical Insights From Rocuronium Hypersensitivity," *British Journal of Anaesthesia* 126, no. 1 (2021): e27–e29.

40. A. Toscano, J. Elst, A. L. Van Gasse, et al., "Mas-Related G Protein-Coupled Receptor MRGPRX2 in Human Basophils: Expression and Functional Studies," *Frontiers in Immunology* 13 (2022): 1026304.

41. S. Alvarez-Arango, M. Kumar, T. G. Chow, and V. Sabato, "Non-IgE-Mediated Immediate Drug-Induced Hypersensitivity Reactions," *Journal of Allergy and Clinical Immunology. In Practice* 12, no. 5 (2024): 1109–1119.

42. G. Porebski, K. Kwiecien, M. Pawica, and M. Kwitniewski, "Mas-Related G Protein-Coupled Receptor-X2 (MRGPRX2) in Drug Hypersensitivity Reactions," *Frontiers in Immunology* 9 (2018): 3027.

43. G. Bogas, A. Ariza, P. Vázquez-Revuelta, et al., "Basophil Activation Test Is a Complementary Tool in the Diagnosis of Immediate Reactions to Platinum Salts and Taxanes," *Allergy* 80, no. 1 (2024): 271–286, https://doi.org/10.1111/all.16296.

44. S. Bavbek, M. Pagani, E. Alvarez-Cuesta, et al., "Hypersensitivity Reactions to Biologicals: An EAACI Position Paper," *Allergy* 77, no. 1 (2022): 39–54.

45. B. D. Jakubovic, S. Sanchez-Sanchez, S. Hamadi, D. M. Lynch, and M. Castells, "Interleukin-6: A Novel Biomarker for Monoclonal Antibody and Chemotherapy-Associated Hypersensitivity Confirms a Cytokine Release Syndrome Phenotype-Endotype Association," *Allergy* 76, no. 5 (2021): 1571–1573.

46. T. W. Jimenez- Rodriguez, L. de Las Vecillas, M. Labella, et al., "Differential Presentation of Hypersensitivity Reactions to Carboplatin and Oxaliplatin: Phenotypes, Endotypes, and Management With Desensitization," *Allergy* 79, no. 3 (2024): 679–689.

47. M. Pagani, S. Bavbek, E. Alvarez-Cuesta, et al., "Hypersensitivity Reactions to Chemotherapy: An EAACI Position Paper," *Allergy* 77, no. 2 (2022): 388–403.

48. I. Doña, R. Jurado-Escobar, J. R. Perkins, et al., "Eicosanoid Mediator Profiles in Different Phenotypes of Nonsteroidal Anti-Inflammatory Drug-Induced Urticaria," *Allergy* 74, no. 6 (2019): 1135–1144.

49. M. Marquette, B. V. Tailor, P. C. Calder, P. J. Curtis, Y. Loke, and A. M. Wilson, "Urinary Leukotriene E4 as a Biomarker in NSAID-Exacerbated Respiratory Disease (N-ERD): A Systematic Review and Meta-Analysis," *Current Allergy and Asthma Reports* 22, no. 12 (2022): 209–229.

50. G. Bochenek, K. Nagraba, E. Nizankowska, and A. Szczeklik, "A Controlled Study of 9alpha,11beta-PGF2 (a Prostaglandin D2 Metabolite) in Plasma and Urine of Patients With Bronchial Asthma and Healthy Controls After Aspirin Challenge," *Journal of Allergy and Clinical Immunology* 111, no. 4 (2003): 743–749.

51. K. N. Cahill, K. Murphy, J. Singer, E. Israel, J. A. Boyce, and T. M. Laidlaw, "Plasma Tryptase Elevation During Aspirin-Induced Reactions in Aspirin-Exacerbated Respiratory Disease," *Journal of Allergy and Clinical Immunology* 143, no. 2 (2019): 799–803.e792.

52. A. Gibson, P. Deshpande, C. N. Campbell, et al., "Updates on the Immunopathology and Genomics of Severe Cutaneous Adverse Drug Reactions," *Journal of Allergy and Clinical Immunology* 151, no. 2 (2023): 289–300.e284.

