Review

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HLA and Delayed Drug-Induced Hypersensitivity

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Key Words

Delayed allergy · Drug allergy · Genetic testing · Histocompatibility antigens · Major histocompatibility complex · Pharmacogenetics

Abstract

Delayed drug allergy reactions (DDAR) are potentially fatal. Certain human leukocyte antigen (HLA) alleles have been associated with delayed allergy reactions following the administration of particular drugs. Examples are HLA-B*57:01 (abacavir), HLA-B*15:02/HLA-A*31:01 (carbamazepine), and HLA-B*58:01 (allopurinol). Based on the identification of these associations, it may now be possible to prevent certain allergy reactions that were, until recently, considered unpredictable. In this review, we will focus on the pharmacogenetics of the best-studied associations between specific HLA alleles and delayed allergy reactions and describe the pathogenesis models proposed so far. Finally, we will evaluate the genetic screening strategies available and discuss the clinical relevance of a better understanding of the immunogenetics and mechanisms involved in DDAR.

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Introduction

Adverse drug reactions can be classified into type A reactions, which are based on the pharmacological action of the drug and hence predictable, and type B reactions, which are largely related to host genetics and immunological hypersensitivity and, therefore, less dependent on drug dose [1, 2]. Type B reactions include drug-induced T-cell-mediated hypersensitivity syndromes, consisting of 'delayed drug allergy reactions' (DDAR) as defined by World Allergy Organization nomenclature [3–5]. DDAR comprise a heterogeneous group of distinct clinical syndromes, including severe cutaneous adverse reactions (SCAR), encompassing acute generalized exanthematous pustulosis, drug reactions with eosinophilia and systemic symptoms (DRESS), and Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) [3, 4, 6]. Additionally, DDAR can also predominantly affect particular organs other than the skin and mucosae, with the liver being the most commonly involved, with manifestations ranging from a mild self-limited presentation to a fulminant liver failure episode [7]. Its clinical features and immunopathogenic mechanisms are out of scope of this article and have been reviewed elsewhere [7] (see also table 1).

Concerning SJS and TEN, both conditions are characterized by keratinocyte apoptosis with nearly absent

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Table 1. Associations between specific delayed drug allergy reactions (DDAR) and HLA alleles according to the ethnic group and pattern of reactions

Drug	Ethnic group	Pattern of reactions	Allele	Odds ratio[a] (95% confidence interval)	Ref. No.
Abacavir	Afro-American	AAS	HLA-B*57:01	11.10 (3.78–32.63)[b]	48
				899.80 (38.47–21,045.27)[c]	
	Caucasian	AAS	HLA-B*57:01	31.92 (21.67–47.02)[b]	48
				1,507.01 (200.78–11,311.25)[c]	
	Hispanic	AAS	HLA-B*57:01	17.58 (3.85–80.37)	48
Allopurinol	Caucasian	SCAR	HLA-A*33:03	105.00 (4.48–2,461.61)[d]	108
			HLA-B*58:01	39.11 (4.49–340.51)	88
			HLA-C*03:02	105.00 (4.48–2,461.61)[d]	108
	Han Chinese	SCAR	HLA-A*33:03	9.25 (4.46–19.20)	83
			HLA-B*58:01	580.32 (34.43–9,780.93)	
			HLA-C*03:02	97.68 (27.61–345.51)	
	Japanese	SCAR/EM	HLA-B*58:01	65.6 (2.9–1,497.0)	109
	Korean	SCAR	HLA-A*33:03	20.5 (5.4–78.6)	86
			HLA-B*58:01	97.8 (18.3–521.5)	
			HLA-C*03:02	82.1 (15.8–426.5)	
	Thai	SCAR	HLA-B*58:01	348.3 (19.2–6,336.9)	84
Amoxicillin-clavulanate	Caucasian	DILI	HLA-A*02:01	2.2 (1.6–3.2)[d]	110
			HLA-A*30:02	2.87 (1.42–5.78)[d]	111
			HLA-DQA1*01:02	2.0 (1.2–4.2)[d]	110
			HLA-DQB1*06:02	10.10 (3.59–28.40)[d]	112
			HLA-DRB1*15:01	7.56 (2.85–20.03)[d]	112
			HLA-DRB5*01:01	7.56 (2.85–20.03)[d]	112
Anti-tubercular	Korean	DRESS	HLA-C*04:01	6.90 (2.20–21.66)	113
Carbamazepine	Caucasian	SJS/TEN	HLA-A*31:01	7.9 (2.7–23.6)	75
		DRESS	HLA-A*31:01	24.1 (9.6–60.3)	75
			HLA-B*07:02	0.083 (0–0.646)	114
	Han Chinese	MPE	HLA-A*02:01	3.16 (1.05–9.49)	115
		SJS/TEN	HLA-A*24:02	0.23 (0.1–0.6)	116
			HLA-A*33:03	12.92 (3.58–46.59)	117
			HLA-B*15:02	115.32 (18.17–732.13)	118
			HLA-B*15:11	31.00 (2.74–350.50)[d]	119
			HLA-B*40:01	0.16 (0.1–0.4)	116
			HLA-B*58:01	4.96 (1.26–19.49)	117
			HLA-C*01:02	0.26 (0.1–0.6)	116
			HLA-C*03:02	4.96 (1.26–19.49)	117
			HLA-C*08:01	86.8 (29.3–254.6)	116
			HLA-DQB1*03:03	3.12 (1.14–8.54)	117
			HLA-DRB1*04:05	0.08 (0.01–0.5)	116
			HLA-DRB1*07:01	4.64 (1.57–13.71)	117
			HLA-DRB1*12:02	11.4 (5.6–22.9)	116
		DRESS	HLA-A*31:01	23.0 (4.2–125)	75
			HLA-B*51:01	3.94 (1.2–12.8)	76
	Indian	SJS/TEN	HLA-B*15:02	16.67 (1.70–162.96)	120
	Japanese	SJS/TEN, MPE, and EM	HLA-A*02:06	0.1 (0.0–0.6)	74
			HLA-A*31:01	10.8 (5.9–19.6)	74
			HLA-B*51:01	4.90 (1.22–19.69)	121
		SJS/TEN	HLA-B*15:11	9.76 (2.01–47.5)[d]	122
		SCAR	HLA-B*39:02	9.18 (1.58–53.12)[d]	123
	Korean	SCAR	HLA-A*31:01	7.3 (2.3–22.5)	124
		SJS/TEN	HLA-B*15:11	18.0 (2.3–141.2)	124
	Malay	SJS/TEN	HLA-B*15:02	16.15 (4.57–62.4)[d]	125
	Thai	SJS/TEN	HLA-B*15:02	54.43 (16.28–181.96)	118
	Vietnamese	SJS/TEN	HLA-B*15:02	33.78 (7.55–151.03)	126
		SJS/TEN and DRESS	HLA-B*46:01	0.27 (0.08–4.86)	126

