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Fever, rash and systemic symptoms: understanding the role of virus and HLA in severe cutaneous drug allergy

Rebecca Pavlos, PhD[a], **Simon Mallal, MB BS**[a,b], **David Ostrov, PhD**[c], **Yuri Pompeu, PhD**[c], and **Elizabeth Phillips, MD**[a,b]

[a] Institute for Immunology and Infectious Diseases, Murdoch University, Western Australia

[b] Vanderbilt University School of Medicine, Tennessee, USA

[c] Dept. of Pathology, Immunology and Laboratory Medicine, University of Florida, College of Medicine, Florida, USA

Abstract

Drug hypersensitivity syndromes such as abacavir hypersensitivity and the severe cutaneous adverse drug reactions (SCAR) have been associated with significant short and long-term morbidity and mortality. More recently these immunologically mediated and previously unpredictable diseases have been shown to be associated with primarily Class I and also Class II HLA alleles. The case of the association of HLA-B*57:01 and abacavir hypersensitivity has created a translational roadmap for how this knowledge can be utilized in the clinic to prevent severe reactions. Although many hurdles exist to the widespread translation of such HLA screening approaches, our understanding of how drugs interact with the MHC has contributed to the discovery of new models that have provided considerable insights into the immunopathogenesis of SCAR and other T-cell mediated drug hypersensitivity syndromes. Future translation of this knowledge will facilitate the development of pre-clinical toxicity screening to significantly improve efficacy and safety of drug development and design.

Keywords

DRESS/DIHS/HSS; SJS/TEN; abacavir; carbamazepine; HLA; viral reactivation

Corresponding Author: Professor Elizabeth Phillips, MD, FRCPC, FRACP Vanderbilt University School of Medicine Division of Infectious Diseases 1161 21st Avenue South A-2200 Medical Center North Nashville, TN 37232-2582 elizabeth.j.phillips@vanderbilt.edu.

Conflicts of Interest: Drs. Phillips and Mallal have equity in IIID Pty Ltd which has a patent for HLA-B*57:01 testing for abacavir hypersensitivity

CASE STUDY

A 37 year old Thai woman with stable previously asymptomatic untreated HIV-1 disease (CD4+ count 640/μl) was diagnosed with multi-dermatomal Herpes Zoster infection of the trigeminal nerve (V1/V2) by her general practitioner. There was no clinical eye involvement and she was commenced on acyclovir 800 mg 5 ×/day for 7 days. The next day on follow-up with ophthamology she was not found to have eye involvement and was started on indomethacin, codeine and carbamazepine 200 mg bid p.o. for pain control. On day 7 following commencement of carbamazepine she was found to be well with evidence of healing Herpes Zoster infection. Prescription for carbamazepine 200 mg bid p.o., indomethacin suppositories 100 mg bid and paracetamol-codeine was repeated at this time. On day 10 following commencement of carbamazepine she was noted to have a generalized rash and complained of a sore throat. She was admitted to hospital on day 11 when the rash progressed and was associated with nausea, increasing throat soreness and a fever of 41.3 C and all drugs were ceased. Physical examination at this time showed lesions of the mouth and genitals and an extensive generalized rash with atypical target lesions and skin separation. On day 12 she was transferred to the burn unit with a diagnosis of probable carbamazepine-induced toxic epidermal necrolysis with body surface area involvement greater than 80%. There was no noted eye involvement. Laboratory tests also indicated impaired liver function: alkaline phosphatase was 298 U/L (40-135 U/L normal range) and ALT was 429 U/L (normal range 11-36 U/L). The rest of her hospitalization was uncomplicated and she was discharged on day 30 on flucloxacillin 500 mg qid p.o. She was given the advice to permanently avoid not only carbamazepine but all other aromatic amine anticonvulsants such as oxcarbazepine, phenytoin, phenobarbital and lamotrigine. Follow-up two weeks after discharge revealed her to have healing skin with normalization of liver function and cessation of trigeminal pain (Figure 1A). She remained clinically well from the standpoint of HIV and was started initially on zidovudine 250 mg bid, lamivudine 150 mg bid and indinavir 800 mg tid po 1.5 years later and then switched to Trizivir (zidovudine/lamivudine/abacavir) 3 years later because of concerns of fat redistribution. She remained clinically well and virologically suppressed (current HIV viral load < 40 copies/ml). Patch tests to 0.1, 1 and 10% carbamazepine in petrolatum and petrolatum negative control conducted 9.5 years following carbamazepine TEN when she was still virologically suppressed on Trizivir were strongly positive for all concentrations of carbamazepine and negative for petrolatum control (Figure 1B). The patient also had multiple positive INFγ ELISpot with PBMCs stimulated with carbamazepine with the last being over 17 years following the initial TEN diagnosis (Figure 1B). HLA typing was conducted revealing that the patient carried HLA-A*11:01, -**B*15:02**/58:01, -C*03:02/08;01 and HLA-DRB1*03:01/12:02.

SEVERE CUTANEOUS ADVERSE DRUG REACTIONS (SCARs)

The immunologically mediated, “type B” ADRs are amongst the most dangerous off-target ADRs. Among the type B ADRs are a subset of reactions which can be characterized by severe cutaneous manifestations and are collectively referred to as severe cutaneous adverse reactions (SCAR). There are three phenotypically distinct SCARs (i) Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), (ii) acute generalized exanthematous

pustulosis (AGEP) and (iii) Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as drug-induced hypersensitivity syndrome (DIHS) or hypersensitivity syndrome (HSS)[1]. Abacavir hypersensitivity syndrome (ABC HSR) is a distinct entity which does not clinically fit into any of these categories.