53. S. Mallal, E. Phillips, G. Carosi, et al., "HLA-B*5701 Screening for Hypersensitivity to Abacavir," *New England Journal of Medicine* 358, no. 6 (2008): 568–579.

54. C. Locharernkul, J. Loplumlert, C. Limotai, et al., "Carbamazepine and Phenytoin Induced Stevens-Johnson Syndrome Is Associated With HLA-B*1502 Allele in Thai Population," *Epilepsia* 49, no. 12 (2008): 2087–2091.

55. T. Y. Mehta, L. M. Prajapati, B. Mittal, et al., "Association of HLA-B*1502 Allele and Carbamazepine-Induced Stevens-Johnson Syndrome Among Indians," *Indian Journal of Dermatology, Venereology and Leprology* 75, no. 6 (2009): 579–582.

56. H. Niihara, T. Kakamu, Y. Fujita, S. Kaneko, and E. Morita, "HLA-A31 Strongly Associates With Carbamazepine-Induced Adverse Drug Reactions but Not With Carbamazepine-Induced Lymphocyte Proliferation in a Japanese Population," *Journal of Dermatology* 39, no. 7 (2012): 594–601.

57. S. I. Hung, W. H. Chung, L. B. Liou, et al., "HLA-B*5801 Allele as a Genetic Marker for Severe Cutaneous Adverse Reactions Caused by Allopurinol," *Proceedings of the National Academy of Sciences of the United States of America* 102, no. 11 (2005): 4134–4139.

58. C. Lonjou, N. Borot, P. Sekula, et al., "A European Study of HLA-B in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Related to Five High-Risk Drugs," *Pharmacogenetics and Genomics* 18, no. 2 (2008): 99–107.

59. W. Tassaneeyakul, T. Jantararoungtong, P. Chen, et al., "Strong Association Between HLA-B*5801 and Allopurinol-Induced Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in a Thai Population," *Pharmacogenetics and Genomics* 19, no. 9 (2009): 704–709.

60. M. Gonçalo, I. Coutinho, V. Teixeira, et al., "HLA-B*58:01 Is a Risk Factor for Allopurinol-Induced DRESS and Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis in a Portuguese Population," *British Journal of Dermatology* 169, no. 3 (2013): 660–665.

61. H. R. Kang, Y. K. Jee, Y. S. Kim, et al., "Positive and Negative Associations of HLA Class I Alleles With Allopurinol-Induced SCARs in Koreans," *Pharmacogenetics and Genomics* 21, no. 5 (2011): 303–307.

62. Q. Zhao, K. Alhilali, A. Alzahrani, et al., "Dapsone- and Nitroso Dapsone-Specific Activation of T Cells From Hypersensitive Patients Expressing the Risk Allele HLA-B*13:01," *Allergy* 74, no. 8 (2019): 1533–1548.

63. A. Barbaud, J. Castagna, and A. Soria, "Skin Tests in the Work-Up of Cutaneous Adverse Drug Reactions: A Review and Update," *Contact Dermatitis* 86, no. 5 (2022): 344–356.

64. L. G. Santiago, F. J. Morgado, M. S. Baptista, and M. Gonçalo, "Hypersensitivity to Antibiotics in Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS) From Other Culprits," *Contact Dermatitis* 82, no. 5 (2020): 290–296.

65. C. Mayorga, G. Celik, P. Rouzaire, et al., "In Vitro Tests for Drug Hypersensitivity Reactions: An ENDA/EAACI Drug Allergy Interest Group Position Paper," *Allergy* 71, no. 8 (2016): 1103–1134.

66. R. Fernandez-Santamaria, G. Bogas, F. Palomares, et al., "Dendritic Cells Inclusion and Cell-Subset Assessment Improve Flow-Cytometry-Based Proliferation Test in Non-Immediate Drug Hypersensitivity Reactions," *Allergy* 76, no. 7 (2021): 2123–2134.