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Table 1 (continued)

Drug	Ethnic group	Pattern of reactions	Allele	Odds ratio[a] (95% confidence interval)	Ref. No.
Dapsone	Han Chinese	Fever, rash, and systemic symptoms	HLA-B*13:01	20.53 (11.55–36.48)	127
			HLA-C*03:04	9.00 (5.87–15.50)	
Flucloxacillin	Caucasian	DILI	HLA-B*57:01	80.6 (22.8–248.9)[d]	128
			HLA-DRB1*07:01	7.2 (3.15–16.45)[d]	
Lamotrigine	Caucasian (predominantly)	SCAR	HLA-A*68:01	19.22 (1.01–365)	129
			HLA-B*58:01	9.45 (2.76–32.32)[d]	
			HLA-DQB1*06:09	5.80 (1.40–24.07)[d]	
	Han Chinese	SJS/TEN	HLA-B*13:01	3.7 (1.4–10.0)	130
			HLA-B*15:02	5.1 (1.8–15.1)	
			HLA-C*08:01	3.0 (1.1–7.8)	
			HLA-DRB1*16:02	4.3 (1.4–12.8)	
		SJS/TEN and MPE	HLA-B*15:19	24.78 (1.50–408.76)[d]	131
			HLA-B*44:08	24.78 (1.50–408.76)[d]	
			HLA-B*55:01	24.78 (1.50–408.76)[d]	
			HLA-B*81:01	27.05 (1.64–447.38)[d]	
Lapatinib	Multiethnic (predominantly Caucasian)	DILI	HLA-DQA1*02:01	2.6 (1.1–5.7)	132
			HLA-DQB1*02:02	2.9 (1.3–6.6)	132
			HLA-DRB1*07:01	22.5 (6.9–74.1)	133
Lumiracoxib	Multiethnic (predominantly Caucasian)	DILI	HLA-DQA1*01:02	6.3 (4.1–9.6)	134
			HLA-DQB1*06:02	6.9 (4.6–10.3)	
			HLA-DRB1*15:01	7.5 (5.0–11.3)	
			HLA-DRB5*01:01	7.2 (4.8–10.8)	
Methazolamide	Han Chinese	SJS/TEN	HLA-B*59:01	305.0 (11.3–8,259.9)	135
			HLA-C*01:02	12.1 (1.3–111.7)	
	Korean	SJS/TEN	HLA-B*59:01	249.8 (13.4–4,813.5)	136
			HLA-C*01:02	22.1 (1.2–414.3)	
Nevirapine	Black	SJS/TEN	HLA-C*04:01	17.52 (3.31–92.8)	137
	Caucasian	Skin rash and systemic or organ-specific symptoms	HLA-B*14	30.0 (5.06–177.71)	65
			HLA-C*08	30.0 (5.06–177.71)	
			HLA-DRB1*01:02	15.56 (2.49–97.34)	
		Skin rash	HLA-DRB1*01:01	70.0 (3.65–1,342.66)	138
		Skin rash and hepatitis	HLA-DRB1*01:01	4.77 (1.55–14.73)	60
		DILI	HLA-DRB1*01:01	3.02 (1.66–5.49)	139
	Han Chinese	Skin rash and systemic or organ-specific symptoms	HLA-C*04	3.61 (1.13–11.49)	140
	Indian	Skin rash	HLA-B*35	3.38 (1.54–7.41)	141
	Multiethnic	Skin rash and hepatitis	HLA-C*04	2.51 (1.73–3.62)	139
	Multiethnic (predominantly Black African)	DILI	HLA-B*58:01	3.15 (1.23–8.06)	142
			HLA-C*02:10	0.17 (0.04–0.77)	
			HLA-C*03:02	4.20 (1.01–17.52)	
			HLA-C*12:03	4.34 (1.24–15.13)	
			HLA-DRB1*01:02	4.56 (1.30–15.95)	
	Thai	Skin rash	HLA-B*35:05	16.53 (2.74–98.98)	62
			HLA-C*04	3.18 (1.22–8.63)	143
NSAIDs and 'cold medication'	Brazilian	SJS/TEN	HLA-B*44:03	2.74 (1.12–6.71)[d]	144
	Indian	SJS/TEN	HLA-B*44:03	12.25 (3.57–42.01)[d]	144
	Japanese	SJS/TEN	HLA-A*02:06	5.71 (3.67–8.88)[d]	145
			HLA-A*24:02	0.49 (0.33–0.73)[d]	
			HLA-B*44:03	4.22 (1.59–11.19)[d]	
	Korean	SJS/TEN	HLA-A*02:06	3.00 (1.18–7.57)[d]	144

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Table 1 (continued)

