Human leukocyte antigens: key regulators of T-cell mediated drug hypersensitivity.

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Abbreviations used:

ADR: Adverse drug reaction

AGEP: Acute generalized exanthematous pustulosis

EBV: Epstein Barr virus

CMV: Cytomegalovirus

DILI: Drug-induced liver disease

DRESS: Drug-reaction with eosinophilia and systemic symptoms

HHV: Human herpesvirus

HLA: Human leukocyte antigen

IM-ADR: Immunologically mediated adverse drug reaction

MPE: Maculopapular exanthema

MRGPRX2: Mas-related G protein-coupled receptor

MHC: Major histocompatibility complex

NNT: Number needed to treat (to prevent one case)

NPV: Negative predictive value

p-i: pharmacological interactions

PPV: Positive predictive value

SJS: Stevens-Johnson syndrome

TAP: transporter associated with antigen presentation

TCR: T-cell receptor

TEN: Toxic epidermal necrolysis

T_{reg}: Regulatory T cells

Abstract

Adverse drug reactions (ADR) can be broadly categorised as either on-target or off-target. On-target ADRs arise as a direct consequence of the pharmacological properties of the drug and are therefore predictable and dose dependant. On-target ADRs comprise the majority (>80%) of ADRs, relate to the drug's interaction with its known pharmacological target and are a result of a complex interplay of genetic and ecologic factors. In contrast off-target ADRs, including immune mediated ADRs (IM-ADRs), are due to unintended pharmacological interactions such as inadvertent ligation of host cell receptors or non-pharmacological interactions mediated through an adaptive immune response. IM-ADRs can be classified according to the primary immune cell involved and include B cell-mediated (Gell-Coombs type I-III reactions) and T cell-mediated (Gell-Coombs type IV or delayed hypersensitivity) reactions. IM-ADRs mediated by T cells are associated with phenotypically distinct clinical diagnoses and can vary from a mild delayed rash to a life threatening cutaneous, systemic or organ disease, such as Stephen Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and drug-induced liver disease (DILI). T-cell mediated ADRs are strongly linked to the carriage of particular HLA risk alleles which in the case of abacavir hypersensitivity and HLA-B*57:01 has led to translation into the clinic as a routine screening test. In this review, we will discuss the immunogenetics and pathogenesis of IM-ADRs and how HLA associations inform both pre-drug screening strategies and mechanistic understanding.

Introduction.

Adverse drug reactions (ADRs) are major causes of iatrogenic, potentially preventable patient morbidity and mortality. These reactions have a significant impact on health care systems and are the source of approximately 3-6% of inpatient admissions, comprising 5-10% of inpatient cost. They are estimated to be the fourth most common cause of death[1-4]. ADRs classified as "on-target" (also known as type A), account for up to 80% of all ADRs, and can be predicted based on the pharmacological activity of the drug. On-target reactions are typically dose dependent and may be compounded by altered pharmacokinetics resulting from comorbidities such as impaired renal or liver function, drug interactions or polymorphisms within drug receptor, transporter or metabolism genes and include reactions such as prolonged bleeding following warfarin therapy.

ADRs arising from "off-target" (also known as type B) interactions account for approximately 20% of all ADRs, however off-target effects may be under-recognized and under-reported. Off-target reactions include those that are directly immune-mediated ADRs (IM-ADRs) and are associated with immunological memory as well as pharmacological drug effects where an interaction of a drug with a receptor can lead to an immunological phenotype (urticaria) but there is no adaptive response. The latter includes interaction of drugs with the mas-related G-protein coupled receptor (MRGPRX2) on mast cell leading to non-IgE mediated mast cell activation[5]. IM-ADRs encompass several phenotypically distinct clinical entities comprising B-cell (antibody-mediated, Gell Coombs Types I-III) and T-cell (delayed type hypersensitivity, Gell-Coombs Type IV) mediated reactions. IM-ADRs display a range of clinical features including anaphylaxis, angioedema, urticaria, maculopapular exanthema, fever and internal organ involvement (e.g., hepatitis). T-cell mediated - delayed hypersensitivity - reactions present as a variety of clinical phenotypes including severe cutaneous syndromes, such as

maculopapular exanthema (MPE), acute generalised exanthema pustulosis (AGEP) and Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), systemic reactions such as abacavir hypersensitivity syndrome (AHS) and drug reaction with eosinophilia and systemic symptoms (DRESS), or as organ specific manifestations such as drug induced liver injury (DILI) and pancreatitis[6,7] (Figure 1).

Mechanisms and Specific Immunologically-mediated Adverse Drug Reactions

HLA

Multiple phenotypically distinct T-cell mediated ADRs have been associated with carriage of specific human leukocyte antigen (HLA) risk alleles (Table 1). HLA alleles (Figure 2), and particularly HLA-B which has been prevalently associated with drug-induced IM-ADR, are highly polymorphic with in excess of 8000 class I molecules and just over 3000 class II β-chain variants[8]. Regions of highest variability map to the peptide binding groves, maximising the diversity of self and pathogen derived peptides that can be presented to T cells. The amino acid sequence of peptides presented by individual HLA class I and class II molecules depends on components of the antigen processing pathway, such as tapasin and the proteasome[9], and on the amino acid anchor residues favoured by particular HLA alleles. The binding affinity for these anchor residues is dictated by pockets within the peptide binding groove of the particular HLA allele, designated A, B, C, D, E and F for class I molecules (Figure 2B) and P1, P4, P6 and P9 for class II molecules.