67. W. J. Pichler and J. Tilch, "The Lymphocyte Transformation Test in the Diagnosis of Drug Hypersensitivity," *Allergy* 59, no. 8 (2004): 809–820.

68. I. Luque, L. Leyva, M. José Torres, et al., "In Vitro T-Cell Responses to Beta-Lactam Drugs in Immediate and Nonimmediate Allergic Reactions," *Allergy* 56, no. 7 (2001): 611–618.

69. G. Porebski, T. Pecaric-Petkovic, M. Groux-Keller, M. Bosak, T. T. Kawabata, and W. J. Pichler, "In Vitro Drug Causality Assessment in Stevens-Johnson Syndrome—Alternatives for Lymphocyte Transformation Test," *Clinical and Experimental Allergy* 43, no. 9 (2013): 1027–1037.

70. A. Rozieres, A. Hennino, K. Rodet, et al., "Detection and Quantification of Drug-Specific T Cells in Penicillin Allergy," *Allergy* 64, no. 4 (2009): 534–542.

71. M. E. Polak, G. Belgi, C. McGuire, et al., "In Vitro Diagnostic Assays Are Effective During the Acute Phase of Delayed-Type Drug Hypersensitivity Reactions," *British Journal of Dermatology* 168, no. 3 (2013): 539–549, https://doi.org/10.1111/bjd.12109.

72. C. Mayorga, G. E. Celik, M. Pascal, et al., "Flow-Based Basophil Activation Test in Immediate Drug Hypersensitivity. An EAACI Task Force Position Paper," *Allergy* 79, no. 3 (2024): 580–600.

73. V. Gil-Ocana, I. M. Jimenez, C. Mayorga, et al., "Multiepitope Dendrimeric Antigen-Silica Particle Composites as Nano-Based Platforms for Specific Recognition of IgEs," *Frontiers in Immunology* 12 (2021): 750109.

74. C. Mayorga, E. Perez-Inestrosa, J. Rojo, M. Ferrer, and M. I. Montanez, "Role of Nanostructures in Allergy: Diagnostics, Treatments and Safety," *Allergy* 76, no. 11 (2021): 3292–3306.

75. J. Elst, V. Sabato, M. M. van der Poorten, et al., "Basophil and Mast Cell Activation Tests by Flow Cytometry in Immediate Drug Hypersensitivity: Diagnosis and Beyond," *Journal of Immunological Methods* 495 (2021): 113050, https://doi.org/10.1016/j.jim.2021.113050.

76. M. Labella, J. A. Céspedes, I. Doña, et al., "The Value of the Basophil Activation Test in the Evaluation of Patients Reporting Allergic Reactions to the BNT162b2 mRNA COVID-19 Vaccine," *Allergy* 77, no. 7 (2022): 2067–2079.

77. M. Pascal, S. M. Edelman, A. Nopp, et al., "EAACI Task Force Report: A Consensus Protocol for the Basophil Activation Test for Collaboration and External Quality Assurance," *Allergy* 79, no. 2 (2024): 290–293.

78. L. F. Pennington, P. Gasser, D. Brigger, P. Guntern, A. Eggel, and T. S. Jardetzky, "Structure-Guided Design of Ultrapotent Disruptive IgE Inhibitors to Rapidly Terminate Acute Allergic Reactions," *Journal of Allergy and Clinical Immunology* 148, no. 4 (2021): 1049–1060.

79. M. C. Dispenza, J. A. Pongracic, A. M. Singh, and B. S. Bochner, "Short-Term Ibrutinib Therapy Suppresses Skin Test Responses and Eliminates IgE-Mediated Basophil Activation in Adults With Peanut or Tree Nut Allergy," *Journal of Allergy and Clinical Immunology* 141, no. 5 (2018): 1914–1916.e1917.

80. D. G. Ebo, R. Bahri, C. Tontini, et al., "Potential and Limitations of the Human Mast Cell Activation Test in Amoxicillin Hypersensitivity," *Allergy* 80, no. 2 (2024): 594–597.