Drug	Ethnic group	Pattern of reactions	Allele	Odds ratio[a] (95% confidence interval)	Ref. No.
Oxcarbazepine	Han Chinese	MPE	HLA-B*13:02	7.83 (2.32–26.41)[d]	146
			HLA-B*15:02	8.8 (1.85–41.79)[d]	147
			HLA-B*15:19	124.2 (4.94–3,117.64)[d]	146
			HLA-B*15:27	40.54 (3.56–461.64)[d]	146
			HLA-B*15:58	22.85 (2.01–259.72)[d]	148
			HLA-B*27:04	5.73 (1.13–28.93)	146
			HLA-B*27:09	124.2 (4.94–3,117.64)[d]	146
			HLA-B*38:02	6.33 (1.78–22.46)[d]	148
			HLA-B*48:04	124.2 (4.94–3,117.64)[d]	146
			HLA-B*56:01	22.85 (2.01–259.72)[d]	148
Phenytoin	Han Chinese	SJS/TEN	HLA-B*13:01	3.7 (1.4–10.0)	130
			HLA-B*15:02	5.1 (1.8–15.1)	
			HLA-C*08:01	3.0 (1.1–7.8)	
			HLA-DRB1*16:02	4.3 (1.4–12.8)	
	Thai	SJS/TEN	HLA-B*15:02	18.50 (1.82–188.40)	149
Sulfamethoxazole	Thai	SJS/TEN	HLA-B*15:02	3.91 (1.42–10.92)	150
			HLA-C*06:02	11.84 (1.24–566.04)	
			HLA-C*08:01	3.53 (1.21–10.40)	
Sulfasalazine	Han Chinese	DRESS	HLA-B*07:02	5.80 (3.10–108.60)	151
			HLA-B*13:01	13.00 (1.76–95.80)	
			HLA-B*15:05	5.80 (3.10–108.60)	
			HLA-B*39:01	33.89 (1.39–826.08)	
			HLA-B*58:01	5.80 (3.10–108.60)	
Ticlopidine	Japanese	DILI	HLA-A*33:03	13.04 (4.40–38.59)	152
			HLA-B*44:03	6.65 (2.38–18.55)	
			HLA-C*14:03	7.30 (2.59–20.61)	
			HLA-DRB1*13:02	9.00 (3.10–26.17)	
			HLA-DQB1*06:04	10.13 (3.42–30.05)	

AAS = Abacavir allergy syndrome (general malaise, fever, skin rash, fatigue, and gastrointestinal or respiratory symptoms); DILI = drug-induced liver injury; DRESS = drug reactions with eosinophilia and systemic symptoms; EM = erythema multiforme; MPE = maculopapular exanthema; SCAR = severe cutaneous adverse reactions; SJS/TEN = Stevens-Johnson syndrome/toxic epidermal necrolysis.

[a] Unless otherwise specified, odds ratios are obtained comparing delayed drug allergy cases with drug-tolerant controls. [b] Diagnosis of abacavir allergy performed by clinical criteria only. [c] Diagnosis of abacavir allergy performed by epicutaneous tests. [d] Odds ratio calculated using healthy controls from the general population.

dermal inflammation and subsequent epidermal detachment. The extent of the affected skin area – <10% in SJS, 10–30% in SJS/TEN overlap syndrome, and >30% in TEN [6, 8] – determines the different prognoses of these conditions, with mortality rates in the range of 1–5% for SJS and 25–35% for TEN [9–11]. Early symptoms of both SJS and TEN include influenza-like symptoms. These can last from anywhere between 1 day and 2 weeks, and are followed by skin lesions that first appear on the trunk and then on the neck, face, and proximal upper limbs [9, 10]. Because SJS and TEN present with mucocutaneous manifestations, they were traditionally considered to be more severe forms of erythema multiforme. Nevertheless, this notion was abandoned with the identification of demographic and etiologic differences between SCAR and erythema multiforme (erythema multiforme, for example, although sometimes drug related, is mostly associated with herpes infections) [12].

Although DRESS is also characterized by cutaneous manifestations, its diagnosis is challenging, since its symptoms mimic those of many other disorders. Several tools have been developed to facilitate the diagnosis of DRESS, including the European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples (RegiSCAR) and the diagnostic criteria established by the Japanese consensus group led by Shiohara [13] in 2007 as well as other criteria [14]. Although there are typical patterns of the mucocutaneous signs of DDAR (fig. 1), the diagnosis of these conditions is further complicated by the existence of concomitant syndromes,

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Fig. 1. Typical patterns of the mucocutaneous signs of DDAR. **a** DRESS induced by allopurinol. **b** Erythema multiforme related to herpes simplex infection with typical target lesions. **c** SJS due to trimethoprim-sulfamethoxazole for a urinary tract infection with atypical skin target lesions and mucosal involvement. **d** SJS/TEN overlap in a HIV+ patient related to trimethoprim-sulfamethoxazole. **e** TEN induced by piroxicam with severe skin involvement.

which lack a single diagnostic procedure [15] and are characterized by the coexistence of diagnostic features from different entities [16].

While the underlying immunopathogenic mechanisms are still not completely understood, drug presentation by class I human leukocyte antigen (HLA) molecules and subsequent activation and clonal expansion of CD8+ T cells seem to be necessary for immunological responses to be triggered [6]. Concerning SJS and TEN, besides playing an important role in the initiation phase [17, 18], cytotoxic T lymphocytes also participate in the amplification of the immune response both by cell-cell contact (particularly Fas-Fas ligand interaction) and synthesis of cytolytic proteins and cytokines [19, 20]. The Fas-Fas ligand interaction might not only mediate keratinocyte apoptosis but also promote inflammation via NF-κB activation [20]. Additionally, cytotoxic proteins, such as perforin/granzyme B and granulysin (produced not only by cytotoxic T lymphocytes but also by natural killer cells) also contribute to keratinocyte apoptosis [19, 20]. Finally, several cytokines, including TNF-α and IL-6, have been ascribed a potential role in the pathogenesis of SJS and TEN [19, 21].

Certain HLA alleles have been associated with several DDAR. HLA molecules are highly polymorphic and are, therefore, involved in variable interactions with drug antigens [19]. Thus, an immunological response to certain drug antigens may be triggered in patients carrying specific HLA alleles, leading to T-cell activation and clonal expansion [19]. Drugs strongly associated with DDAR in the presence of particular HLA alleles include allopurinol, antiretrovirals (namely abacavir and nevirapine), aromatic amine anticonvulsants (in particular carbamazepine and phenytoin), and sulfonamides [10, 22, 23].