HLA class I molecules are present on the surface of all nucleated cells and, predominantly, present endogenously processed peptides to CD8 T cells. HLA class II molecules are present on antigen

presenting cells such as dendritic cells, macrophages and B cells. Class II molecules present exogenous peptides to CD4 T cells. Typically, class I presented peptides are in the order of 9-11 amino acids in length. As a result of the more open nature of the peptide binding groove, peptides presented by class II molecules are typically in the order of 11-15 amino acids in length. The mechanism by which small drug molecules, typically in the size range of 1-3 amino acids[10], stimulate T-cell responses remains incompletely understood, although three non-mutually exclusive models have been proposed to explain this apparent contradiction. These are (1) the hapten/prohapten model, (2) the pharmacological interaction with immune receptors (p-i) model and (3) the altered peptide repertoire model (Figure 3).

The hapten/prohapten model proposes that drug or drug metabolite binds covalently to a host protein which then undergoes intracellular antigen processing to generate a pool of chemically-modified peptides. When presented in the context of HLA these modified peptides are recognized as foreign by T cells and elicit an immune response[11,12]. Examples of this model include allergy to penicillin and reactive metabolites of sulfamethoxazole (nitroso-sulfamethoxazole)[13,14]. The pharmacological interaction with immune receptors (p-i) model postulates that the offending drug binds, non-covalently, to either the T-cell receptor (TCR) or HLA protein in a peptide-independent manner to directly activate T cells. This model has been hypothesized to explain T-cell reactivity that is labile (i.e., reactivity is abrogated by washing drug from the surface of antigen presenting cells) and/or is observed within seconds of drug exposure, a time course too short for intracellular antigen processing[15,16]. Finally, in the altered peptide repertoire model, the drug occupies a position in the peptide binding groove of the HLA protein changing the structure of the binding cleft and therefore the peptide

specificity of the HLA risk allele. The neo-epitopes displayed as a result of altered binding specificity are recognized as foreign by the immune system and therefore elicit a T-cell response[17,18].

The T-cell receptor.

HLA risk allele restricted T-cell responses have been detected to a range of drugs including HLA-B*57:01 presented abacavir[17,19-22], -B*58:01 restricted allopurinol and oxypurinol SJS/TEN and DRESS[23,24], -B*15:02 restricted SJS/TEN and -A*31:01 presented carbamazepine MPE>>DRESS>>>SJS/TEN[25-27] as well as -B*57:01 restricted flucloxacillin DILI[28]. Despite the clear role that T cells play in these reactions, the nature of the TCR is poorly defined and the degree of TCR specificity/clonality is likely unique for each drug-HLA combination. Abacavir specific T-cell responses are polyclonal[17,19,20] in keeping with the altered peptide model. Oxypurinol specific T-cell lines derived from the blood of patients with allopurinol SJS/TEN appear more restricted and show preferential Vβ TCR use within individual patients. However, public TCRs, those shared across different patients, were not identified in one study[29]. In contrast, in carbamazepine induced SJS/TEN patients, shared $CD8^+$ T-cell clonotypes bearing a public CDR3 sequence have been identified[30]. Zhou and colleagues have suggested that carbamazepine may make more intimate contacts with the TCR loops than the HLA molecule[31]. The carbamazepine data are significant as they suggest for the first time the concomitant involvement of both a specific HLA allotype and a specific TCR clonotype in the pathogenesis of a serious IM-ADR. However, it remains the case that a crystal structure of drug/HLA/TCR complex has yet to been solved for any T-cell mediated IM-ADR.

Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

SJS and TEN are two of the most severe IM-ADRs with an estimated patient mortality rate over 30% at one year following disease onset[32]. Cardinal features of SJS/TEN include widespread epidermal necrosis that resembles a severe burn injury and manifests clinically with skin, mucous membrane and eye involvement. SJS/TEN is a single disease with a cohesive immunopathogenesis and is defined by the percentage of body surface area involvement (SJS: 10% BSA affected; SJS/TEN overlap: 10-30% BSA affected; TEN: >30% BSA affected). Internal organ failure and secondary complications such as infection, thrombosis and deconditioning are frequently associated with acute SJS/TEN. Further, the long-term sequelae of this disease, including scarring, blindness and psychiatric illness, are a source of significant disability for survivors. SJS/TEN pathogenesis is characterised by widespread epidermal necrosis and detachment. Early skin lesions are characterized by the epidermis and dermoepidermal infiltration of $CD14^+CD16^+CD11c^+HLA\text{-}DR^+$ monocytes[33]. The pathogenesis is however, driven by cytotoxic $CD8^+$ T cells, NK cells and $CD3^+CD56^+$ NK T cells (NKT cells) which are enriched in blister fluid of patients with acute SJS/TEN[34-37]. Granulysin, a cytotoxic peptide produced by $CD8^+$ T cells, NK and NKT cells, is present in high concentrations in the blister fluid and is the key mediator of epidermal cell death in SJS/TEN[38]. Serum levels of granulysin associate with the severity of acute SJS/TEN and predict mortality[39,40].

Drug Reaction with Eosinophilia and Systemic Symptoms

DRESS, also known as drug induced hypersensitivity syndrome (DIHS), presents as a widespread rash of varying severity, without skin separation or blistering, and is frequently accompanied by fever, internal organ involvement (usually hepatitis) and hematologic abnormalities (often atypical lymphocytes and/or eosinophilia). Diffuse lymphadenopathy, pneumonitis, encephalitis, cardiac failure (myocarditis) and nephritis are variable features of this syndrome, which may mimic a viral illness.

