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*HLA-B*58:01* is a Universal Pharmacogenetics Marker of Allopurinol- Induced Cutaneous Adverse Drug Reactions

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Abstract

Allopurinol is the most frequently prescribed serum urate-lowering drug in the management of gout due to its efficiency, widespread availability, and cost-effectiveness. However, although rare, the usage of allopurinol can cause severe cutaneous adverse reactions (SCARs) with high mortality rates such as Steven-Johnsons Syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reactions with eosinophilia and systemic symptoms (DRESS). A number of studies around the world has shown that *HLA-B*58:01* is the strongest pharmacogenetics marker for allopurinol-induced cutaneous adverse drug reactions, and most particularly for Asians, especially in Han Chinese (OR= 580.3, [95% CI: 34.4-9780.9], P= 4.7 x 10^{-24}), (OR= 123.5, [95% CI: 12.8-1195.1], P= < 1 x 10^{-4}), (OR= 580.07, [95% CI: 32.18–10,456.80], P= 7.01 × 10^{-18}), Thai (OR= 696, [95% CI: 74.81-1905.57], P= <0.001), (OR= 348.3, [95% CI: 19.2–6336.9], P= 1.61 x10^{-13}), and Korean (OR= 97.8, [95% CI: 18.3–521.5], P= 2.45 x10^{-11}) populations. Therefore, the worldwidestudy of *HLA-B*58:01* and its role in the immunopathogenesis of allopurinol-induced CADRs is incredibly significant. A routine screening for the presence of HLA-B*58:01 must be carried out before the administration of allopurinol as a preemptive measure to avoid severe cutaneous adverse reactions.

Keywords: allopurinol, *HLA-B*58:01*, cutaneous adverse drug reactions, SCARs

INTRODUCTION

Allopurinol [l H-pyrazolo (3,4-d) pyrimidin-4- 01] is a xanthine oxidase inhibitor that is used as a hypouricemic agent, it is a slightly water soluble with a molecular weight of 136.11. [1,2] It was initially developed in the 1960s to increase the effect of the drug mercaptopurine by inhibiting its xanthine oxidoreductase-catalysed metabolism. Thereupon it was discovered that allopurinol has the property of decreasing plasma concentrations of urate and significantly lessens the chances of an individual developing acute gout. The therapeutic effects of allopurinol are largely attributed to oxypurinol, which is allopurinol in its major metabolite form, but both function as xanthine oxidoreductase inhibitors. [3] Allopurinol is currently used as the standard urate-lowering therapy in the preemptive management of gout, primary and secondary hyperuricemia regardless of the recent development of new urate-lowering therapies. This is due to its accessibility, economical advantages and its efficacy when dosed appropriately. [4] Moreover, allopurinol is less acknowledged for other indications such as ischemia-

reperfusion injury, protozoal diseases, prevention of stones in the urinary tract and as a measure of liver impairment.[3]

