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Research Article

Use of the Biopharmaceutics Drug Disposition Classification System (BDDCS) to Help Predict the Occurrence of Idiosyncratic Cutaneous Adverse Drug Reactions Associated with Antiepileptic Drug Usage

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Abstract. Cutaneous adverse reactions (CARs) from antiepileptic drugs (AEDs) are common, ranging from mild to life-threatening, including Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). The identification of subjects carrying the HLA-B*15:02, an inherited allelic variant of the HLA-B gene, and the avoidance of carbamazepine (CBZ) therapy in these subjects are strongly associated with a decrease in the incidence of carbamazepine-induced SJS/TEN. In spite of the strong genetic associations, the initiation of hypersensitivity for AEDs is still not very well characterized. Predicting the potential for other AEDs to cause adverse reactions will be undoubtedly beneficial to avoid CARs, which is the focus of this report. Here, we explore the use of the Biopharmaceutics Drug Disposition Classification System (BDDCS) to distinguish AEDs associated with and without CARs by examining the binding relationship of AEDs to HLA-B*15:02 and data from extensive reviews of medical records. We also evaluate the lack of benefit from a Hong Kong population policy on the effects of screening for HLA-B*15:02 and previous incorrect structure–activity hypotheses. Our analysis concludes that BDDCS class 2 AEDs are more prone to cause adverse cutaneous reactions than certain BDDCS class 1 AEDs and that BDDCS Class 3 drugs have the lowest levels of cutaneous adverse reactions. We propose that BDDCS Class 3 AEDs should be preferentially used for patients with Asian backgrounds (i.e., Han Chinese, Thai, and Malaysian populations) if possible and in patients predisposed to skin rashes.

KEY WORDS: antiepileptic drugs; BDDCS; drug hypersensitivity; HLA-B alleles.

INTRODUCTION

Cutaneous adverse reactions (CARs) from antiepileptic drugs (AEDs) are common, ranging from mild to life-threatening, including maculopapular eruption, drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) (1,2). The mortality rates are approximately 10–15% in SJS, 30% in overlapping SJS/TEN, and up to 50% in TEN (3). For years, the pathological determinants of SJS/TEN remained elusive. The identification of subjects carrying the HLA-B*15:02, an inherited allelic variant of the HLA B gene, and the avoidance of carbamazepine (CBZ) therapy in these subjects are strongly associated with a decrease in the incidence of carbamazepine-induced SJS/TEN (4–9). HLA-B*15:02 screening policies have been implemented in a number of countries with respect to CBZ dosing, including the USA when in 2007 the FDA published an alert (10) stating that "Patients with ancestry from areas in which HLA-B*1502 is present should be screened for the HLA-B*1502 allele before starting treatment with carbamazepine." In a research setting, screening in Taiwan was associated with a reduced incidence of CBZ-induced SJS/TEN (11). Recently, however, the results of a routine clinical service policy at a system-wide level in Hong Kong implemented in 2008 was reported to be associated with the prevention of CBZ-induced SJS/TEN without reducing the overall burden of AED-induced SJS/TEN in more than 110,000 epilepsy patients (12). Attempts to predict the potential for various AEDs to cause cutaneous hypersensitivity through structure–activity relationships, suggesting that CARs occur with aromatic AEDS, but not with non-aromatic AEDs (13,14), have ignored data for aromatic AEDs exhibiting low CARs incidence such as clobazam and clonazepam. Thus, in spite of the strong genetic associations and some structure–activity success, the initiation of hypersensitivity for AEDs is still not very well characterized. Predicting the potential for other AEDs to cause adverse reactions will be beneficial to avoid CARs, which is the focus of this report.

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In 2005, Wu and Benet proposed the Biopharmaceutics Drug Disposition Classification System (BDDCS) (15). BDDCS provides a useful tool in early drug discovery for predicting routes of elimination, oral drug disposition, food effects on drug absorption, transporter effects on drug absorption, and potentially clinically significant drug interactions that may arise in the intestine, liver, and brain (15,16). BDDCS recognizes that drugs exhibiting a high passive intestinal permeability rate (BDDCS class 1 and BDDCS class 2) are extensively metabolized in humans, while low passive permeability rate drugs (BDDCS class 3 and BDDCS class 4) are primarily eliminated as unchanged drug in the bile or the urine (Figure S1).

Because the specific drug characteristics linking to adverse events remain controversial, here we expand the use of BDDCS in assisting the prediction of AED drug hypersensitivity reactions, conducted a systematic review to appraise the strength of BDDCS in the association of the incidence of CARs induced by AEDs, and performed *in vitro* studies to identify specific HLA/drug interaction patterns. In addition to exploring the use of BDDCS in the pathogenesis of CARs, the results of this work may help identify other AEDs or drugs in other therapeutic categories that can elicit SJS/TEN.