SJS and TEN are considered to be clinically and immunopathogenetically the same syndrome representing different severities across the spectrum. The level of skin detachment is used to demarcate the two syndromes. SJS is characterised by 1–10% detachment, there is 10-30% overlap and then TEN represents the most severe cases with >30% detachment. SJS/TEN can also be characterised by mucous membrane involvement and systemic symptoms including fever, liver chemistry elevations, intestinal and pulmonary manifestations, or the presence of lymphopenia. With prevalence of 2-6 cases / million per year, both syndromes are associated with high morbidity and mortality; 1-5% mortality for SJS and 30-50% for TEN. The most common drugs causing SJS/TEN are allopurinol, aromatic amine anticonvulsants (eg. carbamazepine, eslicarbazepine acetate, oxcarbazepine, fosphenytoin, phenytoin, phenobarbital, lamotrigine), antiretrovirals (particularly nevirapine), NSAIDS and sulfa antimicrobials).

AGEP is an acute febrile drug eruption characterized by numerous small, primarily nonfollicular, sterile pustules, arising within large areas of edematous erythema. In AGEP drug-specific T cells produce interleukin-8/CXCL8, leading to neutrophil recruitment resulting in acute widespread edematous erythema followed by a sterile pustular eruption. The onset of disease is typically rapid and often within 1-3 days of drug initiation. The condition is also characterised by fever and possible eosinophilia[2, 3]. Beta-lactam antibiotics, quinolones, hydroxycholoroquine, pristinamycin, sulfonamides, diltiazem, and terbinafine are all known to cause AGEP[4]. AGEP has been rarely associated with infections, non-drug antigens and viral reactivation[3, 5-10]. The prognosis is usually good, with resolution occurring within 15 days. Although an early report suggested a possible association between AGEP and HLA-B*51, it is currently uncertain as to whether AGEP is strictly HLA-restricted[11].

DRESS/DIHS/HSS by definition is associated with fever, rash, eosinophilia and/or atypical lymphocytosis, cutaneous involvement and hepatitis typically occurring 2 or more weeks after first drug initiation. Although there have been many drugs described as causing DRESS/DIHS/HSS, drugs typically involved overlap considerably with those causing SJS/TEN and include antimicrobial sulphonamides, aromatic amine anticonvulsants, beta-lactam antibiotics, allopurinol, NSAIDs and antiretrovirals (nevirapine)[1]. The Japanese definition of DIHS also includes viral reactivation as a criteria for diagnosis and this tends to occur in the most severe cases with the most prevalent being reactivation of HHV-6 and other viruses in the Human Herpesvirus (HHV) family[12, 13].

MANAGEMENT OF SCAR

The mainstay of treatment of SJS/TEN, ABC HSR and other SCAR is causality assessment and immediate withdrawal of the most likely implicated drug(s). Early and rigorous supportive care is crucial [14]. For SJS/TEN this includes early ophthamology consultation

and severe cases should be managed in an intensive care setting with dermatology consultation and care. Multidisciplinary care with ear nose and throat, gynecology and psychiatry may also be necessary for short and long-term complications of SJS/TEN. Current treatment remains controversial and there is really no good evidence that a specific treatment or combination of treatments has a benefit over rigorous supportive care at a specialized center. In small studies calcineurin inhibitors such as cyclosporine appear to have some benefit in halting disease progression and early reports have also suggested a possible benefit for tumor necrosis factor receptor antagonists and plasmaphoresis. Large controlled studies are lacking and there are no multicenter studies of a factorial design comparing different treatments. Although early studies suggested a potential benefit for intravenous immunoglobulin (IVIg) for SJS/TEN more recent studies and pooled analyses have not shown an effect on mortality. Long-term follow-up for SJS/TEN is necessary in view of the eye and mucous membrane complications. For DRESS/DIHS similar controversies apply and a study looking at IVIg was stopped prematurely because of adverse events including pulmonary embolism. Steroids are recommended for use in DRESS when there is severe internal organ involvement (ie renal, lung or ALT > 10 × ULN). AGEP is a self-limited disease with general recovery within 2 weeks of disease onset. Topical steroids have been successfully applied in both DRESS/DIHS and AGEP but without controlled data.

HLA IN SCAR

There are many known genetic associations between specific HLA alleles and drug hypersensitivity and SCARs, supporting an immunologically driven mechanism for the development of SJS/TEN and DRESS/DIHS/HSS (Table I). The best characterized examples are abacavir HSS and its association with HLA-B*57:01, carbamazepine SJS/TEN associated with HLA-B*15:02, as in the current patient, and allopurinol DRESS/DIHS/HSS and SJS/TEN associated with HLA-B*58:01. The prevalence of these reactions in a specific population correlates well with the prevalence of allele carriage (Figure 2). The antiretroviral drug nevirapine appears to be associated with different HLA allele and haplotype associations which are ethnicity and phenotype dependent[15-22]. ABC HSR now provides a roadmap for successful translation of laboratory based research into pharmacogenetics in the clinic (Figure 3).