Allopurinol is typically administered orally and is absorbed in the gastrointestinal tract, reaching peak concentrations at approximately 2mg/L about 1.5 hours after a standard oral dose of 300mg.[3] It is a structural isomer of hypoxanthine, thus it operates as a purine analogue and binds with the enzyme xanthine oxidoreductase as the substrate, subsequently inhibiting the oxidation of hypoxanthine and xanthine which produces uric acid. Consequently, an increased concentration of hypoxanthine and xanthine in urine and plasma and a decreased concentration of uric acid in plasma is observed. [1] Approximately 90mg of its active metabolite form, oxypurinol, is formed from every 100mg oral dose of allopurinol which serves the same function. The peak concentrations of oxypurinol are much higher at about 7 mg/L after the same single dose of allopurinol, but occurs at approximately 4 hours after dosing, which is longer than observed with allopurinol. [3] Findings have shown that capsules of sodium oxypurinol, with the bioavailability from these capsules at only 75%, produce only a slightly lesser hypouricemic effect than allopurinol when the two drugs are administered at equimolar doses. This proves the major mode of xanthine oxidoreductase inhibition to be done by oxypurinol. Oxypurinol's half-life is much longer but depends entirely on kidney function of an individual, ranging from approximately 18-30 hours in typical individuals up to a week in individuals with kidney impairment whilst the half-life of allopurinol is only approximately 1-2 hours. [2] The remaining estimated 10% of allopurinol is converted into allopurinol 1'-riboside. Thereafter, 76 ± 8% of the dosage is excreted as oxypurinol in the urine whilst 12 ± 6% of the dosage is left unchanged and excreted in the form of allopurinol. [3] The oxidation of allopurinol into oxypurinol is not carried out by the enzyme xanthine oxidoreductase, but rather aldehyde oxidoreductase. Thus, the conversion of allopurinol to oxypurinol in humans is not self-inhibitory. This is supported by the findings that the steady-state plasma concentrations of oxypurinol are proportional to the dose of allopurinol and oxypurinol is readily produced with every dose of allopurinol. [3] As aforementioned, allopurinol is the primary hypouricemic agent used to manage gout. Gout is the disease caused by an inflammatory response to the deposition of urate crystals in the joint. Persistent hyperuricemia results in urate accumulation in the vascular compartment beneath the inguinal ligament which causes the formation of urate crystals in the joints. Due to allopurinol and oxypurinol's property in inhibiting xanthine oxidoreductase and subsequently inhibiting the degradation of purines into urate, the production of uric acid is successfully stopped. [5]

Nevertheless, adverse drug reactions resulting from allopurinol intake can manifest with varying degrees of severity. Generally, reactions can be observed as gastrointestinal upset. Mild erythematous maculopapular rash is observed in approximately 2% of the patients but symptoms abate after drug discontinuation. [6] Other more serious and life-threatening adverse reactions, although seldom observed (occuring in 0.1% of patients), are collectively referred to as allopurinol hypersensitivity syndrome (AHS) or allopurinol-induced severe cutaneous reactions (SCAR).[7] AHS is characterized by a rash combined with eosinophilia, leukocytosis, fever, hepatitis and progressive kidney failure. [7] However, these terms do not make clear the distinction between Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and system symptoms (DRESS). [4] Discussions have been raised about the similarities of the clinical pictures between DRESS and AHS, and whether or not they are two distinct clinical entities. [2] We will use the term allopurinol-induced SCAR in this review as an umbrella term for all severe adverse reactions unless specifically stated otherwise. SCARs usually occur within eight weeks after beginning allopurinol therapy, with the median time to onset around 3 weeks and approximately 90% of cases occurring within 8-9 weeks after starting allopurinol. [4] Allopurinol-induced SCAR is rare but associated with notable morbidity and mortality ranging from 9% to 20%. Only 6 out of 100000 allopurinol users develop SJS/TEN, yet according to registry data, allopurinol is the most common cause of SJS/TEN in Europe and Israel, and the second most common cause of DRESS in Europe, Israel and Taiwan. [4] Mortality from SJS/TEN of any cause has been reported to be 23% at 6 weeks and 34% (95% CI 30-39%) at 1 year, and mortality of DRESS

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is approximately 10% [4,5]. According to the data from the spontaneous reports during 1984-2016 by the Health Product and Vigilance Center of Thailand, allopurinol is the 2nd ranked culprit drug causing SJS/TEN and DRESS in Thailand (http://thaihpvc.fda.moph.go.th/thaihvc/Public/News/uploads/hpvc 1_3_4 1007 18.pdf).

Adverse Drug Reactions: Types and Classification

Adverse drug reactions (ADRs) are defined by the World Health Organisation on the International Drug Monitoring in 1972 as a 'response to a medicine which is noxious and unintended, and which occurs at doses normally used in man'. [8] Additionally, they are described as "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product." They usually predict danger from consequent administration and mandate discontinuation, prevention, a different treatment or an alteration of dosage. [9] ADRs are fairly common and has remained relatively unchanged over time, with research suggesting that between 5% and 10% of patients may suffer from ADRs at admission, during admission or at discharge, despite various preventative efforts. [10] Moreover, ADRs are the cause of an approximate 6.5% of hospital admissions. A number of causes of ADRs have been identified, yet some still remain unclear. [11]