Mortality rates in DRESS approximates 10%[41]. The onset of symptoms typically occurs 2-8 weeks following initiation of the inciting drug and can persist for weeks. Prolonged or recurrent symptoms, sometimes weeks following cessation of the offending drug, as well as late onset autoimmune diseases including thyroiditis, systemic lupus erythematosis and type I diabetes have been described up to four years following disease resolution[42]. Numerous drugs are associated with the development of DRESS including the allopurinol, antiepileptic medications (carbamazepine, phenytoin, phenobarbital and lamotrigine), beta-lactam antibiotics, NSAIDs, sulfa antimicrobials, other antibiotics such as vancomycin and minocycline and drugs used to treat other infections such as anti-mycobacterial drugs (rifamycins, isoniazid, ethambutol), dapsone and drugs used to treat HIV such as nevirapine, raltegravir and darunavir.

DRESS is associated with expansion of circulating and dermal-infiltrating effector T cells as well as $CD4^+FoxP3^+$ regulatory T cells (T_{reg})[43,44]. Skin homing $CD4^+FoxP3^+$ T cells are postulated to limit the severity of acute disease by suppressing effector T-cell responses[45]. Reactivation of human herpesviruses, in particular human herpesvirus (HHV)-6, but also Epstein-Barr virus (EBV), HHV-7 and cytomegalovirus (CMV) is universally observed during acute and recovery phase disease. HHV-6 and EBV reactivation has been observed as early as 2-3 weeks after onset of rash and antiviral $CD8^+$ effector T cells are expanded during this phase of disease. Whether viral replication contributes to the events inciting DRESS or is the result of general immune dysfunction, such as breakdown of T_{reg} suppressor function or the up-regulation of the HHV-6 receptor, CD134, on $CD4^+$ T cells, has not been defined[44-47]. Nevertheless, viral replication and a virus-specific T-cell responses likely contribute to the clinical features of DRESS including prolonged duration, multi-organ involvement and relapsing disease following withdrawal of glucocorticoid steroids.

Drug-induced Liver Disease

DILI is one of the more common causes of primarily single organ IM-ADR and accounts for 10% of all episodes of acute hepatitis and up to 13% of all instances of liver failure in the USA[48]. DILI can manifest within several days and up to 8 weeks post drug exposure. In some cases where the primary phenotype is severe drug-induced liver disease other features such as skin rash of varying severity have been described. Several drugs have been associated with the development of DILI including drugs withdrawn from the market such as ximelagatran, lumiracoxib, diclofenac, amoxicillin-clavulanate and flucloxacillin (Table 1). Amoxicillin-clavulanate (AC), one of the most heavily prescribed antibiotics, accounts for up to 17% of DILI cases requiring hospitalisation[49,50]. AC-DILI was first associated with carriage of the class II allele HLA-DRB1*15:01[51-53]. AC-associated DILI can present as either cholestatic, hepatocellular or mixed, phenotypes. This presentation appears to be subject to ethnicity, with French and Belgian populations experiencing a bias toward a cholestatic presentation. In contrast, Spanish populations presented with an almost equal proportion of cholestatic, hepatocellular or mixed phenotypes[54]. A later study of Spanish populations indicated that HLA-A*30:02 was associated with hepatocellular liver injury and the class II haplotype DRB1*15:01-DQB1*06:02 was associated with cholestatic or mixed pattern DILI[55]. Finally, HLA-A*02:01 which is haplotypic with DRB1*1501-DQB1*06:02 is associated with AC-induced DILI in Northwestern Europeans[56].

HLA and IM-ADRS: Representative Examples

Abacavir

AHS is an exemplar of T-cell mediated ADR, explaining both the HLA association and the mechanism of T-cell activation. The clinical features of abacavir hypersensitivity are not consistent with DRESS and the AHS is quite unique in its rapid onset and lack of associated eosinophilia and organ involvement paralleled only perhaps by azathioprine hypersensitivity which can present in a similar fashion. Abacavir is a guanosine analogue that is used as part of combination antiretroviral therapy for the treatment of HIV-1 infection. Early use of abacavir was associated with hypersensitivity reactions in 5-8% of patients[57]. Early reports described that AHS typically manifests within the first 6 weeks of therapy, however patch test positive or immunologically confirm AHS occurs from 1.5 days to 3 weeks following first drug exposure[58]. AHS is characterized by fever, malaise, gastrointestinal, respiratory symptoms, and/or generalized rash. In 2002, a strong association between carriage of the HLA class I allele, HLA-B*57:01, and AHS was reported[59], an association borne out by subsequent studies[60,61]. Using immunologically defined (patch test positive[62]) cases as a co-primary clinical endpoint, the PREDICT-1 study demonstrated that screening for, and exclusion of HLA-B*57:01 carriers from abacavir drug exposure could completely eliminate the incidence of true immunologically mediated (patch test positive) AHS. Another case-control study, the SHAPE study confirmed carriage of HLA-B*57:01 as a risk allele for AHS, generalizable across race. The PREDICT-1 study also demonstrated that HLA-B*57:01 carriage provided a 100% negative predictive value (NPV) and a 55% positive predictive value (PPV)[63,64] for AHS.