METHODS

HLA-B *In Vitro* Assay

We used the Biacore T200 SPR biosensor for analyzing the interaction between HLA-B proteins and drugs according to the manufacturer's protocol (GE). We immobilized the purified soluble HLA-B proteins (acting as ligands) on the chips by an amine coupling reaction, and the immobilized levels of sHLA-Bs were 9373-9812 response units (RU). PBS was used as running buffer and the flow rate was 10 mg/min. The compounds (ten AEDs, two active metabolites, and one non-active backbone structure) dissolved in PBS with 5% DMSO were evaluated and flowed through the solid phase with the running buffer PBS with 5% DMSO. Responses of the interaction were reference subtracted and corrected with a standard curve for the DMSO effects. We used BIA evaluation Version 3.1 for data analysis.

Compilation of AED-Related Adverse Cutaneous Reactions Studies

Data were extracted from four systematic published reviews of medical records of patients with epilepsy for documentation of CARs from AEDs. AED-related skin reactions studies were found in three main populations: American, Chinese, and Norwegian patients. We also used DailyMed (http://dailymed.nlm.nih.gov/dailymed/) to review rash and more serious dermatologic conditions reported in FDA package inserts, in addition to literature reports/reviews.

American Retrospective Study

The study in America was carried out at the Columbia Comprehensive Epilepsy Center between January 1, 2000, and January 1, 2005. A total of 1875 patients were included with altogether 5050 exposures to 15 different AEDs (17). The attribution of rash was based on the patient's description of the rash or on the medical examination, if the physician concluded it was most likely due to the AED. Overall, 14.3% (269/1875) of patients experienced skin reactions to at least one AED.

Chinese Retrospective Studies

Although two Chinese studies were available in the literature and were carried out around the same time, we have analyzed them independently. The studies were carried out at the Epilepsy Center of the Chinese PLA General Hospital in Beijing, China. The first study period was from February 1999 to April 2010. A total of 3793 patients were included with altogether 7353 exposures to 11 different AEDs (18). Overall, 3.61% (137/3793) of patients experienced a skin reaction to at least one AED. The second study period was between February 1999 and September 2010. A total of 4037 patients were included with altogether 5355 exposures to 9 different AEDs (14). Overall, 4.06% (164/4037) of patients experienced a skin reaction to at least one AED. A CAR was defined as any type of rash (erythematous, maculopapular, papular, pustular, or unspecified) that had no other obvious cause apart from an AED that resulted in contacting a physician.

Norwegian Retrospective Study

The study in Norway was carried out in three specialist outpatient clinics in middle Norway served by neurologists from Trondheim University Hospital. A total of 663 patients were included with altogether 2567 exposures to 15 different AEDs (19). A skin reaction was defined as a diffuse rash (including MPE, DRESS, urticaria, erythema nodosum, and SJS) that was reported in the medical records and had no other obvious reason than a drug. As initial symptoms of hypersensitivity most frequently occur up to 8 weeks after starting a drug, treatments lasting less than 3 months and stopped for any other reason than a rash were not included as an exposure. Overall, 14% (93/663) of patients experienced skin reactions to at least one AED.

Determining the Changes in AED Prescribing Practice with HLA-B*15:02 and the Incidence of SJS/TEN

Data were extracted from the Hong Kong Hospital Authority Clinical Data Repository to determine changes in AED prescribing practice in all patients, in AED-naïve patients and in patients with newly treated epilepsy and the incidence of AED-induced SJS/TEN, following implementation of the HLA-B*15:02 screening policy (12). The study period covered 3 years before the implementation date (prepolicy: September 16, 2005, to September 15, 2008) and 3 years after (postpolicy: September 16, 2008, to September 15, 2011). Patients of interest were those who had at least one AED newly commenced and/or underwent testing for HLA-B*15:02 in the study period. An AED was defined as newly commenced if there was no record of its prescription in at least the previous 12 months. A total of 111,242 patients were

included and 4149 were tested for HLA-B*15:02. SJS/TEN was attributed to an AED if the patient was hospitalized for SJS/TEN within 90 days of commencing an AED, and the patient's allergy histories did not suggest other pharmaceutical products (12).

Compilation of BDDCS Properties, Correlation, and Statistical Analyses

Data are expressed as percentages of cutaneous incidence rate given the number of patients affected divided by the number of exposures associated with each AED together with the BDDCS class. The BDDCS class assignment and properties were obtained from the BDDCS applied to over 900 drugs paper (20). Missing data were complemented by literature searches. Data with absolute values of each AED exposure along with BDDCS were also included.