Traditionally, ADRs are classified into two types, A and B: Type A reactions, or often referred to as augmented reactions, are dose-dependent and predictable based on the basis of the pharmacology of the drug as shown in Table 1. [10,12,13] Approximately 80% of ADRs fall in this category.[14] Such reactions are usually revealed in clinical trials and are well recognised before the marketing of a drug. On the contrary, type B reactions, or bizarre reactions, are sporadic and idiosyncratic, they are not predictable on the basis of pharmacology of the drug in question. [10,11] These reactions are often influenced by immunological and genetic factors. The reactions, although relatively infrequent, tend to be more severe or fatal. Reactions in this category include undesirable effects like drug intolerance, idiosyncratic reactions which are inexplicable in terms of known pharmacological actions of the drug, and allergic or hypersensitivity reactions which are dependent on immunological mechanisms and can be further categorized. Therefore, type B ADRs often go unnoticed during clinical trials. Only approximately 15 % of ADRs cases are of type B. [14]

Factors that contribute to ADRs include the following patient characteristics: age, polypharmacy, sex, smoking, atopy and/or previous exposure. Furthermore, possible genetics and non-genetics factors or antigens can induce an immune response. [9] Immune responses, involving the formation of antibodies, can lead to drug hypersensitivity reactions. The drug hypersensitivity syndrome involves phenotypically different clinical diagnosis. Types I-III are mediated by antibodies. Type I reactions are due to IgE mediation and mainly cause urticaria, anaphylaxis, and asthma; type II are due to IgG, IgM mediation and reactions are based on immunoglobulin-mediated cytotoxic mechanisms, accounting mainly for hemolytic anemia, neutropenia and thrombocytopenia; type III reactions are immune complex-mediated such as serum sickness, vasculitis and lymphadenopathy; and type IV reactions are mediated by T cells, causing delayed hypersensitivity. [15] In this article, we will be specifically reviewing type IV hypersensitivity reactions.

T-cell mediated delayed-type hypersensitivity reactions (type IV reactions) have been classified by Gell and Coombs and classification scheme has been modified to 4 subtypes to represent the effector cell. [10] It encompasses a wide clinical spectrum which ranges from fixed drug eruption (FDE), maculopapular eruption (MPE), general exfoliative dermatitis or erythroderma, drug reaction with eosinophilia and systemic symptoms (DRESS) or drug-induced hypersensitivity syndrome (DIHS), Stevens- Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP). The severe cutaneous adverse drug reactions (SCARs) include DIHS or DRESS, SJS, TEN and AGEP. [16]

Severe Cutaneous Adverse Reactions (SCARs)

Drug-induced hypersensitivity syndrome (DIHS)/drug reaction with eosinophilia and system symptoms (DRESS)

The terms DRESS and DIHS are often used interchangeably and they are categorised as type IVb

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hypersensitivity reaction. According to a nationwide survey of DIHS patients, DIHS and DRESS could be part of a continuum of the same disease. [17,18] DRESS presents as a widespread rash with varying severity but without skin separation or blistering. [19] From a Thai study of 52 DRESS patients, the majority of the rashes were identified as maculopapular type (94.2%). [20] It is occasionally accompanied by fever (>38℃), internal organ involvement (usually hepatitis ALT>100U/L), hematologic abnormalities (often atypical lymphocytes and/or eosinophilia), edema or conjunctival injection [19,20]. Variable features of this syndrome include diffuse lymphadenopathy, pneumonitis, encephalitis, cardiac failure (myocarditis) and nephritis, which may be akin to viral infection (human herpesvirus 6, HHV-6 and cytomegalovirus, CMV). [19] Onset of symptoms typically occurs 2-8 weeks following the introduction of the drug to the patient and can be persistent. Prolonged or recurrent symptoms, sometimes weeks after discontinuation of the offending drug, have been linked to reactivation of virus infection.[21] However, because there is great overlap in the clinical features of symptoms with other syndromes, the diagnosis and identification of DRESS is particularly challenging. Different diagnostic criterias for DRESS are thus created, with the simplest and most commonly used being the European Registry of Severe Cutaneous Adverse Reactions to Drugs and Collection of Biological Samples (RegiSCAR). It requires the presentation of three or more of the following clinical features: hospitalization, acute rash, fever >38℃, enlarged lymph nodes involving at least two sites, involvement of at least 1 internal organ, blood count abnormalities with either lymphocytes above or below normal, eosinophil count above or platelets below laboratory limit.[18] In Asia, DRESS accounts for almost 1/10 of all ADRs cases, with a mortality rate ranging 3-10%, although majorly caused by multiple organ failure and sepsis. [18] Drugs that may induce DRESS are allopurinol, carbamazepine, phenytoin, phenobarbital, dapsone, mexiletine, salazosulfapyridine, minocycline, nevirapine and cotrimoxazole. [19,20]