Abacavir shows exquisite specificity for HLA-B*57:01, failing to interact with closely related HLA alleles, HLA-B*57:02, HLA-B*57:03 and HLA-B*58:01, which differ by 2-4 amino acids. Amino acid differences between these alleles locates abacavir binding to the C-terminal end of the peptide binding groove[19]. The capacity of HLA-B*57:01 to present abacavir requires antigen processing, being dependent on

transporter associated with antigen presentation (TAP) and tapasin[19], although it does not require the proteasome[20]. The abacavir binding site on HLA-B*57:01, and the potential mechanism of disease, was defined in 2012 with the simultaneous publication of the crystal structures of HLA-B*57:01 in complex with abacavir and peptide by two independent groups[17,65]. Abacavir binds non-covalently within the HLA-B*57:01 peptide binding groove at the C, D, E and F pockets (Figure 4). Abacavir interacts directly with the two residues, Asp114 and Ser116, that distinguish HLA-B*57:01 from HLA-B*57:03. This binding alters the F pocket, under the C-terminus of the bound peptide, and induces a change in the binding properties of HLA-B*57:01. The canonical terminal anchor residues for HLA-B*57:01 are large aromatic amino acids such as Tyr or Phe. In the presence of abacavir, peptides with small aliphatic C-terminal residue (Ile, Leu, Val, Ala) are preferentially used as a terminal anchor residue, specificity for the p7 is also altered by the binding of abacavir[17,65,66]. Consequently, binding of abacavir alters the peptide specificity of HLA-B*57:01 such that 20-45% of the peptides eluted from abacavir-treated HLA-B*57:01 antigen presenting cells are distinct from those recovered from untreated cells[17,65,66]. These studies defined the altered peptide repertoire model of IM-ADRs and predicts that in the context of drug, numerous novel self-peptides are presented to T cells. These neo-epitopes are not subject to traditional tolerance mechanisms and can activate naïve T cells or stimulate cross reactive pre-formed memory T cells in a manner analogous to graft rejection and graft versus host disease, where T cells are also exposed to novel HLA molecules presenting self-antigens.

The exact mechanisms driving the pathology seen in AHS are not fully understood. Drug altered peptide binding should generate a vastly different immunopeptidome leading to the generation T cells with multiple specificities in patients with AHS. Abacavir specific $CD8^+$ T cells are present in patients with AHS[20,67] and are polyclonal in nature[17,19,20]. Abacavir specific $CD8^+$ T cell lines can be generated from

both memory and naïve precursors[21,68], suggesting that abacavir can stimulate cross reactive memory responses as well as promote the generation of de novo responses from naïve T cells. In support of the former proposition, AHS can occur rapidly after administration of the drug, in some instances within 2 days[21], well before the generation of de novo responses could occur. Memory responses are also suggested by the rapid and exaggerated clinical responses such as fever and shock seen in AHS patients inadvertently re-challenged with abacavir. Finally, abacavir reactive T cells can be identified in the blood of abacavir-naïve individuals[21]. The activation threshold for memory T cells is low compared to naïve cells as they do not require second signal. How abacavir leads to the activation of naïve T cells is less clear as these is no obvious danger signal associated with the drug. However a recent study, using supra-physiological concentrations of abacavir suggests that the drug is able to activate the NLRP3 inflammasome following phorbol ester TPA or Toll-like receptor pre-stimulation[69]. Inflammasomes, a component of the innate immune response, are triggered by pathogen associated patterns and facilitate inflammatory responses by cleaving pro-interleukin 1β to IL-1β. It is possible that naïve T cells are activated via the effects of drug on components of the innate response, such as the NLRP3 inflammasome that creates the initial danger signal, coupled with signals derived from cross reactive memory responses to the drug or response to infectious agents such as HIV.

Carbamazepine.

Carbamazepine is anticonvulsant used in the treatment of epilepsy and can lead to the development of MPE, DRESS and SJS/TEN (Table 1). MPE is most strongly associated with the carriage of HLA-A*31:01 Several class I alleles, including HLA-A*31:01 as well as, -A*01:01 and -Cw*07:01, -B*08:01 and class II alleles, DRB1*03:01, DQA1*05:01, DQB1*02:01 have been associated with the development of carbamazepine DRESS. SJS/TEN is associated with carriage of HLA-B*15:02 and HLA-A*31:01 (Table 1). The best characterised of these associations is carriage of HLA-B*15:02 and SJS/TEN. This association

was first noted for Han Chinese and later for Thai, Indian and Malaysian and Japanese populations[70-82]. Other members of the HLA-B75 serotype, HLA-B*15:08, HLA-B*15:11 and HLA-B*15:21 are also associated with carbamazepine SJS/TEN (Table 1). Modelling studies demonstrate that carbamazepine binding to HLA-B*15:02 maps to the B pocket with a likely primary contact at the Arg62 residue on the edge of the cleft, which is a conserved amino acid among HLA B75 serotypes[83]. Additional contacts at the Asn63, Ile95 and Leu156 residues also likely participate in carbamazepine HLA-B*15:02 interactions, as alteration of these residues results in reduced carbamazepine binding affinity[83]. Although peptide loading of class I is required, neither drug nor antigen processing is essential for T-cell activation which suggests an alternative mechanism to the altered peptide repertoire of MHC-drug interaction[17,83,64].

Allopurinol

Allopurinol is a purine analogue that is used in the treatment of gout and hyperuricemia. Like carbamazepine, allopurinol can cause a range of IM-ADRs (Table 1) including, MPE, DRESS and SJS/TEN. However, unlike carbamazepine, a single HLA risk allele, HLA-B*58:01, is linked to all these phenotypes. The association between allopurinol induced SJS/TEN and HLA-B*58:01 was first reported for the Han Chinese population[84] and later in other populations including Europeans[85], Thai[86] and Japanese[82]. Carriage of HLA-B*58:01 has a 100% NPV for allopurinol induced SJS/TEN in Han Chinese populations, but only a ~2.7% PPV[87]. Functional studies indicate that HLA-B*58:01 restricted reactivity is stronger to the metabolite oxypurinol than the parent drug. This and non-covalent interactions between HLA-B*58:01 and oxypurinol are supported by the fact that allopurinol is rapidly metabolised to oxypurinol and patients with renal insufficiency are at higher risk of developing allopurinol SJS/TEN and DRESS and have a poorer prognosis[88,89]. These later data are consistent with the dose dependency evidenced during the induction of allopurinol and oxypurinol specific T-cell lines[24,29].