81. L. E. Hsieh, J. Song, A. H. Tremoulet, J. C. Burns, and A. Franco, "Intravenous Immunoglobulin Induces IgG Internalization by Tolerogenic Myeloid Dendritic Cells That Secrete IL-10 and Expand Fc-Specific Regulatory T Cells," *Clinical and Experimental Immunology* 208, no. 3 (2022): 361–371.

82. B. D. McNeil, P. Pundir, S. Meeker, et al., "Identification of a Mast-Cell-Specific Receptor Crucial for Pseudo-Allergic Drug Reactions," *Nature* 519, no. 7542 (2015): 237–241, https://doi.org/10.1038/nature14022.

83. V. Sabato, D. G. Ebo, M. M. Van Der Poorten, et al., "Allergenic and Mas-Related G Protein-Coupled Receptor X2-Activating Properties of Drugs: Resolving the Two," *Journal of Allergy and Clinical Immunology. In Practice* 11, no. 2 (2023): 395–404, https://doi.org/10.1016/j.jaip.2022.12.014.

84. I. Doña, N. Pérez-Sánchez, I. Eguiluz-Gracia, et al., "Progress in Understanding Hypersensitivity Reactions to Nonsteroidal Anti-Inflammatory Drugs," *Allergy* 75, no. 3 (2020): 561–575.

85. E. M. Abud and A. A. White, "Mast Cells in Aspirin-Exacerbated Respiratory Disease," *Current Allergy and Asthma Reports* 24, no. 2 (2024): 73–80.

86. H. Mita, N. Higashi, M. Taniguchi, A. Higashi, and K. Akiyama, "Increase in Urinary Leukotriene B4 Glucuronide Concentration in Patients With Aspirin-Intolerant Asthma After Intravenous Aspirin Challenge," *Clinical and Experimental Allergy* 34, no. 8 (2004): 1262–1269.

87. R. Jurado-Escobar, I. Doña, G. Bogas-Herrera, et al., "Platelet-Adherent Leukocytes Associated With Cutaneous Cross-Reactive Hypersensitivity to Nonsteroidal Anti-Inflammatory Drugs," *Frontiers in Pharmacology* 11 (2020): 594427.

88. A. Tailor, X. Meng, K. Adair, et al., "HLA DRB1*15:01-DQB1*06:02-Restricted Human CD4+ T Cells Are Selectively Activated With Amoxicillin-Peptide Adducts," *Toxicological Sciences* 178, no. 1 (2020): 115–126.

89. M. Almutairi, A. Lister, Q. Zhao, et al., "Activation of Human CD8+ T Cells With Nitroso Dapsone-Modified HLA-B*13:01-Binding Peptides," *Journal of Immunology* 210, no. 8 (2023): 1031–1042.

90. J. L. Castrejon, N. Berry, S. El-Ghaiesh, et al., "Stimulation of Human T Cells With Sulfonamides and Sulfonamide Metabolites," *Journal of Allergy and Clinical Immunology* 125, no. 2 (2010): 411–418.e414.

91. P. T. Illing, J. P. Vivian, N. L. Dudek, et al., "Immune Self-Reactivity Triggered by Drug-Modified HLA-Peptide Repertoire," *Nature* 486, no. 7404 (2012): 554–558.

92. F. R. Zhang, H. Liu, A. Irwanto, et al., "HLA-B*13:01 and the Dapsone Hypersensitivity Syndrome," *New England Journal of Medicine* 369, no. 17 (2013): 1620–1628.

93. A. P. Villani, A. Rozieres, B. Bensaid, et al., "Massive Clonal Expansion of Polycytotoxic Skin and Blood CD8(+) T Cells in Patients With Toxic Epidermal Necrolysis," *Science Advances* 7, no. 12 (2021): eabe0013.

94. D. J. Naisbitt, A. Olsson-Brown, A. Gibson, et al., "Immune Dysregulation Increases the Incidence of Delayed-Type Drug Hypersensitivity Reactions," *Allergy* 75, no. 4 (2020): 781–797.