The BDDCS class prescription pattern across the three different groups: all patients, AED-naïve patients, and patients with newly treated epilepsy in the AED prescribing practice for HLA-B*15:02, was also analyzed. Data are expressed as the percent of each AED prescription in the prepolicy along with absolute values of each AED exposure and BDDCS class. Differences in the proportions of BDDCS classes associated with CARs and prescription patterns were determined using chi-squared tests. The differences of SJS/TEN incidence between the prepolicy and postpolicy were calculated using the Fisher's exact test.

The 12 AED-related compounds were evaluated using the *in vitro* assay relative response binding to HLA-B*15:02 *versus* the incidence of cutaneous adverse drug reactions reported with the Spearman rank correlation coefficient (ρ) and Spearman correlation test. For statistical tests, a p value less than 0.05 was considered significant. Analyses and plots were carried out using R (http://cran.r-project.org) and GraphPad Prism software version 6.0 (GraphPad Software, Inc., San Diego, CA).

RESULTS

Incidence of Cutaneous Adverse Reactions and BDDCS Class

Using the BDDCS classification, the drugs associated with the highest incidence of cutaneous adverse reactions fall in BDDCS class 2 in four retrospective studies (17–19,21), with the lowest incidence for BDDCS class 3 AEDs as depicted in Fig. 1. BDDCS class 2 drugs (lamotrigine, oxcarbazepine, carbamazepine, and phenytoin) showed the highest rate of cutaneous adverse drug reactions across all retrospective studies. Gabapentin, felbamate, clobazam, clonazepam, valproate, topiramate, levetiracetam, and vigabatrin consistently had the lowest rates of CARs. Hence, it appears that BDDCS class 2 AEDs exhibit the highest trend of causing cutaneous adverse reactions followed by certain BDDCS class 1 drugs, in particular zonisamide, phenobarbital, and tiagabine. Valproic acid, a widely used AED, clonazepam, and clobazam are BDDCS class 1 presenting lower levels of adverse cutaneous reactions than the other aforementioned BDDCS class 1 drugs. Levetiracetam, a BDDCS class 3 drug, shows a high efficacy in vulnerable populations, e.g., elderly (22) and children (23), and low levels of CARs. Felbamate is the only BDDCS class 4 AED, and it shows a low rate of CARs.

Numbers of AED Exposure and BDDCS Classification

When examining AED exposure, the drugs associated with the highest exposure number are BDDCS class 2 in each of the four studies, followed by class 1. Figure S2 depicts the numbers of exposure for each AED across the four retrospective studies. Carbamazepine, phenytoin, and valproate are among the highest prescribed AEDs across all studies. Although BDDCS classes 2 and 1 have the highest rates of cutaneous adverse reactions, they are three times more likely to be prescribed than BDDCS classes 3 and 4 AEDs, which show the lowest rate of cutaneous adverse reactions.

It is interesting to note that the same general pattern of CARs outcome is found in the American and Norwegian studies in Fig. 1 as seen for the Chinese studies, suggesting that CARs potential occurs for populations not exhibiting the HLA-B*15:02 to a significant extent. We plan to examine this finding in our future studies.

HLA-B*15:02 Binding to AEDs

Figure 2b depicts the differential BDDCS response in binding observed among 10 AEDs, two active metabolites and one non-active backbone structure (5HB) when analyzed using an HLA *in vitro* binding assay. The results are depicted as the mean ± standard error of the mean (SEM) for six independent experiments with each compound. The HLA *in vitro* binding data depict that the drugs associated with the strongest binding to HLA-B*15:02 are BDDCS class 2 (see Table I and Fig. 2a). Carbamazepine, oxcarbazine, eslicarbazepine acetate, phenytoin, and lamotrigine demonstrate a strong binding interaction with HLA-B*15:02, but not with other HLA-B alleles. AEDs presenting a weak binding interaction with HLA-B*15:02 were levetiracetam, topiramate, gabapentin, ethosuximide, and valproic acid, as well as the non-active structural backbone of some AEDs, iminostilbene (5-HB). That is, BDDCS class 3 drugs and the class 1 drugs ethosuximide and valproic acid interact poorly with HLA-B*15:02. Class 2 carbamazepine-10,11-epoxide, a carbamazepine metabolite, also presented a strong binding affinity to HLA-B*15:02. The primary metabolite and active entity of oxcarbazepine, licarbazepine had three times lower binding affinity to HLA-B*15:02 than the stereospecific eslicarbazepine acetate and other strong binding AEDs.