Stevens-Johnson Syndrome (SJS) / Toxic Epidermal Necrolysis (TEN)

SJS and TEN are categorized as type IVc hypersensitivity reactions. They are the most fatal cutaneous hypersensitivity syndromes and consist of a spectrum of disease defined by the percentage of total body surface area (TBSA) involvement. [21] SJS is characterised by erythematous or purpuric macules, widespread blisters predominantly on the chest, and involvement of at least 2 mucosal surfaces and less than 10% detachment. Upon starting and withdrawal of the offending drug, re-epithelialization occurs, and which may be accompanied by post-inflammatory hyperpigmentation and scaling, with the average course of the disease lasting 2-3 weeks. Mortality is around 5% and reports show that withdrawal of the culprit drug reduces the risk of death by 30% per day, in the case of drugs with short half-lives. [22] TEN syndrome is characterized by the same atypical target lesions as SJS but with the detachment of large epidermis on more than 30% of BSA and a frequently positive Nikolsky sign. Laboratory abnormalities may include anemia, lymphopenia or neutropenia. Inflammation of internal mucosal surfaces such as the gastrointestinal and/or respiratory tract may be involved due to the massive release of proinflammatory cytokines into the systemic circulation. This can lead to metabolic imbalance, multiorgan failure, pulmonary embolism and gastrointestinal hemorrhage. Mortality rate of TEN is incredibly high at 30-50% thus the management of these cases require admission to burns or intensive care units and the discontinuation of the drug must be carried out immediately. [22] SJS and TEN are clinically similar but are distinct in the fact that SJS is used to define cases where blistering and epidermal detachment occur on <10% of TBSA whereas TEN is used to define cases with >30% TBSA affected. However, there is an overlap in this spectrum which could be defined as SJS/TEN in which 10-30% of TBSA is affected. [21].

Drug Recognition by HLA & Immunopathogenesis of Drug Hypersensitivity Reactions

The human leukocyte antigen (HLA), also known as the major histocompatibility complex (MHC) is majorly responsible for regulating immune responses, especially the immunopathogenesis of SCARs. It is encoded by two polymorphic gene families located at chromosome 6p21.3. [23] HLA molecules are

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membrane bound glycoproteins that bind processed antigenic peptides and present them to T cells. HLAs are generally grouped into two definite classes, HLA class I and HLA class II as shown in table 2. [21,23,24] HLA class I is a heterodimer containing transmembrane 3 α domains and β2-microglobulin. The highly polymorphic α1 and α2 domains form the peptide binding cleft. HLA class I is divided into 3 nomenclatures: HLA-A, HLA-B and HLA-C. [25,26] HLA class II is a heterodimer containing two polypeptide chains, α and β, which traverses the cell membrane and associate to form a heterodimer. Its two polymorphic domains, α1 and β1, form the peptide binding site. Its three nomenclatures are HLA-DR, HLA-DQ and HLA-DP. [25,27] However, because of the HLA genes' polymorphic tendencies that lead to great diversity, it can be divided into a few other classes including III and IV. [24]