Similar to carbamazepine, the presentation of allopurinol to T cells does not require-antigen processing. HLA-B*58:01 differs to HLA-B*57:01, which does not present allopurinol, by only 4 amino acids, 45 (Thr/Met), 46 (Glu/Ala), 97 (Arg/Val), and 103 (Leu/Val). Site directed mutagenesis studies suggested that Arg97, between the E and C pocket of HLA-B*58:01, may be a key contact residue for oxypurinol[90]. These data are consistent with molecular modelling studies which indicate that oxypurinol should make van der Waals interactions with residues surrounding the F pocket and established a hydrogen bond with Arg97 in HLA-B*58:01[23]. These studies also predict that allopurinol has a lower binding affinity for HLA-B*58:01 due to the lack of a critical oxygen molecule at position six in the pyrimidine ring which affects the hydrogen bond to Arg97. These data are consistent with finding that T-cell responses are skewed toward oxypurinol rather than the parent drug[23,29]. The putative binding sites of drug and metabolite are not consistent with a p-i model of T cell engagement leading some to suggest that intermittent disassociation of peptide and HLA could allow drug to bind under the peptide without requiring antigen processing[23].

Nevirapine

Nevirapine is a non-nucleoside reverse transcriptase inhibitor used in the treatment of HIV-1. NVP hypersensitivity affects approximately 5% of HIV infected individuals who start the drug and encompasses different clinical phenotypes with cutaneous, hepatic or systemic symptoms that include SJS/TEN, DRESS and DILI. The different IM-ADR phenotypes are associated with both shared and specific class I and class II HLA alleles, which have variable distribution and risk across ethnic groups. Cutaneous reactions range in severity from mild rash through to severe diseases with high morbidity

and mortality such as SJS/TEN and DRESS. Nevirapine DRESS and SJS/TEN share the same HLA-C*04:01 risk allele in African, Asian and European populations[91-93]. However the associations of HLA risk alleles with nevirapine DRESS show phenotype and ethnic specific differences with HLA-B*35 a risk allele for DRESS with grade III or IV rash in Asian populations[91,94], HLA-DRB1*01:01 and DRB1*01:02 associated with hepatic effects in African, Asian and European populations[91] and the HLA-C*08-B*14 haplotype associated with eosinophilia in Caucasians populations[95,96].

A recent analysis of cutaneous NVP hypersensitivity across Caucasian, African and Asian patients has shown unique distributions of risk alleles in each ethnic group, and a common F pocket of the HLA-C peptide binding groove and position 156R that are associated with hypersensitivity. The risk HLA-C F pocket and 156R are carried by HLA-C*04:01, as well as HLA-C*05:01 and HLA-C*18:01. An independent association with cutaneous hypersensitivity was demonstrated in a group of class II alleles which share the HLA-DRB1-P4 pocket, as well as NVP HSR protection attributed to a cluster of HLA-B alleles, including HLA-B*15:01, defined by a characteristic peptide binding groove B pocket[97]. This approach, considering HLA alleles according to specific shared pockets within the peptide binding groove may provide insight into other IM-ADRs in which multiple HLA risk alleles with shared peptide binding specificities are implicated across different ethnic groups.

Translation into Clinical Practice

Mapping of IM-ADR to specific HLA alleles permits the use of pharmocogenomic screening to identify patients are greatest risk for the development of severe drug reactions. However, for all HLA alleles so far identified, even those with NPV as has high as 100%, the PPVs are typically much lower (Table 1).

Therefore, where the NPV is 100%, specific HLA risk alleles are necessary but not sufficient for the development of IM-ADR. The utility and safety of pharmocogenomic screening for HLA risk alleles is influenced by the NPV as well as the number needed to treat to prevent one case (NNT). The NNT is a function of PPV, the frequency of the risk allele in the target population and the prevalence of the IM-ADR. Other factors may influence the utility of genetic screening including the cost effectiveness of screening in clinical practice, the severity of the clinical or economic consequences of the disease and the availability of alternative drugs that have a wider safety margin and/or do not require genetic testing[98,99]. Together these factors determine the cost and number of patients required to be tested to avoid one IM-ADR case and have implications for patients who may unnecessarily be denied optimal treatment, those that carry risk allele, but would not have developed an adverse reaction.

Despite these constraints, screening for risk HLA genes has been successfully applied to the prevention of IM-ADR. The first global screening program for HLA-B*57:01 prior to starting abacavir therapy has successfully eradicated reported cases of AHS in areas where routine HLA-B*57:01 screening has been introduced[100,101]. The high positive predictive value of HLA-B*57:01 for AHS (55%) has meant that this has been a cost-effective approach. For HLA-B*15:02 driven carbamazepine SJS/TEN, the prevalence of HLA-B*15:02 is highest amongst Asian populations (0.057–0.145 in Han Chinese, 0.085–0.275 in Thais and 0.12–0.157 in Malays) compared with European (0.01–0.02), Japanese (0.002) and Korean populations (0.004). Studies based in Taiwan and Thailand have demonstrated utility and cost-effectiveness of HLA-B*15:02 screening in such populations where the risk allele is most common[102,103]. Other screening programs currently being implemented or evaluated include HLA-B*58:01 testing prior to allopurinol initiation and CYP2C9*3/HLA-B*15:02/HLA-B*13:01 screening prior to phenytoin prescription in Southeast Asians[104-106].