Comparison of Cutaneous Adverse Reactions and the HLA-B *In Vitro* Assay

Table I illustrates the relationship between the incidence of cutaneous adverse reactions and the HLA-B binding assay. The 14 drugs in Table I are ordered based on the mean% incidence of AED rash for the four studies presented in Fig. 1, highest to lowest, when an AED was reported in two or more evaluations. We arbitrarily classified the rash incidence as high when the mean for a drug in the four evaluations was ≥5%, intermediate when mean rash incidence was between 2 and 5%, and low when the mean

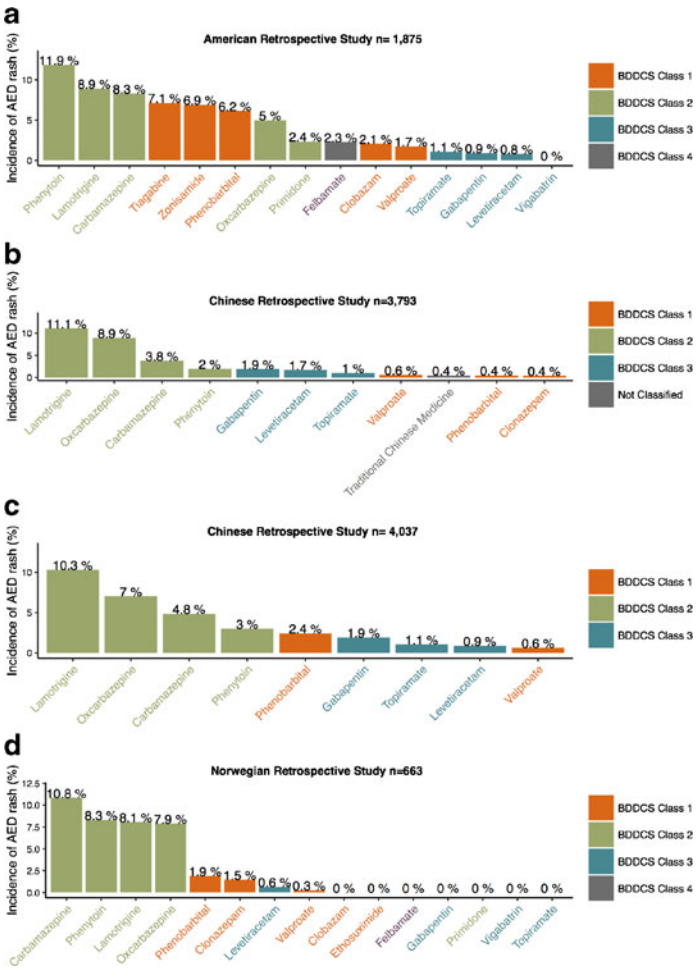

Fig. 1. Incidence of AED-related skin rash (%) and BDDCS classification in Americans, Chinese, and Norwegians. **a** BDDCS class 2 drugs accounted for 55.6% incidence rates of AED-related skin rashes, followed by 36.6% for BDDCS class 1, 4.3% for BDDCS class 3, and 3.5% BDDCS class 4 in the American retrospective study. **b** BDDCS class 2 drugs accounted for 80% incidence rates of AED-related skin rashes, followed by 4.3% for BDDCS class 1, 14.4% for BDDCS class 3, and 1.3% for the not classified compounds in the Chinese retrospective study. **c** BDDCS class 2 drugs accounted for 78.5% incidence rates of AED-related skin rashes, followed by 9.5% for BDDCS class 1, 12.0% for BDDCS class 3 in the Chinese retrospective study. **d** BDDCS class 2 drugs accounted for 89.2% incidence rates of AED-related skin rashes, followed by 9.2% for BDDCS class 1, 1.6% for BDDCS class 3, and 0% BDDCS class 4 in the Norwegian retrospective study. For all studies, p values were <0.05 (using the chi-squared test), providing evidence that rates of AED-related skin rashes differed significantly between BDDCS classes

incidence was <2%. For the eight drugs where *in vitro* binding to HLA-B*15:02 was available, the strength of binding was also included. For each of the retrospective studies, correlation between incidence of AED and the strength of HLA-B*15:02 binding for eight AEDs is very high and significant as presented in Figure S3 (American study ($n = 1875$): $\rho = 0.762$, p value = 0.028; Chinese study ($n = 3793$): $\rho = 0.810$, p value = 0.015, Chinese study ($n = 4037$): $\rho = 0.857$, p value = 0.007; Norwegian study ($n = 663$): $\rho = 0.763$, p value = 0.017). These data reflect the BDDCS class 2 *vs.* class 3 differentiation. Hence, these strong correlations show a high concordance between the available clinical data and the potential of the HLA-B *in vitro* assay to predict these cutaneous adverse reactions.