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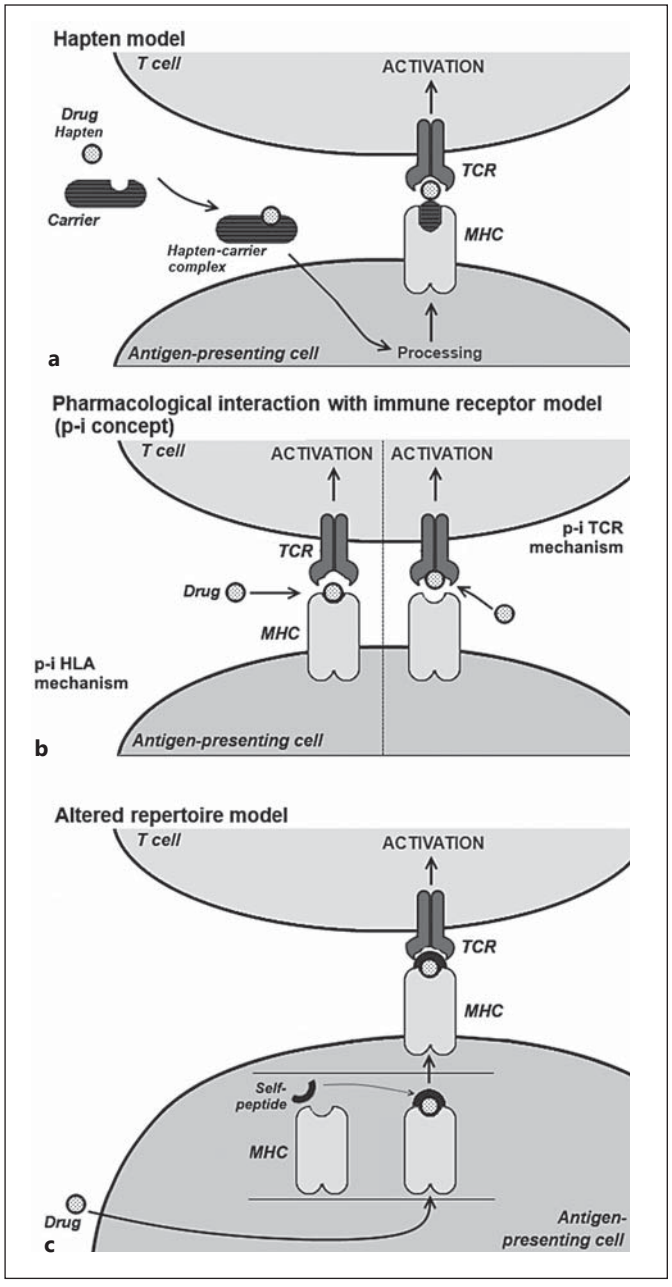

Fig. 2. Immunopathogenic models of DDAR. Three immunological models have attempted to explain the role of drug interactions with human MHC molecules (HLA) in the pathogenesis of DDAR. According to the hapten model (**a**), drugs bind to carriers, generating hapten-carrier complexes, which are subsequently processed by antigen-presenting cells. The processed complexes are then presented to the TCR bound to MHC molecules. According to the pharmacological interaction with the immune receptor model (p-i concept) (**b**), drugs bind directly to MHC molecules and/or TCR, activating T cells. Finally, the altered repertoire model (**c**) holds that drugs bind to MHC molecules, changing the repertoire of self-peptides capable of binding to these molecules. In other words, some self-peptides become capable of binding to MHC molecules, inducing T-cell activation.

Immunological Models

The immunopathogenesis of DDAR and their association with HLA alleles are currently explained by different immunological models (fig. 2), namely the hapten (and prohapten) model and the concept of direct pharmacological interaction with immune receptors (p-i concept). Nevertheless, some questions remain unexplained by these models, raising the hypothesis that viral infections may also play a major role in the immunopathogenesis of DDAR.

The Hapten and Prohapten Model

Haptens are small reactive molecules (<1 kDa) incapable of inducing a specific immune response per se. However, haptens bind covalently to soluble or nonsoluble (membrane-bound) high-molecular-weight proteins (carriers), generating hapten-carrier complexes capable of triggering an immune response [24–26]. Prohaptens are nonreactive molecules and as such are incapable of binding to carriers. However, in the liver, prohaptens can be metabolized into haptens, which are capable of binding to carriers and generating hapten-carrier complexes [27]. Metabolism of prohaptens in the liver does not necessarily trigger an immune response, as the liver maintains a tolerogenic environment [27, 28]. However, hepatitis can develop whenever a reactive compound leaves the liver, or whenever the immune response to that compound occurs in lymph nodes near the liver [29].

In order to induce a T-cell response, immunogenic hapten-carrier complexes need to activate the innate immune system (in contrast to what is described for the p-i concept) – for example, sulfamethoxazole activates dendritic cells after being converted into its nitroso metabolite, while imiquimod activates dendritic cells by binding to Toll-like receptor 7 [25, 27, 30]. Processed haptenated peptides are then presented by activated antigen-presenting cells bound to major histocompatibility (MHC) molecules. These latter molecules, in turn, present these peptides to naïve T cells, causing their activation and triggering an immune response in the lymph nodes [24, 25]. Re-exposure to a hapten to which a patient is already sensitized triggers an inflammatory response with memory T-cell proliferation within 24–72 h [25]; effector T cells (including effector memory T cells) subsequently migrate to the site at which the hapten-carrier complexes were generated during the initial exposure, unlike central memory T cells (as well as naïve T cells), which, on expo-

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sure to a hapten-carrier complex, migrate to lymph nodes [24, 26]. Thus, activation of effector T cells results in local responses at the site where hapten-carrier complexes were initially generated and presented, while stimulation of central memory T cells is associated with lymph node involvement [26].

Therefore, the hapten/prohapten model does not convincingly explain why re-exposure to systemically administered drugs often results in allergic reactions with predominant cutaneous manifestations but no significant lymph node involvement [24, 26]. Moreover, neither the hapten nor the prohapten model explains why several drugs (such as penicillin) induce hapten formation and activate the innate immune system, but are only associated with DDAR in a minority of exposed patients [25, 30].

The Pharmacological Interaction with the Immune Receptor Model (p-i Concept)

The p-i concept claims that drugs induce DDAR without binding to a carrier and without forming a hapten-carrier complex [27, 31, 32]. This model therefore posits that a drug can directly stimulate T cells and, consequently, generate a specific immune response without needing to be previously processed or metabolized [27, 31, 32].

According to this model, drugs reversibly and non-covalently bind to MHC molecules or T-cell receptors (TCR), strengthening the affinity between MHC-peptide complexes and the respective TCR [26, 31, 32]. Thus, by directly interacting with MHC molecules (p-i HLA mechanisms), these drugs would form a complex that triggers a strong immune response mediated by T cells [32]. After binding directly to MHC molecules, drugs might also promote a modification in the repertoire of HLA ligands capable of binding and being presented to T cells [32]. This specific mechanism was elegantly described for abacavir DDAR, being sometimes termed 'altered repertoire model'. In fact, abacavir appears to pass from the extracellular milieu to the cell endoplasmic reticulum and binds non-covalently to specific residues in the F pocket of the HLA-B*57:01 peptide-binding cleft, modifying the repertoire of self-peptide ligands capable of binding and being presented to T cells; this alteration would allow peptides that do not usually bind to MHC to be presented to T cells, inducing a polyclonal primary immune response [33, 34].