Knowledge gaps and Future Directions

Despite advances in our understanding of the genetic and phenotypic traits that potentiate IM-ADR risk, a series of unanswered questions remain. Chief amongst these are; Although the presence of an HLA risk allele appears to be necessary for the development of a specific IM-ADR, why is the PPV of such risk alleles typically <10%? What drives the exquisite tissue specificity and clinical presentation of many of these reactions? Why do these reactions occur so rapidly in many cases and show evidence of immunological memory?

The variable and for the most part, low PPV associated with specific HLA risk alleles indicates that other mechanisms contribute to the development of IM-ADRs. Some of these will be patient specific variables such as renal and/or liver function or polymorphisms in genes that regulate drug metabolism[40,91,107-109]. However, many features of the disease may help unravel a more cohesive model of IM-ADR. For some IM-ADRs the first manifestation of disease occurs within 1.5 days of drug exposure[21]. In addition, drug re-exposure is typically associated with rapid and enhanced toxicity[11,57]. Taken together these features suggest the involvement of memory T cells. T cells primed via exposure to previously encountered pathogens mature into one of several memory phenotypes. Central memory T cells (T_{CM}) express CD45RO, CCR7 and L-selectin and circulate through lymph nodes via the circulation. Effector memory T cells (T_{EM}) express CD45R0, but do not express CCR7 and L-selectin and are excluded from the lymph node, being found in the peripheral circulation and tissues. Tissue resident memory T cells (T_{RM}) express CD45RO, CD69 and CD103 but not CCR7[110]. These latter cells are restricted to the tissues and do not recirculate in the peripheral blood. These T_{RM} are poised, ready to activate and proliferate, within tissues known to be affected by IM-ADR. Therefore, it is possible that

T_{RM} play a role as key mediators of disease or in the initiation of disease, these cells remain a critical area of study in understanding the pathogenesis of IM-ADRs.

The heterologous immunity model has been proposed as a means of addressing many of the unexplained features of IM-ADR[19,111]. In this model, pre-formed memory T cells, educated by prior exposure to common pathogens such as HHV, cross recognize the drug-altered self-peptide as foreign and initiates an inappropriate anti-self response. In this model, the tissue specificity is dictated, at least in part, by the location of memory T cells. For instance, skin involvement in SJS/TEN would be mediated by skin T_{RM}, recruited to and resident in the skin following prior infection with pathogens such as herpes simplex type 1 or 2. This may also explain why some patients with risk alleles such as HLA-B*58:01, which predispose to both allopurinol SJS/TEN and DRESS develop one condition over another depending on the specific memory cell population that cross-recognizes drug, the location of this population and the tissue specific repertoire of self-peptides. In an analogous situation, solid organ transplant rejection, it is clear that cross-reactive T cells mediate alloreactivity and in many instances these cross-reactive T cells have cognate specificity HHV[112].

Although many questions remain in explaining the nature of T-cell mediated ADRs, the characterisation of clear HLA associations are the critical first step. Well characterised HLA associations for particular IM-ADRs, such as HLA-B*57:01 and AHS or HLA-B*15:02 and SJS/TEN in Asian populations or HLA-B*58:01 and allopurinol SJS/TEN or DRESS continue to provide invaluable models that allow us to explore the unknown factors that contribute to variation in IM-ADR phenotypes and explain susceptibility of certain individuals such as differences in drug metabolism, TCR interactions and

contributions from the innate immune system. Taken together, these studies increase our understanding of all ADRs and provide a foundation to explore new drug induced adverse reactions as they arise.

Drug	DHR	HLA risk alleles	PPV	NPV	Populations
Abacavir	HSS/DIHS	B*57:01[58,61,113,114]	55%	100%	European, African
Carbamazepine	SJS/TEN	B*15:02[70-80]	3%	100% in Han Chinese	Han Chinese, Thai, Malaysian, Indian
		B*15:11[115,116]			Korean, Japanese
		B*15:18, B*59:01 and C*07:04[81]			Japanese
		B*15:21[117]			
		A*31:01[116,118-120]			Japanese, northern European, Korean
	HSS/DIHS/ DRESS	8.1 AH (HLA A*01:01, Cw*07:01, B*08:01, DRB1*03:01, DQA1*05:01, DQB1*02:01)[121]			Caucasians
		A*31:01[122]	0.89%	99.98%	Europeans
		A*31:01[122]	0.59%	99.97%	Chinese
		A*31:01[116,118-120]			Northern Europeans, Japanese, and Korean
		A*11 and B*51 (weak)[120]			Japanese
	MPE	A*31:01[123]	34.9%	96.7%	
	Any ADR	A*31:01[124]			
Allopurinol	SJS/TEN/DIHS/DRESS/MPE	B*58:01 (or B*58 haplotype)[85,125-131]	3%	100% in Han Chinese	Han Chinese, Thai, European, Italian, Korean
Oxcarbazepine	SJS/TEN	B*15:02 and B*15:18[132-134]	15:02 - 0.73%	15:02 -99.97	Han Chinese, Taiwanese
Lamotrigine	SJS/TEN	B*15:02 (positive)[133]			Han Chinese
		B*15:02 (no association)[135,136]			Han Chinese
Phenytoin	SJS/TEN	B*15:02(weak), Cw*08:01 and DRB1*16:02[72,73,137]			Han Chinese
	DRESS/MPE	B*13:01 (weak) B*5101 (weak)[137]			Han Chinese
Nevirapine	SJS/TEN	C*04:01[138]			Malawian
	HSS/DIHS/DRESS	DRB1*01:01 & DRB1*01:02 (hepatitis and low CD4+)[91,139]	18%	96%	Australian, European and South African
		Cw*8 or Cw*8-B*14 haplotype[96,140]			Italian and Japanese
		Cw*4[91,141]			Blacks, Asians, Whites, Han Chinese
		B*35[91] B*35:01[95] B*35:05[142]	16%	97%	Asian
	Delayed rash	DRB1*01[143]			French
		Cw*04[91,93]			African, Asian, European, and Thai
		B*35:05[142]			Thai
Dapsone	HSS	B*13:01[144]	7.8%	99.8%	
Efavirenz	Delayed rash	DRB1*01[143]			French
Sulfamethoxazole	SJS/TEN	B*38[85]			European
Amoxicillin-clavulanate	DILI	DRB1*15:01 A*02:01 DQB1*06:02, and rs3135388, a tag SNP of DRB1*15:01-DQB1*06:02 DRB1*07 and HLA-A1 (protective)[145-147]			European
Lumiracoxib	DILI	DRB1*15:01-DQB1*06:02-DRB5*01:01-DQA1*01:02 haplotype[148]			International, multi-center
Ximelagatran	DILI	DRB1*07 and DQA1*02[149]			Swedish
Diclofenac	DILI	HLA-A11[150]			European