Changes of AED Prescription Pattern, HLA-B*15:02 Screening, and BDDCS Classification

Figure 3, using BDDCS, depicts the change of AED prescription pattern from prior to post HLA-B*15:02 policy implementation in Hong Kong. Prior to policy implementation, phenytoin, valproic acid, and carbamazepine had the

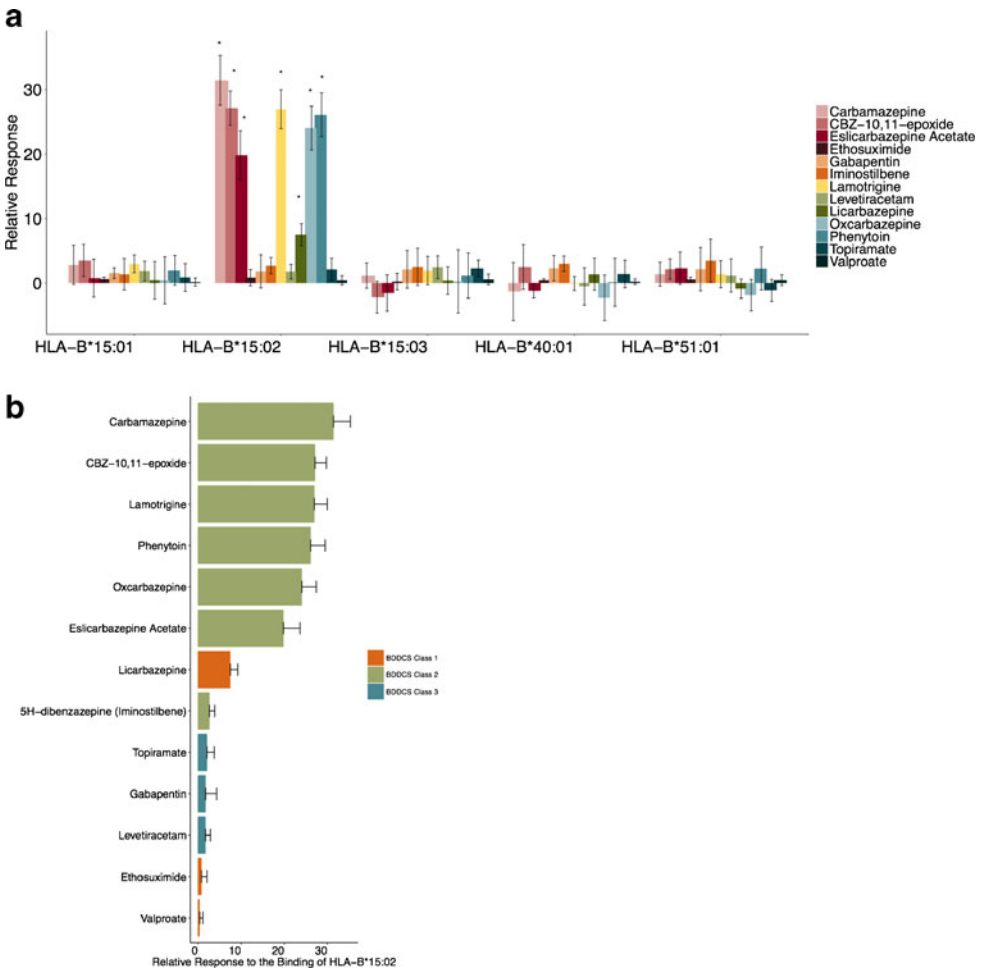

Fig. 2. **a** Surface plasmon resonance (*SPR*) data demonstrating the specific interactions of ten AEDs, two metabolites, and one non-active structural backbone (1 mM) to HLA-B*15:01, HLA-B*15:02, HLA-B*15:03, HLA-B*40:01, and HLA-B*51:01. * $p < 0.05$ shows compounds with a significant difference from the response of vehicle. All p values were calculated with a two-tailed Student's t test. Results are representative of six independent experiments (mean ±SEM). **b** BDDCS classification of the SPR results with the AEDs

Table I. Relationship Between the Incidence of AED Rash from Fig. 1 for Drugs Investigated in at Least Two of the Four Retrospective Studies and Relative Response to the *In Vitro* Binding of HLA-B*15:02 from Fig. 2

Generic name	BDDCS class	Comments
Lamotrigine	2	High rash incidence and strong *in vitro* binding
Oxcarbazepine	2	High rash incidence and strong *in vitro* binding
Carbamazepine	2	High rash incidence and strong *in vitro* binding
Phenytoin	2	High rash incidence and strong *in vitro* binding
Phenobarbital	1	Intermediate rash incidence
Primidone	2	Low/no rash incidence
Gabapentin	3	Low/no rash incidence and weak *in vitro* binding
Felbamate	4	Low/no rash incidence
Clobazam	1	Low/no rash incidence
Clonazepam	1	Low rash incidence
Valproate	1	Low rash incidence and weak *in vitro* binding
Topiramate	3	Low/no rash incidence and weak *in vitro* binding
Levetiracetam	3	Low rash incidence and weak *in vitro* binding
Vigabatrin	3	No reported rash incidence