Many researches have been carried out on the mechanisms underlying the drug hypersensitivity reactions (DHR), and a hypothesis put forward was that T-cell immune responses are pivotal in pathogenesis. Observations that many delayed drug-induced hypersensitivity reactions occur 2-6 weeks after the first drug exposure, are resolved with drug discontinuation and recur quickly with reintroduction, supports the hypothesis. Moreover, the observations suggest that initial drug exposure primes naive T-cells to generate a memory pool of T-cells that are restimulated on reexposure to the drug, directly imitating the natural immune response to infectious pathogens. [21] Multiple models have been proposed to explain how small-molecule pharmaceutical compounds might stimulate such immune activation, namely the hapten/prohapten model, the pharmacological interaction (p-i) model and the altered peptide repertoire model (figure 1). [28] These concepts are crucial in understanding how a drug activates the immune system and initiates delayed-type hypersensitivity by activating T cells.

The Hapten/Pro-hapten Model

Antigens are presented as peptides to T cells in the immune system. Some drugs are intrinsically immunogenic due to their macromolecular structure, thus eliciting the aforementioned response. Many drugs, however, have a molecular mass of <1000Da and are considered incapable of inducing an immune response on their own. They can be classified as haptens. [14] A hapten is a small molecule that covalently binds to a larger protein, soluble or cell-bound, subsequently altering its structure and/or chemical composition. For these drugs to become effective immunogens, they must bind covalently to proteins with high molecular weight to form a hapten-carrier complex which undergoes intracellular processing to generate chemically modified peptides that are incorporated into the HLA complex and presented to T-cells. [29] According to the hapten hypothesis, drugs must bind irreversibly to skin cells to form antigens that will be targeted by skin-infiltrating T-cell clones. [30, 31] Alternatively, some drugs or compounds are not chemically reactive on their own thus unable to form a covalent bond to peptides. These are pro-haptens, and they must be converted into a hapten by being metabolized into a compound that is more chemically reactive. Clinically, pro-haptens are potentially immunogenic for B and T-cells. [29] The hapten-protein interaction model leads to presentation of a hapten-modified peptide by HLA molecule which involves the formation of irreversible covalent bonds between the drugs and the peptides. [30] The drug haptenation effect requires longer time and can occur anywhere in the body. [28].

Pharmacological interaction with immune receptor (p-i) concept

Noncovalent drug binding to immune receptors involved in T-cell stimulation, HLA or TCR, is known as the p-i concept and is unusual in the way that a complete T-cell restricted immune reaction can be initiated. [32] DHRs according to the p-i concept are based on the direct, reversible binding of drugs to either HLA or TCR immune receptor proteins to directly activate T-cells. [21,33] The p-i concept postulates that only the presence of the drug, TCR on T-cells and peptide-HLA complex, which can be antigen-presenting cells or any tissue cell expressing HLA, are the components that leads to the effector functions of T-cells. The p-i mechanism to peptide only takes place on the cell surface, where the drug binds to immune receptors and makes the self-HLA look like an allo-HLA. [28,32] The reactive T cells expand and cause a cytotoxic reaction with a SCARs. [32] The p-i driven T-cell stimulations can be categorized into p-i HLA (indirect p-i) and p-i TCR (direct p-i), in other words, drug binding to HLA or

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TCR. This can result in partial T cell activation, where costimulation is required [33], or full stimulation which requires the drug-modified TCR/T-cell to interact with the HLA on APCs. [32] Previous study found the elution of peptides from *HLA-B*15:02*, which presents carbamazepine to reactive T-cell clones, were carrying a non-covalently bound carbamazepine, which supports this concept. [30] Nonetheless, the p-i concept was not created to negate the hapten or pro-hapten concept, but rather to complement it and provide a more in-depth method to conceptualize and find the root source of SCARs.