Abacavir

Abacavir (ABC) is a guanosine analogue associated with a hypersensitivity syndrome in the pre-marketing phase of its development characterized predominantly by fever, malaise, gastrointestinal symptoms in up to 8% of those starting treatment and mild-moderate rash was a late feature present in only 70%[23]. A strong association between the HLA class I allele, HLA-B*57:01, and ABC HSR was first reported in 2002[24-26]. Later work, improved the clinical diagnosis of true immunologically mediated ABC HSR through the use of patch testing [27-30]. Following this, a case-control study of black and white patients in the US, demonstrated that 100% of both white and black patch test-positive patients with a clinical history consistent with ABC HSR carried HLA-B*57:01[30]. It is now recommend by international guidelines that HLA-B*57:01 screening is carried out before the initiation of

abacavir therapy[31]. Crucially the negative predictive value for this test is 100%. This means that individuals without the HLA-B*57:01 will not develop ABC HSR. Testing results in a reduction in the incidence of ABC HSR[28, 30] and is cost-effective[32, 33].

Due to its narrow HLA restriction and high positive predictive value of 55%, ABC HSR provided a unique model for the study of HLA-related drug hypersensitivity. The PPV refers to the number of HLA-B*57:01+ individuals who would develop HSR if given ABC therapy. Laboratory evidence has shown that ABC HSR is HLA-B*57:01 restricted and mediated by CD8+ T lymphocytes. Infiltrating CD8+ T cells are present within the skin of ABC HSR patients with rash[34] and TNFs and INFγ are produced by ABC HSR patient PBMCs *in vitro*[35, 36]. In addition, CD8+ T cells from patients from ABC-naive patients carrying the HLA-B*57:01 allele proliferate in response to ABC in long term culture and are specifically activated by the drug. These T cells display a polyclonal response with the broad use of V beta receptors. This activation appears to be dependent upon peptide processing via the conventional MHC-I presentation pathway[37].

Carbamazepine

Carbamazepine (CBZ) is a widely used anticonvulsant associated with SJS/TEN in individuals carrying HLA-B*15:02[38, 39]. Initial studies identified the association in the Han Chinese population and this has since been reproduced in individuals of Thai, Malaysian and Indian ethnicities[40-44] and for other alleles on the B75 serotype [42, 43, 45]. Like ABC, genetic testing for HLA-B*15:02 is readily available for routine clinical practice and has been associated with a positive predictive value of up to 3-7.7% for carbamazepine-induced SJS/TEN in the Han Chinese population [39] and is recommended by the FDA for individuals of East and Southeast Asian ethnicity. In a study of 4120 patients of Han Chinese background who tested negative for HLA-B*15:02 and subsequently received carbamazepine, none developed SJS/TEN [46]. However, HLA-B*15:02 has not been found to be a risk factor for CBZ SJS/TEN in Caucasian populations where the carriage rate of this allele is <0.1% (Figure 2). The Taiwanese data as well as more recent European data suggests an association between HLA-A*31:01 and CBZ DRESS/DIHS. Some but not all studies in predominantly Caucasian populations have suggested an association between HLA-A*31:01 and CBZ associated SJS/TEN[47-49].

Similar to abacavir HSR, CBZ-induced SJS/TEN has been shown to be mediated by CD8+ T cells. CBZ specific T cells have been isolated from SJS patients and exposure to drug activates granulysin release[50]. A dominant TCR V beta 11 clonotype VB-11-ISGSY has been identified in blister fluid and PBMCs in 84% of SJS/TEN patients, 14% of healthy controls and absent in CBZ tolerant controls. Furthermore, CBZ-dependent cytotoxicity can be blocked by anti-TCR-Vb-11 antibodies in these cells. Finally, both a VB-11-ISGSY clone and specific VB-11-ISGSY transfectants display cytotoxicity against HLA-B*1502 positive APCs in the presence of CBZ[50]. This study highlights the importance of both HLA type and TCR repertoire in CBZ induced SJS/TEN. However, it is important to note that the identified drug specific clonotypes were not present in all of the CBZ-SJS/TEN patients.

MODELS FOR THE IMMUNOPATHOGENESIS OF ABACAVIR HSR and CARBAMAZEPINE SJS/TEN

Several models have previously been suggested to explain the nature of immune activation during drug induced SCAR, including the hapten hypothesis where small molecule drugs are hypothesized to covalently bind to and modify self-proteins leading to immune recognition of a neoantigen[51] and the pharmacological-interaction (p-i) concept which states that drugs can interact directly and non-covalently with the MHC and/or T-cell receptor inducing the formation of HLA:drug complexes which activate T-cell immune responses directly without requiring a specific peptide ligand[52]. Evidence now supports the ***altered peptide repertoire hypothesis***, which in the case of ABC has now been verified by modelling and crystallography data showing that ABC binds non-covalently to the F anchor pocket of HLA-B*57:01, to alter the chemistry and shape of the antigen binding cleft[53, 54]. It has also been demonstrated that this binding alters the presented peptide repertoire with particular self-peptides presented only in the presence of ABC which are able to be recognized by T cells of hypersensitive patients[53-55]. The presentation of novel peptides therefore explains drug-induced hypersensitivity as the product of drug, HLA-type and the available T-cell repertoire that will respond to newly presented self-peptides (Figure E1 a video that shows this can be found in the online repository). Further insight into the interaction between CBZ and HLA-B*15:02 was provided by demonstrating that PBMCs from patients with CBZ SJS/TEN stimulated a specific population of CTL exhibiting cytotoxicity against B lymphoblastoid cell lines (B-LCLs) or keratinocyte transfectants expressing the HLA-B*15:02 allele. The effect could be blocked by anti-HLA-B antibodies. The study showed that endogenous peptide–loaded HLA-B*15:02 molecules presented CBZ to cytotoxic lymphocytes (CTLs) without the involvement of intracellular drug metabolism or antigen processing yet endogenous peptide binding was required to stabilize the HLA class I complex on the cell surface. Furthermore, the CBZ binding has been shown to be specific to members of the HLA-B75 serotype and modifications of the ring structure of CBZ altered HLA-B*15:02 binding and abrogated the CTL response. Finally, site directed mutagenesis has shown that the residues (Asn63, Ile95, and Leu156) in the peptide binding groove of HLA-B*15:02 are involved in CBZ presentation and CTL activation. In particular, Asn63 shared by members of the B75 family is the key residue. Supporting this, computational modelling shows that CBZ compounds are preferentially bound in the B pocket and consistently observed in the binding groove near Arg62[56]. An independent study also supports binding in this region and predicted that CBZ binds beneath the P4/P6 residues of the peptide, adjacent to position 156[53]. Similar to ABC it was demonstrated that the binding of CBZ to HLA-B*15:02 alters the repertoire of presented self-peptides[53].