Two further BDDCS class 1 drugs (tiagabine, zonisamide) reported in only one study exhibited rash incidence, which would be classified as high

BDDCS Biopharmaceutics Drug Disposition Classification System

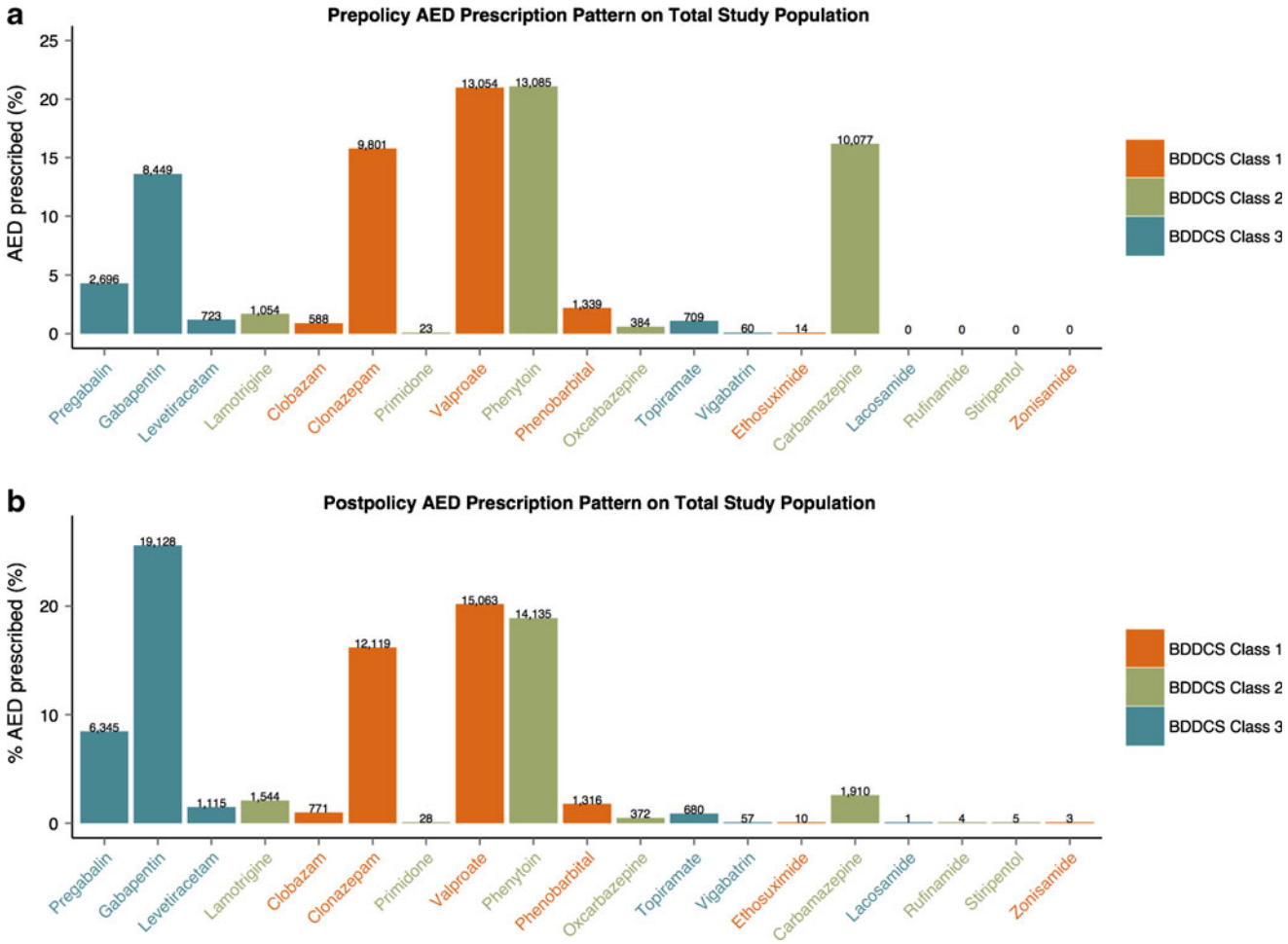

Fig. 3. AED prescription patterns prior and post HLA-B*15:02 screening implementation in the total Hong Kong population. **a** Prior to the policy implementation, BDDCS class 1 drugs accounted for 40.0% of all prescriptions, followed by 39.7% for BDDCS class 2 and 20.3% for BDDCS class 3. **b** In the postpolicy, BDDCS class 1 accounted for 39.2% of all prescriptions, followed by 36.5% for BDDCS class 3 and 24.3% for BDDCS class 2

highest usage numbers in the total population. Following policy implementation, gabapentin, valproic acid, phenytoin, and clonazepam had the highest prescription numbers. Although there was a significant increase in the percent of BDDCS class 3 drugs (pregabalin, gabapentin, and levetiracetam) in the entire population, BDDCS class 2 drugs still represented 24.3% of prescribed AEDs. Similar trends were also observed in the subset of patients receiving their first ever AED where postpolicy 25.3% of prescribed AEDs were BDDCS class 2 drugs (Figure S4). In the newly treated epilepsy subset postpolicy, the decrease in carbamazepine prescriptions from prepolicy numbers was almost matched by the increase in class 2 phenytoin dosing (Figure S5). Thus, the high presence of BDDCS class 2 AEDs potentially hinders the lowering of CAR incidence in this population.