The Altered Peptide Repertoire Model

The altered peptide repertoire model postulates that a drug can interact with HLA molecules in a specific and noncovalent fashion, which leads to the presentation of immunogenic altered peptides and leads to a T-cell response manifesting as a DHR. Small drug molecules may occupy sites within the peptide bind cleft of HLA proteins thereby changing the chemistry and topography of the binding cleft. Binding of drug molecules to HLA occurs intracellularly. [28] This results in the selection of self-peptide antigens that are different from those usually bound by the unaltered HLA protein. Recent studies show that the altered peptide repertoire is the underlying mechanism of the pathogenesis of abacavir hypersensitivity in the context of HLA-B*57:01. [21]

The *HLA-B*58:01* allele has a major role in generating allopurinol or oxypurinol-specific T-cell responses. A study by Yun et al. in 2015 [34] found that allopurinol and oxypurinol can directly and immediately activate the drug-specific T-cells, in the manner that is consistent with the p-i concept proposed by Pichler et al. [28] The p-i mechanism is involved for both allopurinol and oxypurinol in both individuals with *HLA-B*58:01* and without *HLA-B*58:01* individuals, although oxypurinol-specific T-cells were more selectively restricted to *HLA-B*58:01*. This can be explained by the extra oxygen in oxypurinol that strengthens the interaction with the allele. Contrary to assumptions that drug metabolites induced immune response via hapten formation, the metabolite oxypurinol used the p-i mechanism exclusively for t-cell activation, relying on labile, immediate and direct binding of the drug to TCR or HLA instead of forming a hapten. Allopurinol/oxypurinol- specific T-cells require the drug to be present in solution, and the washing of drug-pulsed APCs causes the reactivity to be completely eradicated, which is inconsistent with the hapten/pro-hapten mechanism in which covalently bound hapten is resistant to the washing steps. The T-cell responses were proteasome independent, whereas hapten-dependent flucloxacillin-specific t-cells required drug presentation via a proteasome-dependent antigen processing pathway. Furthermore, the drugs activated T cell clones (TCC) immediately, while the hapten mechanism would exhibit a slower, more delayed response. Thus, it does not fit into the hapten/pro-hapten concept. [34].

***HLA-B*58:01*, the main pharmacogenetic marker associated with allopurinol -induced SCARs**

The HLA alleles are major susceptible genes for drug hypersensitivity. *HLA-B*58:01*, in particular, is reported to be strongly associated with allopurinol-induced SCAR, especially SJS/TEN. [35] A number of studies have been conducted to evaluate the association between *HLA-B*58:01* and allopurinol-induced SCAR in different populations. In this article, we have thoroughly reviewed 11 research studies with high association between *HLA-B*58:01* and cutaneous adverse reactions (CADRs) which include SCARS after allopurinol intake. Significant association is observed, especially within the 2 separate Thai (OR= 696, [95% CI: 74.81-1905.57], P= <0.001), (OR= 348.3, [95% CI: 19.2–6336.9], P= 1.61 $x10^{-13}$) [36,37], 3 separate Han Chinese (OR= 580.3, [95% CI: 34.4-9780.9], P= 4.7 x 10^{-24}), (OR= 123.5, [95% CI: 12.8-1195.1], P= < 1 x 10^{-4}), (OR= 580.07, [95% CI: 32.18-10,456.80], P= 7.01 × 10^{-18}) [38,39,40], and Korean (OR= 97.8, [95% CI: 18.3-521.5], P= 2.45 $x10^{-11}$) [41] case-control studies. These are stronger than the results from the 2 separate Japanese [42,43] and 3 separate European studies [44,45,46]. (Table 3) The distribution of *HLA-B*58:01* allele was carried by 8–15% of Han Chinese, 6.38% of Thai population, 0.6% of Japanese and 0.8% of European population [37,38,42,47]. Additionally, the allele frequency of *HLA-B*58:01* was similar in Thai and other populations such as African Americans, Caucasians, Hispanics, North American, Asians and Southeast Asians (Malaysia, Vietnam, Indonesia and Myanmar) [48,49,50,51,52]. Thus, the *HLA-B*58:01* can be used as a universal

pharmacogenetic marker for allopurinol-induced CADRs including SJS-TEN, DRESS and MPE for all populations.