VIRAL REACTVATION IN DRESS/DIHS/HSS AND ADDITONAL IMMUNOPATHOGENETIC MODELS FOR SCAR

The reactivation of chronic persistent viruses in the HHV family including HHV-6/7, CMV and EBV has been described with most but not all drugs implicated in DRESS/DIHS/HSS (Table II). Viral reactivation has been an uncommon occurrence in other SCAR syndromes. The most prevalent HHV virus reported to reactivate has been HHV-6[57-63] and more

recently HHV-7, EBV and/or CMV reactivation have also been observed in up to 76% of DRESS/DIHS/HSS patients[62, 64, 65]. Sequential reactivation of EBV, HHV-6 and CMV has been described to occur in some patients with DRESS/DIHS/HSS[59, 60]. When viral reactivation occurs it can be asymptomatic, cause recrudescence of DRESS/DIHS/HSS or cause organ specific viral disease, and this is highlighted by recurrent drug specific DRESS/DIHS/HSS and organ specific viral disease in cases where there has been inadvertent rechallenge of the implicated drug[66]. In addition there appears to be an EBV-driven expansion of CD8+ lymphocytes in many DRESS patients in both patients with or without EBV reactivation within the blood, skin, liver and lung. The DRESS/DIHS/HSS associated drugs CBZ, sulfamethoxazole and allopurinol have been shown to contribute to increased EBV production by EBV-transformed B lymphocytes from patients. It has been proposed that the general nature of this effect in DRESS patients may be due to inhibition of enzymes which promote EBV reactivation or via specific interactions of the drugs with enzymes regulating gene transcription but this is controversial[62]. Another complication of DRESS/DIHS/HSS is the development of autoimmune disease after resolution of the initial drug reaction and this has been reported in patients with prior HHV reactivation (Table III)[67-70]. Viruses such as EBV that can persist for the lifetime of the host and are re-activated during DRESS/DIHS/HSS and defective regulatory T cell function have also been proposed to be relevant to the pathogenesis of autoimmune diseases[71]. Alternatively, it has been suggested that another pre-existing predisposition to auto-immune disease may contribute to the development of a drug hypersensitivity syndrome[63, 72].

Several factors are necessary but not sufficient for the pathogenesis of ADRs as exemplified by ABC and CBZ. The HLA-allele-drug interaction as in the altered peptide model is a key factor but does not explain why some individuals with susceptibility alleles are free from adverse effects, in other words why only 55% of HLA-B*57:01 positive patients treated with ABC, and 3% of HLA-B*15:02 positive patients treated with CBZ develop HSR and SJS/TEN respectively. The CBZ example suggests the role of available TCR clonal types. The final requirement for a drug induced adverse reaction is the presence of a self-peptide that will bind to the drug-HLA complex and activate the appropriate T cell. Although viral reactivation appears to be a complication of DRESS/DIHS/HSS associated with many drugs, given the time course of this reactivation and the fact that multiple HHV have been shown to reactivate, it does not explain the immunopathogenesis or onset of DRESS/DIHS and its specific and varied clinical syndromes. Furthermore DRESS/DIHS/HSS appears relatively unique in its association with HHV reactivation. Substantial evidence supports a model of heterologous immunity mediated organ transplant rejection that is likely to apply to at least some drug hypersensitivity syndromes. In organ transplantation, pre-existing class I restricted effector memory T-cell responses to prevalent viral infections can mediate organ rejection[73-78]. It has been shown that allo-HLA reactivity of virus-specific memory T cells is common[77, 79]. Both naïve and memory CD4+ and CD8+ T cells frequently cross-react against allogeneic HLA molecules and this allo-recognition exhibits exquisite peptide and HLA specificity and is dependent on both public and private specificities of the T cell receptor[80]. Finally, allo-HLA cross-reactive responses show tissue specificity depending on presentation of tissue-specific self peptides[27, 77, 78, 81-84]. Similarly, the persistence of patch test reactivity in patients with previous ABC skin symptoms more than 9 years after the

ADR and negative skin patch testing in ABC-naive individuals, despite ABC responsive cells in circulation, supports the presence of tissue specific resident memory cells homing to the skin as a result of a prior systemic reaction[27, 85].

In keeping with this, HSV specific CD8+ effector memory T-cells may reside in the epidermis poised to kill keratinocytes presenting an HSV epitope in the context of the appropriate HLA molecule. In the setting of CBZ associated SJS/TEN for instance it could be proposed that altered peptide presentation by HLA-B*15:02 in the presence of CBZ may be cross recognised by tissue resident-memory CD8+ T-cells specific for viral peptides and mediate SJS/TEN[86-88].