DISCUSSION

We observed a high concordance between the HLA-B*15:02 *in vitro* assay and the incidence of cutaneous adverse reactions associated across all retrospective studies. Phenytoin, lamotrigine, carbamazepine, and oxcarbazepine showed high levels of cutaneous adverse reactions. These drugs are also the major causative AEDs for CARs (2,21). Our BDDCS analysis shows that these AEDs share common properties of being highly metabolized and having low solubility, i.e., BDDCS class 2. In contrast, AEDs showing a high solubility and poor extent of metabolism (gabapentin, levetiracetam, and topiramate) showed a poor interaction for the HLA-B *in vitro* assay. In agreement with this, gabapentin, levetiracetam, and topiramate are also AEDs showing minimal levels of CARS (see Fig. 1, Table I). Iminostilbene, the carbamazepine structural backbone, had a lower binding affinity. We speculate that this low binding affinity is due to the lack of polar groups thereby not allowing the formation of H-bonds with the HLA-B pocket. However, iminostilbene also exhibits low, if any, antiepileptic potency. On the other hand, carbamazepine-10,11-epoxide presented a strong interaction. According to the results from the HLA-B *in vitro* test and the incidence of cutaneous adverse reactions, we observe that compounds that are extensively metabolized and have low solubility are more susceptible to interacting with HLA-B*15:02 *in vitro* and have higher incidences of cutaneous adverse reactions. Thus, we recommend that to minimize

CARs, epileptic patients be placed on BDDCS class 3 AEDs if possible and that for patients exhibiting the HLA-B*15:02 allele, all BDDCS class 2 AEDS may be expected to exhibit the same toxicity potential as carbamazepine. It is more difficult to extrapolate these findings to BDDCS class 1 AEDs, where some of these drugs (e.g., zonisamide and phenobarbital) cause significant CARs, while others (e.g., valproic acid, clobazam, clonazepam, and ethosuximide) exhibit similar adverse reaction profiles to the BDDCS class 3 drugs.

It has been previously hypothesized that "idiosyncratic" hypersensitive reactions occur with AEDs containing an aromatic ring in their chemical structure that can form an arene-oxide intermediate (13). This chemically reactive product may become immunogenic through interactions with proteins or cellular macromolecules in accordance with the hapten hypothesis (24). Apart from the hapten formation hypothesis, another immune mechanism might be involved. In this alternate hypothesis, there is a direct, non-convalent binding of the drug to the T cell receptor to specific T cell clones. Drug-specific T cells have been identified for lamotrigine and carbamazepine (25,26). Handoko and coworkers have also confirmed that the association for T cell-mediated reactions was strongest in cutaneous reactions (13). Although aromatic *vs.* non-aromatic AED studies have demonstrated that cutaneous hypersensitive reactions can be partly explained by a commonality in chemical structures (13,14), these studies did not consider and failed to explain why clobazam and clonazepam, which are AEDs with aromatic rings, do not show a significant number of hypersensitive reactions as observed in our analysis. The strong association of hypersensitivity reactions with BDDCS class 2 drugs, certain BDDCS class 1 drugs, and our *in vitro* results suggests that parent or a combination of parent/metabolite interactions is responsible for the drug hypersensitivity event. One might expect that measures of lipophilicity might differentiate reactive *vs.* nonreactive AEDs with respect to CARs. However, examination of measured Log P, measured Log D7.4, and calculated Clog P, as tabulated by Benet *et al.* (20), do not reveal a consistent pattern (see Table S1).

Although many studies have observed intermediate levels of CARs with phenobarbital, limited or no cases of rash were attributed to primidone in the retrospective studies analyzed here, which is surprising because primidone is metabolized to phenobarbital. It appears that patients tend to be given phenobarbital much more frequently than primidone, from its higher numbers of exposure across all retrospective studies, and those patients with previous rash to phenobarbital are unlikely to be given primidone subsequently; this would result in a low-risk group of patients being given primidone, as proposed by Arif and coworkers (27). Primidone is a BDDCS class 2 drug and therefore shares reactive properties that we hypothesize would cause a drug hypersensitivity event, as observed in the American retrospective study (Fig. 1).