Alternatively, other drugs might directly bind to TCR (p-i TCR mechanisms), either directly stimulating the TCR or altering the TCR and subsequently promoting an increased reactivity to particular HLA-peptide complexes [32].

Therefore, activation of tissue memory T cells as described by the p-i concept adequately explains the development of generalized or predominantly cutaneous manifestations upon drug reexposure (most effector memory T cells, which have a low activation threshold, appear to be located in the skin) [26, 35]. In cases where DDAR develop without an apparent previous sensitization phase (i.e., when the patient first comes into contact with the drug) [27], it is believed that the effector response (occurring according to the p-i concept) is mounted following cross-reaction to other peptides, including viral antigens (vide infra).

Role of Viral Infections

Several epidemiological studies have found viral infections to be associated with DDAR. Human herpes virus (HHV) 6 activation, for example, is associated with carbamazepine-induced DRESS [36], while several cases of HHV reactivation have been described in association with allopurinol DDAR [37, 38]. Furthermore, Epstein-Barr and cytomegalovirus reactivations have been observed in the context of different SCAR [39]. Such observations have prompted researchers to investigate whether viral infections, and HHV infections in particular, might participate in the immunopathogenesis of DDAR.

The heterologous immunity model put forward by White et al. [4] posits that T cells participating in DDAR partially consist of effector memory T cells previously formed in response to HHV infections. Thus, T cells reactive against HHV would cross-react with specific HLA-drug complexes, triggering an immune response. According to this model, the different clinical phenotypes of distinct drug-induced adverse reactions (e.g., the predominantly mucocutaneous manifestations associated with HLA-B*15:02–restricted carbamazepine-induced DDAR versus the mainly systemic symptoms of HLA-B*57:01-related abacavir DDAR) would be explained by activation of T cells primed to different HHV types [4]. Additionally, the heterologous immunity model might explain why some DDAR are associated with relatively rapid development of symptoms (effector memory cell activation requires minimal costimulatory signals), and why certain drug-specific T-cell responses persist for years after drug exposure and withdrawal [4].

HIV might also play a role in the immunopathogenesis of some DDAR and, in fact, HIV-positive patients are

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particularly predisposed to CD8+-mediated allergy reactions, in particular to toxic epidermal necrolysis, evidenced by a higher incidence and mortality in these patients [6, 11, 40]. The discovery of HIV antigens in the skin lesions of SCAR patients led to the suggestion that these might be drug-enhanced cytotoxic reactions to viral cutaneous antigens [41].

Specific DDAR and HLA Alleles

Several associations between specific HLA alleles and DDAR have been described (listed in table 1). However, the best-studied associations, both epidemiologically and immunologically, involve abacavir, nevirapine, carbamazepine, and allopurinol. These associations are described in greater detail below.

Abacavir

Abacavir is an antiretroviral of the reverse transcriptase inhibitor class. Nearly 5% of patients exposed to this drug develop a drug hypersensitivity syndrome characterized by two or more of the following symptoms: malaise, rash, fever, lethargy, gastrointestinal symptoms (nausea, vomiting, and abdominal pain), and respiratory symptoms (cough and dyspnea) [42, 43]. These symptoms tend to appear within the first days or weeks of therapy and disappear after withdrawal [42, 43]. Rechallenge with abacavir is potentially fatal, with symptoms reappearing within hours.

Several studies have shown that abacavir DDAR is more common in HLA-B*57:01 carriers [44–46]. Nevertheless, the sole presence of this allele does not seem sufficient to trigger abacavir DDAR, since not all HLA-B*57:01 carriers develop this reaction [33]. The association between abacavir DDAR and HLA-B*57:01 expression has been studied for several populations and ethnicities, including Caucasians, Afro-Americans, Thais, and Hispanics [45, 47, 48]. While early studies reported HLA-B*57:01 carriage to be a poor predictor of abacavir DDAR in Afro-Americans, current evidence suggests that HLA-B*57:01 expression is strongly associated with abacavir DDAR in both Caucasians and Africans/Afro-Americans, indicating that the apparent lower sensitivity of HLA-B*57:01 was probably due to a high rate of false positives (namely in patients who were diagnosed with abacavir DDAR solely based on their clinical symptoms) in populations with a low prevalence of the allele [45, 48].

Before initiating therapy with abacavir, patients should be tested for the HLA-B*57:01 allele. According to several studies conducted in Caucasians, genotyping for HLA-B*57:01 is highly cost-effective, and has high specificity and sensitivity; as previously mentioned, the initial evidence of low sensitivity was obtained from studies where abacavir DDAR was not diagnosed by epicutaneous tests but by clinical criteria only [48–50].

Abacavir DDAR is immunologically mediated, as evidenced by the presence of cytotoxic T cells in the cutaneous lesions of patients developing rash [51]. According to the most widely accepted hypothesis, abacavir (but not its metabolites) binds noncovalently to the bottom of the MHC antigen-binding cleft, modifying the shape and structure of the F pocket, and thereby inducing a preference for smaller amino-acid residues (valine, isoleucine, or leucine) [33, 34]. Abacavir thus alters the repertoire of peptides that are able to bind to MHC, allowing for presentation of novel self-peptides, which in the absence of abacavir would not bind to HLA-B*57:01 (this mechanism is sometimes termed 'altered repertoire model'; vide supra [34]). As these peptides are perceived as foreign by T cells, a cytotoxic response is triggered [33]. Abacavir restriction to HLA-B*57:01 is thus explained by the sensitivity of abacavir to the F pocket of HLA-B*57:01, namely to its Ser^{116} residue [34]. The absence of this residue in similar allotypes (*57:11, *58:01, and *57:03) would explain their lack of association with abacavir DDAR [34].