Flucloxacilin	DILI	B*57:01 DRB1*07:01-DQB1*03:01 [151]	0.12%	99.99%	European
Lapatinib	DILI	DRB1*07:01- DQA2*02:01-DQB1*02:02/02:02[152]			International, multi-center
Methimazole/ Carbimazole/ Anti-thyroid drugs	Agranulocytosis	HLA-B*38:02 (*5 SNPs)[153-155] HLA-B*27:05(3/5 SNPs)[155,156] HLA-DRB1*08:03[153,155,157]	7% *30%	99.9% >99%	Chinese, Northern Han Chinese *European/Northern Han Chinese Chinese, Japanese, Northern Han Chinese Northern Han Chinese
Clozapine	Agranulocytosis/ Neutropenia	HLA-B*59:01[158] HLA-DQB1 (126Q) HLA-DQB1*05:02; HLA-B (158T) (HLA-B*39:01, HLA-B*39:06, HLA-B*38:01)[159] HLA-DQB1[160]	 35.1%		Japanese European European
Azathioprine	Pancreatitis	HLA-DQA1*02:01; HLA-DRB1*07:01[161]	9%		European
Statins	Myopathy	HLA-DRB1*11:01[162]			European, African
Asparaginase	Anaphylaxis	DRB1*07:01[163]			European

Table 1: HLA associations for IM-ADR

Figure 1. Gell and Coombs classification of hypersensitivity reactions. Drugs can elicit all of the defined reaction types, examples are shown in the text boxes at the bottom of the table. These include antibody mediated reactions (Type I-III) and T-cell and cytokine mediated reactions (Type IVa-d). Acute generalised exanthemetous pustulosis (AGEP), polymorphonuclear leukocyte (PMN), cytotoxic T cell (CTL), granulocyte macrophage colony stimulating factor (GM-CSF). Adapted from Pichler, 2007. Drug Hypersensitivity Reactions: Classification and Relationship to T-Cell activation, in Drug Hypersensitivity.

Figure 2. The human leukocyte antigen (HLA). **A**. The HLA genes are amongst the most polymorphic of all human genes and are located on the short arm (p) of human chromosome 6. The class I regions encodes the HLA-A, HLA-C and HLA-B genes whilst the class II regions encode HLA-DR, HLA-DQ and HLA-DP. **B**. Peptides are presented on the surface of cells in the context of HLA to the T cell receptor (TCR). For class I HLA alleles peptides bind within specific pockets, A, B, C, D, E and F, of the peptide binding groove. The B and F pockets bind the anchor residues, P2 and P9 of each peptide providing binding specificity to a particular HLA molecule. The TCR engages with the CDR3 region of the HLA molecule and appropriate solvent exposed peptide residues.

Figure 3. Models of T cell-mediated drug hypersensitivity. (I) In the hapten/prohapten model the drug forms covalent bonds with endogenous peptides or proteins. This modified complex is processed via conventional antigen processing pathways and presented on the surface of cells in the context of HLA. The de novo antigens thus displayed are recognised as foreign by host T cells. (ii) In the p.i model non-modified drug binds directly to immune receptors such as the TCR via non-covalent bonds (dashed line), this response is independent of peptide or antigen processing. (iii) In the altered peptide model drug binds non-covalently within the peptide binding groove thereby altering the chemistry of the antigen binding cleft. This alters the repertoire of peptides capable of binding to a specific allele - creating a pseudo-allogenic HLA molecule - which presents non-tolerised altered self to T cells.

Figure 4. Solved structure of abacavir-peptide-HLA complex. **A**. Intramolecular contacts within the peptide binding cleft of HLA-B*57:01 and peptide and abacavir. HLA-B*57:01 in grey, synthetic peptide (HSITYLLPV) in cyan. Abacavir is shown as orange for carbon, blue for nitrogen and red for oxygen. Residues that distinguish HLA-B*57:01 from the abacavir insensitive allele, HLA-B*57:03, are shown in magenta for carbon, blue for nitrogen and red for oxygen. Black dashed lines show hydrogen bonds from abacavir to both the peptide and HLA-B*57:01. **B**. Model of abacavir-peptide-HLA interacting with the TCR. HLA is depicted in grey, peptide in cyan (carbons) and abacavir as orange for carbon and blue for nitrogen. TCR is depicted in pink.