CONCLUSIONS

We report a case study of a HLA-B*15:02, CBZ induced SJS/TEN patient who has shown a durable drug-specific immune response 17 years after her initial reaction, as also observed in HLA-B*57:01 positive ABC HSR patients[27, 85]. Our case was also unusual in having a positive patch test 9.5 years after the original reaction as patch testing has been reported to be less than 30% sensitive in SJS/TEN. The less than 100% negative predictive value and <50% sensitivity of patch testing for most SCAR (abacavir hypersensitivity>DRESS/DIHS/AGEP>>SJS/TEN) mean that clinical diagnosis is still the gold standard that drives management. Similarly in terms of *ex vivo* assays ELISpot appears to be more sensitive than lymphocyte transformation tests but these are also adjunctive research tests not available to most centers and they lack 100% sensitivity/negative predictive value. Current evidence for the pathogenesis of HLA-mediated drug hypersensitivity, including ABC and CBZ supports a complex model of HLA-drug non-covalent interactions which result in an altered repertoire of self-peptides presented to the available T-cell population. Both the speed and tissue specificity of the immunological response also support the stimulation of pre-existing memory cell response. Furthermore, although Ag-specific T-cell responses are actively maintained, they are reversible and short lived in the absence of drug exposure to provide the stimulating antigen[89-91]. It is known that the patient is HSV-2, VZV, CMV and HIV positive and it is possible that a viral epitope(s) (or overlapping epitope(s)) may be responsible for the previous systemic immune response and subsequent maintenance of the CBZ-HLA-B*15:02-self peptide responsive memory T cells.

Although very different clinical phenotypes, there are significant immunopathogenetic parallels between ABC HSR and CBZ SJS/TEN suggesting that many SCARs may share common immunopathogenetic mechanisms. An increased understanding of structural and biochemical basis of how drugs interact with HLA molecules, the functional consequences and the pathogenesis of the incomplete positive predictive value and varying clinical phenotypes will provide a strategy for pre-clinical screening and approaches to improve the safety and cost-effectiveness of drug development. HLA screening to prevent life-threatening immunologically mediated drug reactions such as CBZ SJS/TEN and others can be useful and cost-effective measures to improve drug safety. This has been evidenced by marked decreases in the incidence of CBZ associated SJS/TEN in Taiwan, related to decreased off-label use of CBZ, but also due to the recommendation and government funding of HLA-B*15:02 screening prior to CBZ prescription. However, there are

population specific considerations for many of these drugs and testing may not be available in all jurisdictions. There are also numerous hurdles that exist to clinical translation. The ABC “roadmap” for genetic screening to prevent ABC HSR, from discovery through to translation of a genetic test in routine clinical practice acts as a successful example that can be applied to the development of screening tests for other drugs to improve patient care (Figure 3).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

ADR	Adverse drug reactiony
SCAR	Severe cutaneous adverse drug reaction
SJS	Steven-Johnson syndrome
TEN	Toxic epidermal necrolysis
AGEP	Acute generalized exanthematous pustulosis
HSS	Hypersensitivity syndrome
HSR	Hypersensitivity reaction
DRESS	Drug reaction with eosinophilia and systemic symptoms
DIHS	Drug-induced hypersensitivity syndrome
NSAIDS	Non-steroidal anti-inflammatory drugs
ABC	Abacavir
CBZ	Carbamazepine
HLA	Human leukocyte antigen
TCR	T cell receptor
PBMC	Peripheral blood mononuclear cell
INF-g	Interferon gamma
HHV	Human Herpesvirus
CMV	Cytomegalovirus (HHV-5)
EBV	Epstein–Barr virus (HHV-4)
HSV2	Herpes simplex virus (HHV-2)