A complementary study of abacavir DDAR by Adam et al. [52] found that T-cell reactivity is determined by TCR avidity, with in vitro T-cell activation being influenced by MHC molecule density on the cell surface, as well as drug dose and abacavir pulsing duration. In addition, another study showed that costimulatory signs are not needed for primary activation of abacavir-reacting T cells, suggesting that these cells partly originate from memory T cells [53]. Finally, according to Lucas et al. [54], these memory T cells might have been formed after early exposure to other exogenous antigens cross-reacting with abacavir-HLA-B*57:01-endogenous peptide ligand complexes.

Nevirapine

Nevirapine is an antiretroviral of the class of non-nucleoside reverse transcriptase inhibitors; it acts by binding to a hydrophobic cleft of the viral reverse transcriptase, disrupting its normal activity [47]. Eight to 16% of patients exposed to nevirapine develop DDAR, which can

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range from a simple cutaneous reaction to hepatitis [55–57]. These reactions mostly occur during the first 18 weeks of treatment [55]. Nevertheless, only a minority of patients develop potentially life-threatening conditions, such as SJS or TEN [57, 58]. As occurs with abacavir, rechallenge with nevirapine is associated with allergy reactions characterized by greater severity and a decreased lag period [57, 59].

Several studies have found nevirapine DDAR to be associated with distinct specific MHC I and MHC II alleles. In Caucasians, for example, HLA-DRB1*01:01 expression has been linked to rash, fever, and hepatitis [60], while in an Australian study, HLA-B*35:01 expression has been linked to rash [61]. HLA-B*35 was also identified as a risk factor for nevirapine-induced DDAR in Caucasians, Thais, and Indians [56, 62]. Other alleles described in association with nevirapine-induced allergy/DRESS include HLA-C*04 (in Caucasians, Afro-Americans, Africans, and Han Chinese) [56, 63], HLA-C*08 (in Caucasians and Japanese) [64], and the haplotype HLA-C*08-B14 (in Italians) [65]. As several HLA alleles have been described to be associated with nevirapine DDAR, genetic screening for this condition might be difficult to implement [56].

Nevirapine DDAR appears to be mediated both by CD8+ and CD4+ T cells (which can explain its association with both MHC class I and II molecules) [22, 66], and adverse reactions are more common and more severe in immunologically uncompromised patients undergoing HIV postexposure prophylaxis [67]. The risk of severe allergy is higher among patients with a CD4+ count >250 cells/μl (for females) or >400 cells/μl (for males). Nevirapine should, therefore, not be prescribed in these patients [55].

Concerning the immunopathogenesis of nevirapine DDAR, 12-OH-NVP and other reactive metabolites formed during biotransformation phase I reactions act as haptens, which, unlike nevirapine, are able to bind a carrier protein and, therefore, trigger an immune response [67]. Although the specific mechanism of drug-HLA interaction largely remains to be discovered, it is known that 12-OH-NVP formation is influenced by the patient's genotype [63]. Moreover, unlike drug exposure, both gender and CD4+ T-cell levels are known to be risk factors for nevirapine DDAR [63]. It has also been suggested that genes outside the HLA complex [namely noncodifying single nucleotide polymorphisms (SNP) within the *CCHCR1* gene] might play an additional role in the development of particular DDAR phenotypes [68]. This could possibly explain the large diversity of genotypes in patients who develop nevirapine DDAR.

Carbamazepine

Carbamazepine is an aromatic anticonvulsant mainly used in the treatment of epilepsy, bipolar disorder, and trigeminal neuralgia [69]. It has been associated with DRESS and SCAR occurring 2–8 weeks after treatment initiation [69]. These reactions are rare in Europeans (1–6 cases per 10,000 exposed patients) but almost 10 times more common in Han Chinese [22].

Many HLA alleles associated with carbamazepine-induced SCAR have been identified, and the strongest associations have been reported for HLA-B*15:02 and HLA-A*31:01 [70]. Carriers of these alleles are mainly of South Asian ancestry. In fact, the association between HLA-B*15:02 and the development of carbamazepine-induced SJS was first described among Han Chinese [71]. Several other studies have provided evidence to strengthen this association, which has been found in other Asian ethnicities such as Thai, Korean, Malay, and Indian populations, but not Japanese [70]. In a European case-control study including 12 carbamazepine-induced SJS/TEN cases, however, only 4 patients (all of Asian ancestry) were HLA-B*15:02 positive [72]. Therefore, this allele cannot be considered a universal marker for carbamazepine-induced SJS.

On the other hand, the HLA-A*31:01 allele has been described as a predictor of carbamazepine-induced DDAR in Northern European [73] and Japanese [74] patients. However, a subsequent meta-analysis found that HLA-A*31:01 expression was associated only with carbamazepine-induced DRESS (in Chinese and European individuals) not with carbamazepine-induced SCAR [75].

Protective HLA alleles (such as HLA-B*40:01 and HLA-A*24:02) against the development of carbamazepine cutaneous DDAR have also been identified, particularly in Asian populations [70]. It is still unknown, however, whether these alleles exert a true protective effect or simply appear to be more frequent in the general population than in SJS/TEN cases [70, 76].

Concerning genetic screening, in the case of HLA-B*15:02, a retrospective study performed in Thailand concluded that screening for this allele is less costly than treating carbamazepine-induced SJS cases [77]. However, according to the US Food and Drug Administration, screening for HLA-B*15:02 is only recommended for patients of Asian ancestry, since this allele is mainly expressed in those individuals [62]. On the contrary, although not routinely performed, screening for HLA-A*31:01 before carbamazepine prescription might prove cost-effective in some European countries, as the results of one British study suggested [78].

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According to Wei et al. [79], carbamazepine does not require intracellular metabolism or antigenic processing prior to HLA-B*15:02 binding. The authors also reported the existence of key residues in the HLA-B*15:02 peptide-binding groove (Ile^{95}, Leu^{156}, and, in particular, Asn^{63}) that are required for carbamazepine presentation and T-cell activation. Nevertheless, this study does not exclude the possibility that carbamazepine metabolites irreversibly bound to HLA-B*15:02 peptides might also play a role in triggering an immunological response [79]. Another possibility is that the role of HLA-B*15:02 in the immunopathogenesis of carbamazepine DDAR involves the modification of the peptides which are capable to bind HLA-B*15:02, allowing for the presentation of self-peptides [34].