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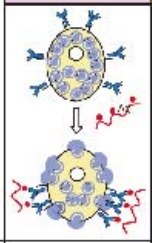
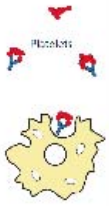
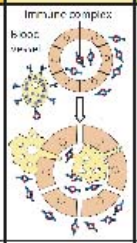
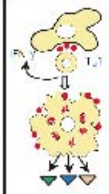
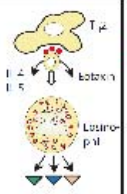
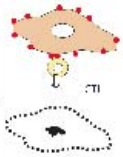
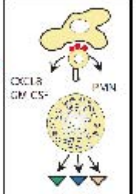
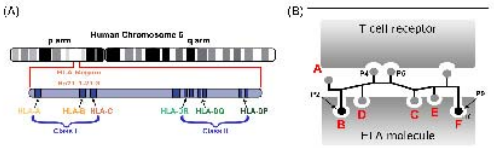
Figure 1. Gell and Coombs classification of hypersensitivity reactions. Drugs can elicit all of the defined reaction types, examples are shown in the text boxes at the bottom of the table. These include antibody mediated reactions (Type I-III) and T-cell and cytokine mediated reactions (Type IVa-d). Acute generalised exanthemetous pustulosis (AGEP), polymorphonuclear leukocyte (PMN), cytotoxic T cell (CTL), granulocyte macrophage colony stimulating factor (GM-CSF). Adapted from Pichler, 2007. Drug Hypersensitivity Reactions: Classification and Relationship to T-Cell activation, in Drug Hypersensitivity.

Figure 2. The human leukocyte antigen (HLA). **A**. The HLA genes are amongst the most polymorphic of all human genes and are located on the short arm (p) of human chromosome 6. The class I regions encodes the HLA-A, HLA-C and HLA-B genes whilst the class II regions encode HLA-DR, HLA-DQ and HLA-DP. **B**. Peptides are presented on the surface of cells in the context of HLA to the T cell receptor (TCR). For class I HLA alleles peptides bind within specific pockets, A, B, C, D, E and F, of the peptide binding groove. The B and F pockets bind the anchor residues, P2 and P9 of each peptide providing binding specificity to a particular HLA molecule. The TCR engages with the CDR3 region of the HLA molecule and appropriate solvent exposed peptide residues.

Figure 3. Models of T cell-mediated drug hypersensitivity. (I) In the hapten/prohapten model the drug forms covalent bonds with endogenous peptides or proteins. This modified complex is processed via conventional antigen processing pathways and presented on the surface of cells in the context of HLA. The de novo antigens thus displayed are recognised as foreign by host T cells. (ii) In the p.i model non-modified drug binds directly to immune receptors such as the TCR via non-covalent bonds (dashed line), this response is independent of peptide or antigen processing. (iii) In the altered peptide model drug binds non-covalently within the peptide binding groove thereby altering the chemistry of the antigen binding cleft. This alters the repertoire of peptides capable of binding to a specific allele - creating a pseudo-allogenic HLA molecule - which presents non-tolerised altered self to T cells.

Figure 4. Solved structure of abacavir-peptide-HLA complex. **A**. Intramolecular contacts within the peptide binding cleft of HLA-B*57:01 and peptide and abacavir. HLA-B*57:01 in grey, synthetic peptide (HSITYLLPV) in cyan. Abacavir is shown as orange for carbon, blue for nitrogen and red for oxygen. Residues that distinguish HLA-B*57:01 from the abacavir insensitive allele, HLA-B*57:03, are shown in magenta for carbon, blue for nitrogen and red for oxygen. Black dashed lines show hydrogen bonds from abacavir to both the peptide and HLA-B*57:01. **B**. Model of abacavir-peptide-HLA interacting with the TCR. HLA is depicted in grey, peptide in cyan (carbons) and abacavir as orange for carbon and blue for nitrogen. TCR is depicted in pink.

	Type I	Type II	Type III	Type IVa	Type IVb	Type IVc	Type IVd
Immune reactant	IgE	IgG	IgG	IFN-γ, TNF-α (T_H1 cells)	IL-5, IL-4 / IL-13 (T_H2 cells)	Perforin/ granzyme B (CTL)	CXCL8, GM-CSF (T cells)
Antigen	Soluble antigen	Cell or matrix associated antigen	Soluble antigen	Antigen presented by cells or direct T cell stimulation	Antigen presented by cells or direct T cell stimulation	Cell associated antigen or direct T-cell stimulation	Soluble antigen presented by cells or direct T cell stimulation
Effector	Mast cell activation	FcR– cells (phagocytes, NK cells)	FcR– cells Complement	Macrophage activation	Eosinophils	T cells	Neutrophils
							
Example of hypersen-sitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Hemolytic anemia, thrombocyto-penia (e.g., penicillin)	Serum sickness, Arthus reaction	Tuberculin reaction, contact dermatitis (with IVc)	Drug reaction with eosinophilia and systemic symptoms, Maculopapular exanthema with eosinophilia	Stevens-Johnson-Syndrome/Toxic Epidermal Necrolysis, Fixed drug eruption, Hepatitis	Acute generalized Exanthematous Pustulosis, Behçet's disease



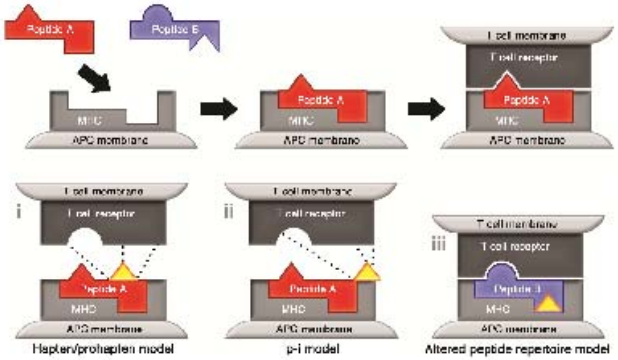


Figure 4