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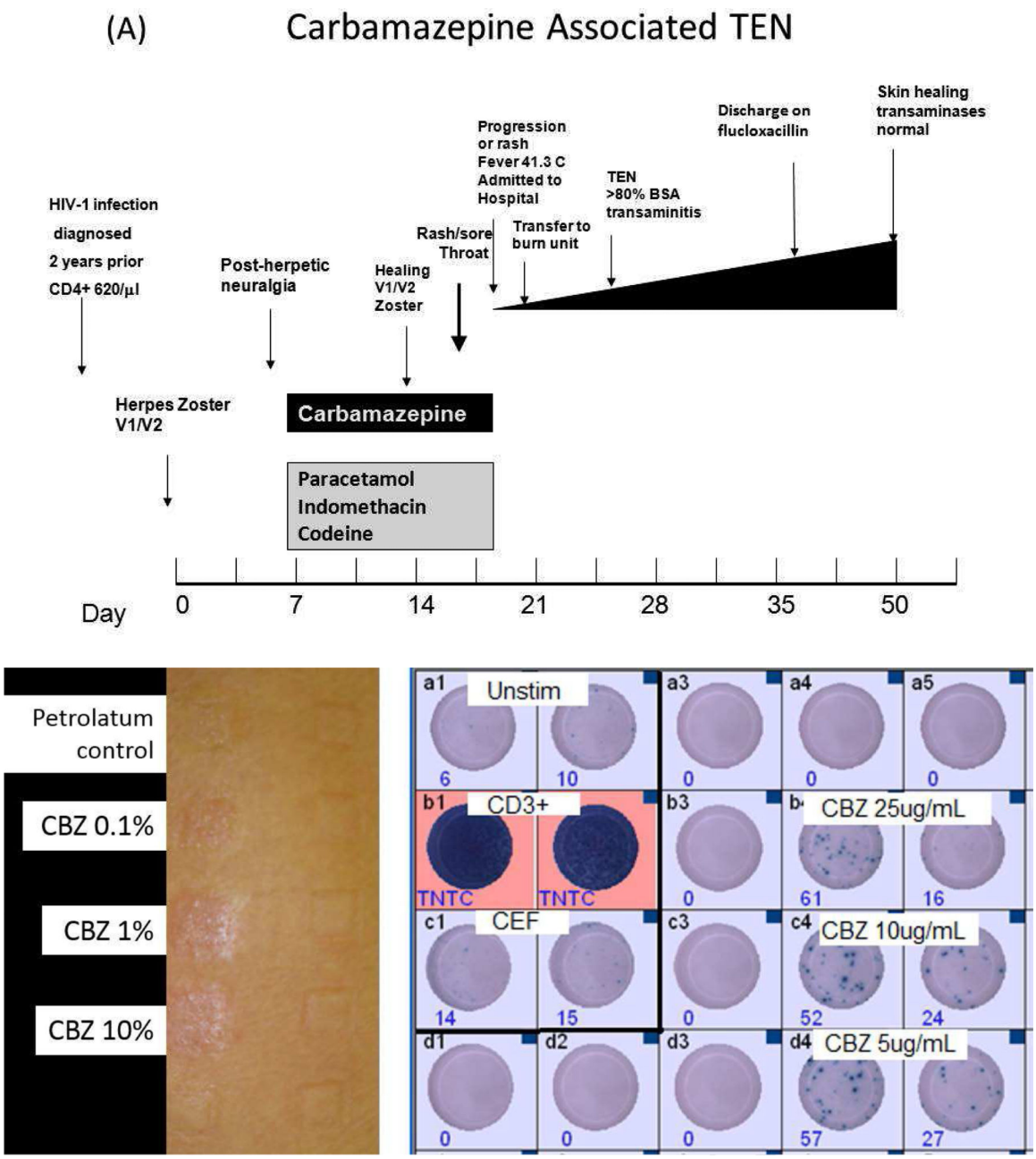
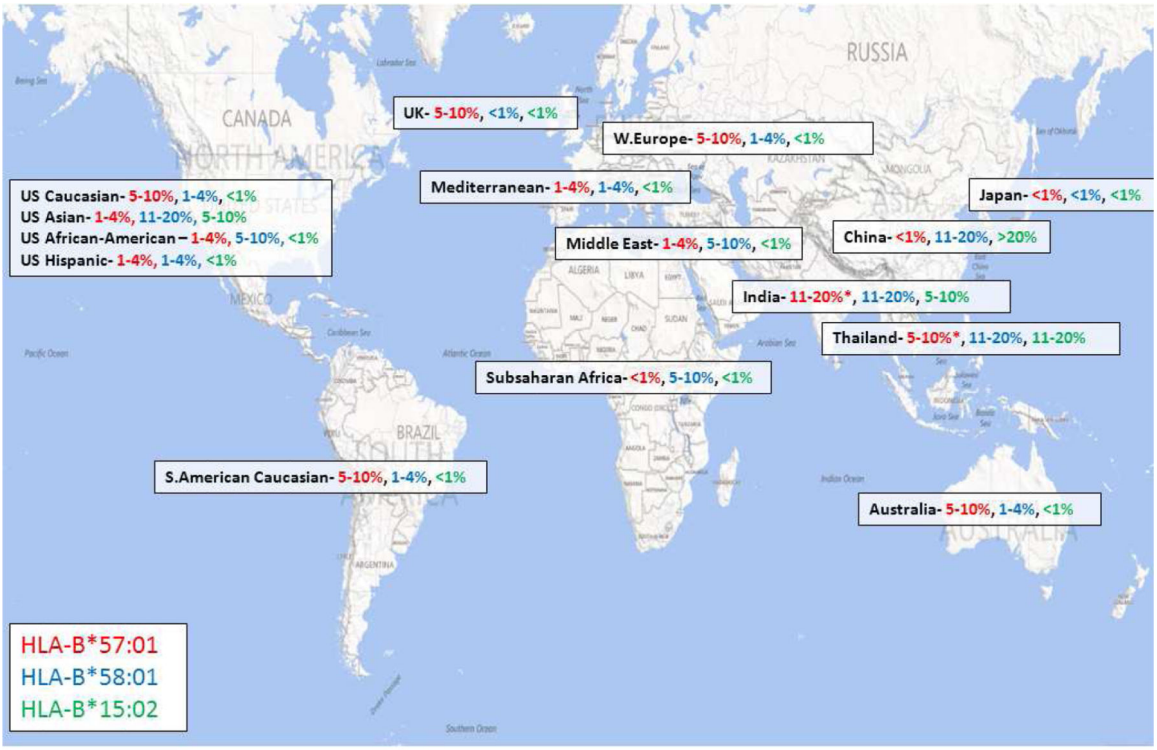


Figure 1.

(A) Clincial timeline for the development of Carbamazepine associated TEN in the case study patient. **(B)** Negative petrolatum control and positive patch test for 0.1%-10% carbamazepine in the patient 9.5 years after the original TEN reaction (left) and positive PBMC INF-g Elispot for 5-10ug/mL carbamazepine for 100 000 cells/well for a sample taken 17 years after the clinical TEN reaction (right). Positive controls (CD3+ and CEF peptide pool) and unstimulated PBMCs are also shown.



**High prevalence of HLA-B*57:01 refers to Northern Thailand and Northern India only with intermediate percentages or <1% prevalence reported in other regions*

Figure 2.