A specific TCR clonotype – Vβ-11-ISGSY – has also been found to be present in 84% of patients with carbamazepine-induced SCAR, but absent in carbamazepine-tolerant individuals [80]. Thus, the pathogenesis of adverse drug reactions to carbamazepine appears to involve both a specific HLA allotype and a TCR clonotype [4].

Allopurinol

Allopurinol, a xanthine oxidase inhibitor that blocks uric acid production, is used for the treatment of chronic gout, hyperuricemia secondary to tumor lysis syndrome, and uric acid nephrolithiasis [81, 82]. Approximately 5% of patients exposed to allopurinol develop a DDAR, with manifestations ranging from mild rash to life-threatening conditions such as SJS and TEN, potentially accompanied by fever, hepatic dysfunction and kidney failure [82].

In 2005, a case-control study performed in Han Chinese found HLA-B*58:01 expression to be strongly associated with the development of allopurinol-induced SCAR [83]. Similar results were obtained in studies of other Asian populations, namely Thais, Japanese, and Koreans [84–86]. A significant, albeit weaker, association was also found in European patients [81]. A study by Lonjou et al. [87] found HLA-B*58:01 to be expressed in only 55% of patients with allopurinol-induced SJS/TEN, while a study by Gonçalo et al. [88] in Portuguese patients found the same allele to be present in 64% of patients with allopurinol-induced SJS/TEN and DRESS. The weaker association reported in Europeans might be due to differences in HLA-B*58:01 carriage rates – 20% of Han Chinese carry this allele compared with <6% of Caucasians [81]. Thus, screening for HLA-B*58:01 appears to be cost-effective in some Asian populations and in patients with advanced renal failure (vide infra) [4, 89, 90].

HLA-B*58:01 carriage is thus an important risk factor for the development of allopurinol-induced SCAR. According to one systematic review, allergy risk is 80–97 times higher in patients expressing this allele [91]. Nevertheless, HLA-B*58:01 expression is not sufficient to explain the occurrence of allopurinol DDAR [87], and, in fact, other risk alleles have been identified. One genome-wide association study conducted in European patients found 6 SNP to be associated with allopurinol-induced SJS/TEN [92]. The authors of the study also reported that carriers of the HLA-B*58 allele had a higher frequency of the haplotype CACGAC, which is formed by the risk allele of each of the 6 SNP [92]. The authors concluded that there is incomplete linkage disequilibrium between CACGAC and the HLA-B*58 allele and hypothesized that the main genetic determinants of allopurinol DDAR might not be the HLA-B alleles but rather some loci in linkage disequilibrium with these alleles. Finally, a Korean case-control study found that, compared with controls, patients with allopurinol-induced SCAR had a higher frequency of HLA-Cw*03:02 and HLA-A*33:03 but a lower frequency of HLA-A*02:01 [86]. Besides gout, allopurinol is also widely used for preventing hyperuricemia secondary to tumor lysis syndrome in patients with hematological neoplasms prior to starting chemotherapy [93]. However, the maculopapular eruptions recorded in this setting do not appear to be associated with HLA-B*58:01 expression but rather with the presence of HLA-DR9 and HLA-DR14 alleles [93].

Concerning the immunopathogenic mechanisms, as allopurinol is rapidly converted to oxypurinol by xanthine oxidase, recent studies have suggested that allopurinol DDAR might be mediated by both T cells reacting to allopurinol and T cells reacting to oxypurinol (fig. 3) [94]. T cells reacting to oxypurinol would appear to play a more important role, as this compound has a longer half-life and appears to bind more strongly to HLA-B*58:01 than allopurinol [94, 95]. Additionally, T cells reacting to oxypurinol are more restricted by HLA-B*58:01 for their activation [95].

Allopurinol and oxypurinol appear to activate a polyclonal effector T-cell response after binding directly to HLA-B*58:01 [95]. In fact, allopurinol and oxypurinol bind to HLA when its drug binding site is exposed (something which happens only transiently), 'forcing' a change of conformation in previously HLA-bound endogenous peptides. This new conformation is perceived as 'foreign' by T cells and triggers an immune response [95].

Activation of T cells reactive to allopurinol and oxypurinol occurs in a dose-dependent manner, and, therefore,

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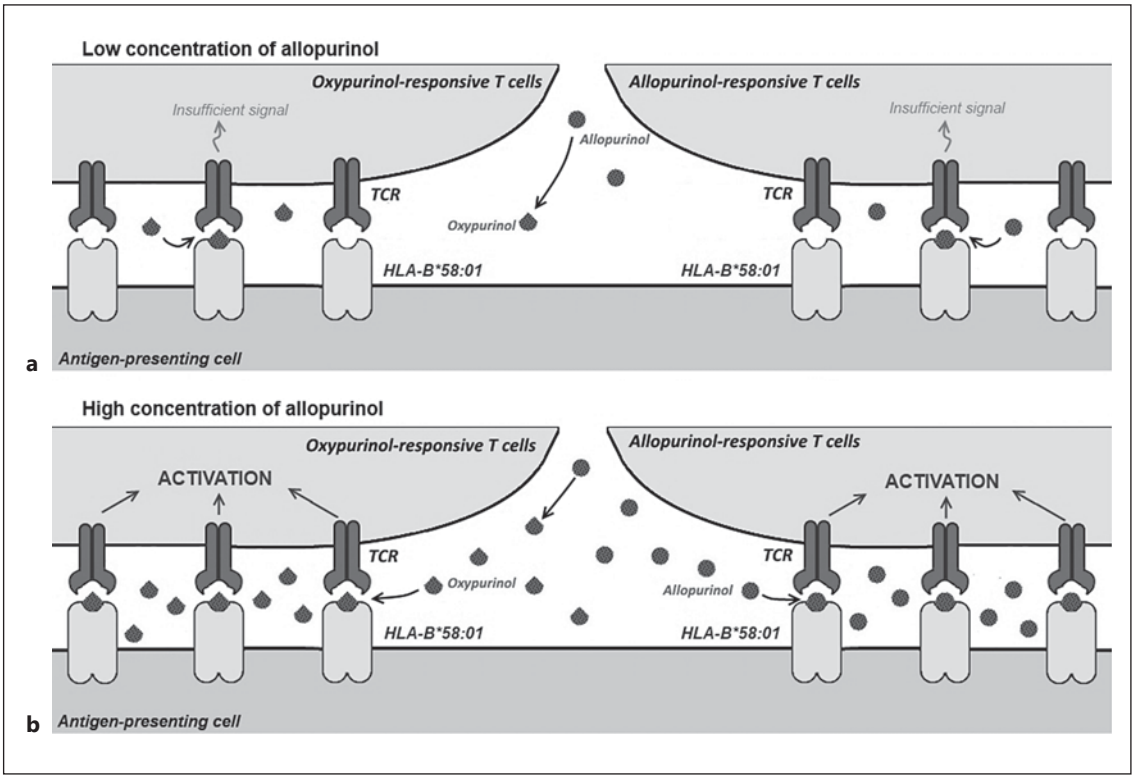