95. S. Hammond, A. Olsson-Brown, S. Grice, and D. J. Naisbitt, "Does Immune Checkpoint Inhibitor Therapy Increase the Frequency of Adverse Reactions to Concomitant Medications?," *Clinical and Experimental Allergy* 52, no. 5 (2022): 600–603.

96. A. Prieto, C. Muñoz, G. Bogas, et al., "Single-Dose Prolonged Drug Provocation Test, Without Previous Skin Testing, Is Safe for Diagnosing Children With Mild Non-Immediate Reactions to Beta-Lactams," *Allergy* 76, no. 8 (2021): 2544–2554.

97. T. Bellón, S. Rodríguez-Martín, R. Cabañas, et al., "Assessment of Drug Causality in Stevens-Johnson Syndrome/Toxic Epidermal

Necrolysis: Concordance Between Lymphocyte Transformation Test and ALDEN," *Allergy* 75, no. 4 (2020): 956–959.

98. E. D. Ogiji, N. Aboheimed, K. Ross, et al., "Greater Mechanistic Understanding of the Cutaneous Pathogenesis of Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis Can Shed Light on Novel Therapeutic Strategies: A Comprehensive Review," *Current Opinion in Allergy and Clinical Immunology* 24, no. 4 (2024): 218–227.

99. L. C. E. Chan, R. Sultana, K. J. L. Choo, Y. W. Yeo, S. M. Pang, and H. Y. Lee, "Viral Reactivation and Clinical Outcomes in Drug Reaction With Eosinophilia and Systemic Symptoms (DRESS)," *Scientific Reports* 14, no. 1 (2024): 28492.

100. B. K. Park, D. J. Naisbitt, S. F. Gordon, N. R. Kitteringham, and M. Pirmohamed, "Metabolic Activation in Drug Allergies," *Toxicology* 158, no. 1–2 (2001): 11–23.

101. W. J. Pichler, "The Important Role of Non-Covalent Drug-Protein Interactions in Drug Hypersensitivity Reactions," *Allergy* 77, no. 2 (2022): 404–415.

102. T. Liu, K. M. Khanna, B. N. Carriere, and R. L. Hendricks, "Gamma Interferon Can Prevent Herpes Simplex Virus Type 1 Reactivation From Latency in Sensory Neurons," *Journal of Virology* 75, no. 22 (2001): 11178–11184.

103. T. Yoshikawa, A. Fujita, A. Yagami, et al., "Human Herpesvirus 6 Reactivation and Inflammatory Cytokine Production in Patients With Drug-Induced Hypersensitivity Syndrome," *Journal of Clinical Virology* 37, no. Suppl 1 (2006): S92–S96.

104. U. Radzikowska, M. Ding, G. Tan, et al., "Distribution of ACE2, CD147, CD26, and Other SARS-CoV-2 Associated Molecules in Tissues and Immune Cells in Health and in Asthma, COPD, Obesity, Hypertension, and COVID-19 Risk Factors," *Allergy* 75 (2020): 2829–2845.

105. U. Radzikowska, A. Eljaszewicz, G. Tan, et al., "Rhinovirus-Induced Epithelial RIG-I Inflammasome Suppresses Antiviral Immunity and Promotes Inflammation in Asthma and COVID-19," *Nature Communications* 14, no. 1 (2023): 2329, https://doi.org/10.1038/s41467-023-37470-4.

106. J. Schulte-Schrepping, N. Reusch, D. Paclik, et al., "Severe COVID-19 Is Marked by a Dysregulated Myeloid Cell Compartment," *Cell* 182, no. 6 (2020): 1419–1440.e23.

107. W. J. Pichler and M. C. Brüggen, "Viral Infections and Drug Hypersensitivity," *Allergy* 78, no. 1 (2023): 60–70.

108. Y. Mitamura, D. Schulz, S. Oro, et al., "Cutaneous and Systemic Hyperinflammation Drives Maculopapular Drug Exanthema in Severely Ill COVID-19 Patients," *Allergy* 77, no. 2 (2022): 595–608.