Geographical distribution and frequency of the key drug HSR alleles associated with abacavir HSR, allopurinol DRESS/DIHS/HSS and SJS/TEN and carbamazepine SJS/TEN HLA-B*57:01, HLA-B*58:01 and HLA-B*1502, respectively. Red = HLA-B*57:01 frequency, Blue = HLA-B*58:01 frequency and Green = HLA-B*15:02 frequency.

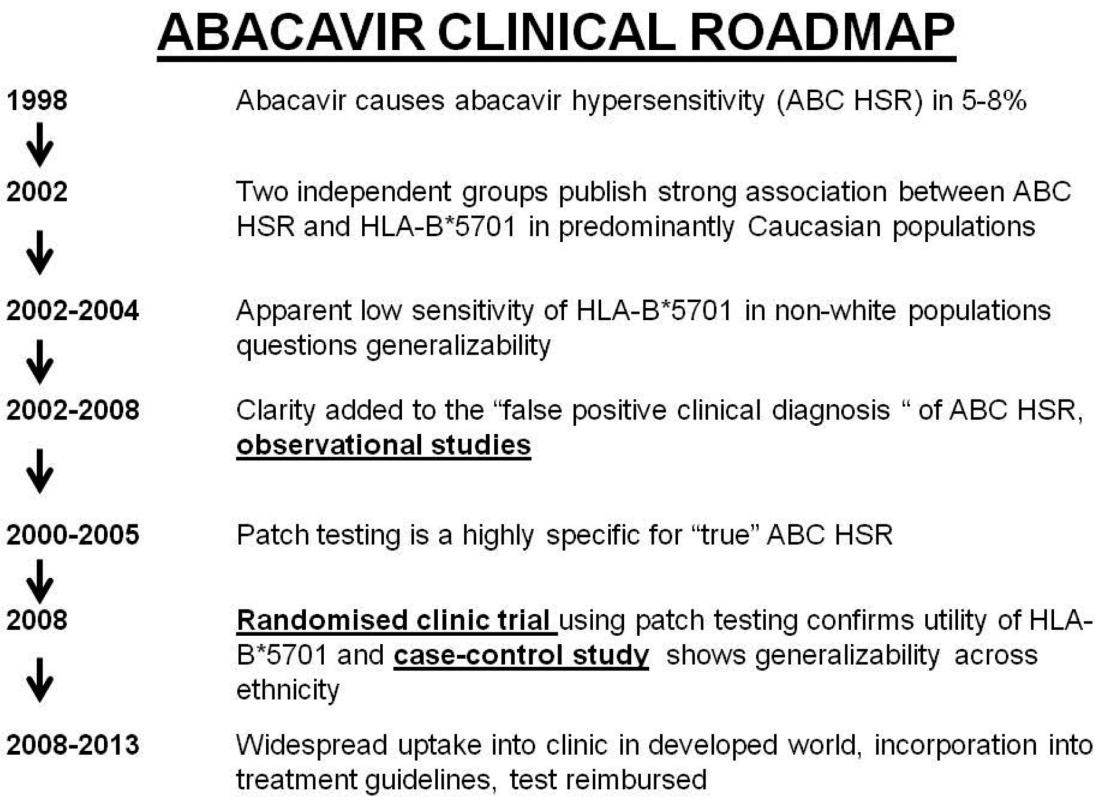


Figure 3. The Abacavir-HLA-B*5701 Clinical Roadmap

The abacavir-HLA-B*5701 example illustrates the necessary steps required to move from identification of the HSR and risk alleles to implementation of clinical screening prior to administration of the drug.

Table I

Pharmacogenomics of HLA associated drug hypersensitivity and related drug-induced syndromes

SJS/TEN (SCAR)				
Allopurinol	B*5801	Han Chinese, Thai, European, Italian, Korean, Portuguese	2005	92-100
Carbamazepine	B*1502	Han Chinese; Thai; Malaysian, Indian	2004	38-40, 43, 44, 101-108
	B*1511	Korean; Japanese	2010	45, 109
	HLA-B*1518, HLA-B*5901 and HLA-C*0704	Japanese	2010	110
	A*3101	Japanese; Northern European; Korean	2011	45, 48, 49, 111
Oxcarbazepine	B*1502	Han Chinese	2010	112
Lamotrigine	B*1502 – Positive	Han Chinese	2010	108, 112
	B*1502 NO ASSOCIATION FOUND	Han Chinese	2010	113, 114
Nevirapine	C*0401	Malawian	2013	22
Phenytoin	B*1502; HLA-B*1301, Cw*0801 and DRB1*1602	Han Chinese	2007	101, 102, 108, 112
Phenobarbital	B*51:01	Japanese	2013	115
sulfamethoxazole	B*38	European	2008	94
Methazolamide	B*59 B*5901, Cw*0102 alleles and B*5901-Cw*0102-A*2402 haplotype	Japanese Korean and Japanese	1997 2011	45
Sulfonamides	A*29, B*12 and DR*7	European	1987	116
Oxicam	B*73	European	2008	94
	A*2,B*12	European	1987	116
Strontium ranelate	*Under investigation in post-marketing period*		2009	117, 118
Zonisamide	A*02:07	Japanese	2013	115
DRESS-DIHS-HSS				
Abacavir	B*5701	European, African	2002	25, 26, 30
Allopurinol	B*5801 (or B*58 haplotype)	Han Chinese, Korean, Japanese, Thai, European	2005	92, 93, 95, 96, 98, 119-121
Nevirapine (Hepatitis)	DRB1*01:01 (CD4+ >/=25%), DRB1*01:02, B*58:01	Australian, European, South African	2005	15-18