Fig. 3. Immunopathogenic mechanism underlying allopurinol DDAR. Allopurinol is extensively converted to oxypurinol by xanthine oxidase, with both molecules interacting with the HLA-B*58:01 allele. Low levels of allopurinol and oxypurinol (**a**) are incapable of generating a sufficiently strong signal to the TCR for cell activation. By contrast, high levels of allopurinol and oxypurinol (**b**) (as recorded in patients with chronic kidney disease) allow for T-cell activation.

higher doses of these compounds are associated with a higher risk of SJS/TEN [94, 96]. In fact, a higher starting dose of allopurinol has been identified as a risk factor for allopurinol DDAR [94]. Renal insufficiency, which is associated with impaired renal clearance and thus higher plasma levels of oxypurinol, is also considered a risk factor for allopurinol-induced SCAR [94, 97]. Moreover, renal insufficiency is associated with a poor prognosis, correlating with higher mortality and prolonged cutaneous reactions [97]. This evidence contests the dogma that type B adverse reactions are totally unpredictable and dose independent, thus opening the possibility for their prevention by desensitization techniques [94, 98]. In fact, no SCAR episodes were observed after Jung et al. [98] treated a sample of patients with a high risk of allopurinol-induced SCAR (HLA-B*58:01+ carriers with chronic kidney disease) to a tolerance induction protocol consisting of a gradual increase in allopurinol dose [98]. As previously mentioned, viral infections also appear to increase the risk of allopurinol-induced DDAR [37, 38].

Genetic Screening

Screening for alleles associated with drug-induced hypersensitivity can prevent the onset of these reactions. However, pharmacogenetic screening should be reserved for alleles whose association with DDAR is strongly supported by scientific evidence [99]. Additionally, the tests must be cost-effective and have high sensitivity, specificity, and predictive values (ideally, the negative predictive value should be 100% to ensure drug safety). Thus, the decision to implement a screening test should also be guided by the target population and the respective prevalence of the alleles being evaluated [22, 99].

There are several methods for identifying HLA-specific alleles. Genomic DNA sequencing-based typing, which is based on the Sanger method, is one of the most common methods, and is the gold standard for HLA-B*57:01 identification [100–102]. However, this method is expensive, not always available, and can yield ambiguous results [100, 101, 103]. Other methods include sequence-specific

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primer PCR and real-time PCR coupled with melting curve analysis. Although once popular, sequence-specific primer PCR can also generate ambiguous results and requires constant sequence updates [101, 103]. Real-time PCR, by contrast, is less prone to ambiguity and is highly specific, sensitive, and efficient [100].

Instead of screening for HLA alleles by sequencing-based typing or PCR, some laboratories opt for detecting SNP in linkage disequilibrium with the respective alleles. In Caucasians and Hispanics, the SNP rs2395029 is in linkage disequilibrium with HLA-B*57:01 [104]. Detection of rs2395029 is associated with a sensitivity of 100% and a specificity of 99% for the identification of HLA-B*57:01 carriers. However, despite this strong association, this disequilibrium is incomplete, and, in fact, detection of rs2395029 is associated with a positive predictive value <100% [104]. Based on the results of a Japanese study, rs9263726 (an SNP located within the *PSORS1C1* gene) is in complete linkage disequilibrium with the HLA-B*58:01 allele [105], leading the authors to conclude that rs9263726 detection can be effectively used to screen for HLA-B*58:01 carriage [105].

Detection of HLA-B*58:01 by loop-mediated isothermal amplification initially appeared to be a simple and rapid screening method, with high sensitivity and specificity. However, the higher risk of contamination and ambiguous results led the authors to recommend additional genotyping methods in the case of positive results [106]. Kostenko et al. [107] developed a monoclonal antibody that reacts against HLA-B*57:01 and HLA-B*58:01 proteins. However, while this antibody identifies HLA-B*57:01 and HLA-B*58:01 carriers, it does not discriminate between them. It could, therefore, be used as a prescreening test to quickly identify low-risk patients (non-carriers) and start them on treatment with abacavir or allopurinol without the need for further tests [107]. Finally, according to De Spiegelaere et al. [102], despite its low specificity, flow-cytometric investigation of the HLA-B*57:01 allele is a highly sensitive technique that would substantially decrease the number of genetic tests required.

Conclusion

DDAR are potentially fatal and hence represent a major health problem. As more and more drugs are becoming available, it is essential to study the immunogenetic mechanisms underlying DDAR. This characterization will enable the formulation of adequate strategies to prevent and treat these reactions. In fact, genetic screening is already a reality for abacavir and carbamazepine, and will help to prevent the development of DDAR in carriers of risk alleles.

Increasing evidence shows the crucial role played by HLA in DDAR. Despite the number of already known interactions between certain drugs and HLA alleles, much remains to be learned. Indeed, only a small number of HLA-drug interactions have been identified, and genetic screening is only routinely applied to an even smaller number of drugs, reminding that there is still a long way to go from bench to bedside. Furthermore, for many HLA alleles, the association with DDAR has only been established by epidemiological studies. However, understanding the underlying immunological mechanisms is of the utmost importance, as they can explain the symptoms and provide the basis for designing new treatment strategies. Nevertheless, HLA-drug interactions do not totally explain the development of DDAR. These reactions are multifactorial, and several polymorphisms and environmental factors might contribute to their onset. Characterization of these factors has only recently begun, and much information is still missing.

In conclusion, HLA alleles are intricately involved in DDAR. Understanding these interactions is essential for ensuring the administration of drugs with the best efficacy/safety profile. In fact, good clinical practice requires not only practical knowledge but also a solid theoretical basis.

Disclosure Statement

The authors declare that they have no conflict of interest.

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