Conclusion and Future Directions

Allopurinol is a highly effective and efficient therapy for most patients if it is administered at adequate doses. However, in rare cases, allopurinol can lead to the development of complex severe adverse drug reactions with variable clinical manifestation and high morbidity and mortality rate. The allele *HLA-B*58:01* is globally a strong pharmacogenetics marker for allopurinol-induced cutaneous adverse reactions (CADRs), and is most prominent in those of Asian (particularly Han Chinese, Thai and Korean) ethnicity. Results from a number of studies have shown that patients who develop allopurinol-induced SCARs are carriers of *HLA-B*58:01.* Therefore, the study of *HLA-B*58:01* and its role in the immunopathogenesis of allopurinol-induced CADRs is significant in future prevention of fatal cases of SJS/TEN and DRESS. Furthermore, with an increased usage of allopurinol, routine screening for the presence of *HLA-B*58:01* in patients before the administration of allopurinol, especially in countries with a prevalence of the allele, would be cost and time-efficient. Nevertheless, with insufficient research in some populations of the world, including Africans, Americans and Indians, high vigilance should still be maintained even after a negative screening result for *HLA-B*58:01.*

Conflicts of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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Table 1: Characteristics of ADRs Type A vs Type B [10,12,13]

Characteristics	Type A (Augmented)	Type B (Bizarre)
Pharmacologically predictable	Yes	No
Related to dose	Yes	Rarely
Frequency	Common	Uncommon
Mortality	Low	High
Morbidity	High	Low
Responsive to a reduction in dose	Yes	No
Rechallenge	Yes, with caution	No
Management	Reduce dose or withhold Consider effects of concomitant therapy	Withhold and avoid in the future

ADRs - Adverse drug reactions

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Table 2: Distinction of HLA class I and II [21,23,24]

	HLA class I	HLA class II
Chromosome	6	6
Structure	α-chain and β2-microglobulin heterodimer	α and β polypeptide chain heterodimer
Expression	On nucleated cells, platelets	B cells, activated T cells, monocyte/macrophage lineage
Nomenclature	HLA-A, HLA-B, HLA-C	HLA-DR, HLA-DQ, HLA-DP (each has two genes, -A and -B)
Source peptide	Cytosolic (intracellular)	Endosomal (extracellular)
Peptide length	8-10 amino acids	14-25 amino acids
Function	Present intracellularly processed peptides (of viral or self origin) to CD8+ cytotoxic T cells. Epitopes on certain expressed molecules also act as ligands for killer inhibitory receptors expressed on NK cells	Present peptides (mostly of exogenous origin) to CD4+ helper T cells

HLA- human leukocyte antigen; NK- natural killer; Ig- immunoglobulin

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Table 3: Presence of *HLA-B*58:01* in patients with allopurinol-induced CADRs

Ethnics	Types of CADRs	Case n/total	Control n/total	P-value	OR	95% CI	References
Thai	CADRs	29/30 (96.7%)	4/100 (4.0%)	<0.001	696	(74.81-1905.57)	[36]
	SJS/TEN	13/13 (100%)	4/100 (4.0%)	<0.001	579	(29.50–11362.67)	
	DRESS	10/10 (100%)	4/100 (4.0%)	<0.001	430.33	(22.64–8958.88)	
	MPE	6/7 (85.7%)	4/100 (4.0%)	<0.001	144	(13.85–1497.03)	
	SJS/TEN	27/27 (100%)	7/54 (13%)	1.61×10^{-13}	348.3	19.2–6336.9	[37]
Han Chinese	SCAR	51/51 (100%)	20/135 (15%)	4.7×10^{-24}	580.3	(34.4-9780.9)	[38]
	SJS/TEN, DRESS	19/20 (95%)	4/30 (13%)	$< 1 \times 10^{-4}$	229.7	(11.7–4520.4)	[39]
	CADRs	38/38 (100%)	7/63 (11.1%)	7.01×10^{-18}	580.07	(32.18–10,456.80)	[40]
	MPE	22/22 (100%)	7/63 (11.1%)	9.21×10^{-14}	339	(18.58–6186.39)	
	SJS/TEN	13/13 (100%)	7/63 (11.1%)	8.24×10^{-10}	203.4	(10.93–3785.04)	
	DRESS	3/3 (100%)	7/63 (11.1%)	0.002	52.73	(2.47–1124.13)	
	SCARs	16/16 (100%)	7/63 (11.1%)	7.40×10^{-12}	248.6	(13.48–4585.35)	
Korean	SCARs	24/26 (92.3%)	59/485 (12.2%)	2.45×10^{-11}	97.8	(18.3–521.5)	[41]
	DIHS	20/21 (95.2%)	59/485 (12.2%)	1.45×10^{-10}	161.5	(18.2–1430.9)	
	SJS/TEN	4/5 (80.0%)	59/485 (12.2%)	1.60×10^{-2}	34	(3.2–356.1)	
Japanese	SJS/TEN	4/20 (20%)*	6/986 (0.61%)	<0.001	40.83	(10.50-158.9)	[42]
	SJS/TEN	10/36 (27.8%)*	6/986 (0.6%)	5.39×10^{-12}	62.8	(21.2-185.8)	[43]
European	SJS/TEN	15/27 (55%)**	28/1822 (1.5%)	$<10^{-8}$	80	(34-187)	[44]
Caucasian (Northern Italian)	SJS/TEN	3/7 (42.8%)	6/115 (5.2%)	0.003	13.625	(2.774-69.448)	[45]
Portuguese	CADRs	16/25 (64.0%)	1/23 (4.3%)	5.9×10^{-4}	39.11	(4.49-340.51)	[46]