Nevirapine (DRESS-DIHS)	Cw*8 or CW*8-B*14 Haplotype	Italian; Japanese	2006	19, 20
	C*4	Han Chinese	2011	21
	B*3505	Asian, Black, white	2011	17
				122
Carbamazepine	8.1 AH (HLA A*0101 : Cw*0701 : B*0801 : DRB1*0301 : DQA1*0501 : DQB1*0201)	Caucasians	2006	123, 124
	A*3101	Northern European; Japanese; Korean	2011	45, 48, 49, 111
	HLA-A11 and HLA-B51 (weak)	Japanese	2011	111
Strontium ranelate	*Under investigation in post-marketing period*		2009	118, 125
Dapsone	HLA-B*13:01	Chinese patients treated for leprosy	2013	126
Delayed rash (non systemic)				
Efavirenz	DRB1*01	French	2008	127
Nevirapine	DRB1*01	French	2008	127
	Cw*04	African, Asian, European, Thai	2009	17, 41
	B*35:05; rs1576*G CCHCR1 status (GWAS)	Thai	2009	128, 129
				122
Aminopenicllins	A*2, DR*52	Italian	1998	130
Carbamazipine (or MPE)	A*3101	Han Chinese, Northern European	2006	39, 48
Oxcarbazepine induced MPE	B*1502, B*3802	Han Chinese	2011, 2013	131, 132
Drug Induced liver disease				
Amoxicillin-clavulanate; co-amoxiclav DILI	DRB1*1501; DRB1*07 protective; HLA-A*0201 and HLA-DQB1*0602 and rs3135388, a tag SNP of HLA-DRB1*1501 -DQB1*0602	European	2009-2011	133-135
	B*1801 DRB1*0301-DQB1*0201	Spanish	2013	116
Lumiracoxib	HLA-DRB1*1501-HLA-DQB1*0602-HLA-DRB5*0101-HLA-DQA1*0102 haplotype	International, multicentre	2010	136
Ximelagatran	DRB1(*)07 and DQA1(*)02	Swedish	2008	137
Diclofenac	ABCB11; C-24T; UGT2B7*2; IL-4 C-590-A	European	2007	138-140
Isoniazid	NAT2 slow acetylator; CYP2E1*5,*1B	European	2009	139, 140

Flucloxacillin	B*5701, HLA-DRB1*0107- DQB1*0103	European	2009	140, 141
Lapatinib	DRB1*0701 -DQA2*0201-DQB1*0202/0202	International, multicentre	2011	142
Ximelagatran	DRB1*07, DQA1*02	European	2008	137
Fixed Drug Eruption				
Febrazone	B*22	Italian	1994	143, 144
sulfamethoxazole	A*30-B*13-Cw*6 haploytpe	Turkish	2001	145
Agranuloytosis				
Clozapine	B*38, DR*4, DQw*3	Jewish	1990	146, 147
	(6672G>C) in HLA-DQB1	North American	2011	148
	Cw7/B*18 or B*39 or B*44/DRB*5	Caucasian	2007	149
Levamisole	B*27	South American	1990	150
Drug induced lupus erythematosis				
Hydralazine	DR*4	European	1980	151
Procainamide, Isonazid, Methyldopa, Quinidine	DR*4	Italian	2009	152
Other				
Aspirin (Uriticaria/angioedema)	DRB1*1302-DQB1*0609-DPB1*0201 haplotype	Korean	2005	150
Aspirin (Asthma)	DPB1*0301	Korean	2008	153
Gold sodium thiomalate (Mucocutaneaous reaction)	DR*5	Spanish	1994	154
Gold sodium thiomalate (Proteinuria, thrombocytopenia or leakopenia)	B*8, DR*3	European	1985	155
NSAIDS (Anaphylactoid and cutaneous reactions)	DR*11	Spanish	1999	156
D-penicillamine (myasthenia gravis)	DR*1	Mixed Caucasian	1983	157
D-penicillamine (Proteinuria)	B*8, DR*3	European	1986	158
Berylium (granulomatous lung disease)	HLA-DPB1 gene and DPR1 gene polymorphisms, DRB1*13 and DQB1*06	North American	2003	159, 160

Table II

DRESS associated viral re-activation

Carbamazepine	HHV-6, HHV-7, CMV, EBV	13, 57-60, 62, 161, 162
Phenobarbital, Phenobarbital /Zonisamide	HHV-6, HHV-7, CMV, EBV	13, 59, 60
Zonisamide	HHV-6, HHV-7, CMV	13, 60
Sulfasalazine/ salazosulfapyridine	HHV-6	13, 58
Ibuprofen	HHV-6	58
Aspirin	HHV-6	163
Mexiletine	HHV-6, EBV, CMV	13, 59
Allopurinol	HSV-2, HHV-6, HHV-7, CMV, EBV	13, 60, 62, 65, 164
Amoxicillin	HHV-6	165
Vancomycin/Teicoplanin	HHV-6	166
Isoniazid, Rifampin, Ethambutol and Pyrazinamide	HHV-7	167
Sulfamethoxazole	HHV-6, HHV-7, EBV	62

Table III

Reported DRESS associated autoimmune diseases

Lupus erythematosus	63, 67
Autoimmune thyroiditis	63, 168
Graves' disease	72, 168
Thrombotic thrombocytopenic purpure	169
Type 1 diabetes mellitus	68, 70, 72
Autoimmune hemolytic anemia	72
Autoimmune hepatitis	170
Juvenile idiopathic arthritis, Rheumatoid Arthritis (preceding DRESS)	171-173
Graft-versus-host disease	69
Kawasaki disease	163