OR- odds ratio; CI- confidence interval; CADRs- cutaneous adverse drug reactions; SJS/TEN- Stevens-Johnsons Syndrome/Toxic Epidermal Necrolysis; DRESS- Drug reaction eosinophilia and systemic symptoms; MPE- maculopapular exanthem; SCARs- severe cutaneous adverse drug reactions; DIHS- drug induced hypersensitivity syndrome; 'European' includes individuals of France, Germany, Italy and Portugal ancestry.

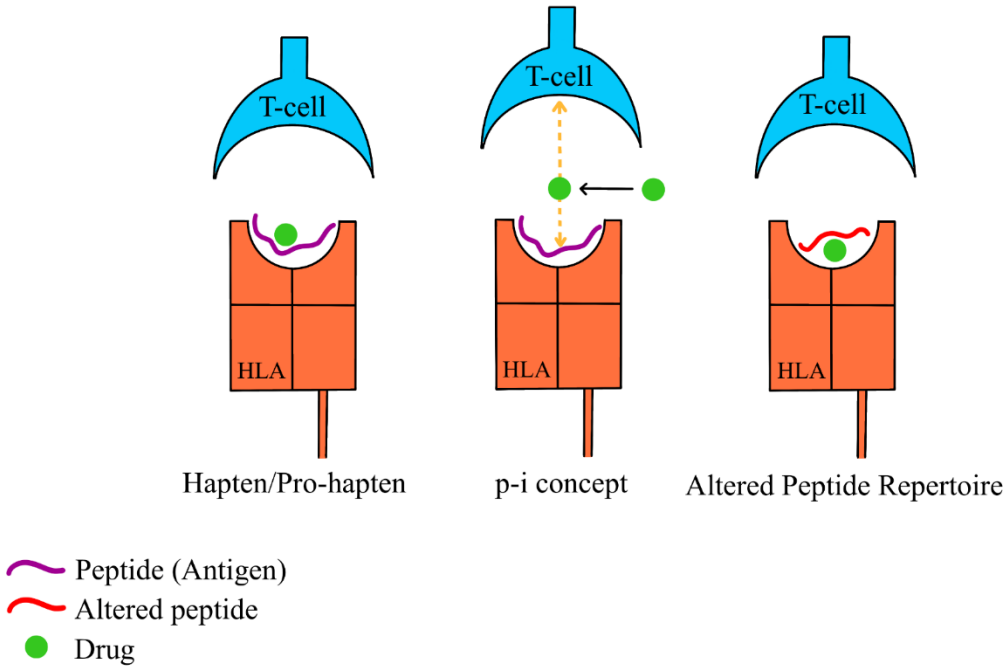

Figure 1: Immunopathogenesis of drug hypersensitivity reactions

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