Carbamazepine-induced SJS/TEN is strongly associated with HLA-B*15:02 across broad Asian populations (4–9). Screening for HLA-B*15:02 in individuals of such ethnic descent before commencing carbamazepine, with avoidance of the drug in individuals testing positive, is recommended by regulatory agencies. Upon examination of the correlation between the HLA-B*15:02 binding affinity and AED SJS/TEN incidence in the Hong Kong population prior to the policy implementation, we found a strong correlation with carbamazepine and phenytoin showing high rates of SJS and levetiracetam and gabapentin showing low rates of SJS (see Table II). Here again, we observe the BDDCS class 2 and class 3 separation. However, the lack of the exact AED SJS/TEN incidence data among the other ethnic groups limits our analysis. Analysis of the AED prescription practice changes on the whole population of Hong Kong shows a marked reduction in carbamazepine use after the implementation of HLA-B*15:02 screening policy. Although carbamazepine-induced SJS/TEN was prevented, the incidence of SJS/TEN induced by AEDs overall was not significantly changed (12). The increase of non-carbamazepine BDDCS class 2 AEDs may have led to an increase in the incidence of SJS/TEN induced by other AEDs, particularly phenytoin. Under the Hong Kong Hospital Authority's drug formulary, one of the older AEDs (carbamazepine, phenobarbital, phenytoin, valproic acid) should be used as first-line treatment for epilepsy. This explains the corresponding increases in phenytoin and valproic acid prescriptions among this patient group. The shift from carbamazepine to phenytoin

Table II. SJS Incidence in the Hong Kong Population and BDDCS Classification

Culprit AED	BDDCS class	Prepolicy patients (*n*)	SJS/TEN (*n*)	SJS/TEN (%)	Postpolicy patients (*n*)	SJS/TEN (*n*)	SJS/TEN (%)	*p* value[a]
Phenobarbital	1	803	1	0.12	875	0	0	0.48
Valproic acid	1	8770	1	0.01	10,061	1	0.01	NS
Carbamazepine	2	8284	20	0.24	1076	0	0	0.16
Phenytoin	2	11,839	18	0.15	12,618	33	0.26	0.07
Gabapentin	3	6984	1	0.01	16,603	2	0.01	NS
Levetiracetam	3	52	0	0	220	1	0.45	NS
Pregabalin	3	1566	0	0	4287	1	0.02	NS
Multiple AEDs[b]	2 and 1		1			1		
Total[c]		45,832	42	0.09	55,326	39	0.07	0.26

NS not significant, *SJS* Stevens–Johnson syndrome, *TEN* toxic epidermal necrolysis, *BDDCS* Biopharmaceutics Drug Disposition Classification System, *AED* antiepileptic drug

[a] Fisher's exact test comparing the incidence of SJS/TEN in the prepolicy and postpolicy periods

[b] Two patients developed SJS/TEN while commenced on phenytoin and valproic acid concurrently

[c] Total incidences of first AED-induced SJS/TEN were calculated based on total patient numbers

Table III. Rash and More Serious Dermatologic Conditions from the FDA Package Insert and Literature Reports

Generic drug name	Rash incidence	BDDCS class
Clobazam	Package insert: • rash listed under Warnings and Precautions and Adverse Reactions (32) SJS/TEN: • listed under Warnings and Precautions and Adverse Reactions (32) Other sources: • approximately 2% (27)	1
Clonazepam	Package insert: • rash listed under Adverse Reactions (32) SJS/TEN: • not mentioned Other sources: • not available	1
Ethosuximide	Package insert: •rash listed under Warnings; Precautions and Adverse Reactions sections (32) SJS/TEN: • listed under Warnings (32) Other Sources: • not available	1
Phenobarbital	Package insert: • rash listed under Adverse Reactions (32) SJS/TEN: • not mentioned Other sources: • 1–2% (33) • 8.1/10,000 (34)	1
Tiagabine	Package insert: • rash rate: adults: 5% (32) • rash listed under Precautions and Adverse Reactions (32) Other sources: • 2.5% (27)	1
Valproate	Package insert: • rash: >1% but less than 5% in both epilepsy and migraine trials (32) • rash listed under Warning and Precautions and Adverse Reactions sections (32) SJS/TEN: • "Rare" (32) Other sources: • approximately 1% (27) • 0.5/10,000 (35)	1
Zonisamide	Package insert: • rash: adults = 1.4–2.2% (32) • rash listed under Warnings; Precautions and Adverse Reactions sections (32) SJS/TEN: • 46 per 1,000,000 (32) • listed under Warnings (32) Other sources: • 4% (27)	1
Carbamazepine	Package insert: • rash: 1/10,000-6/10,000 (32) • rash listed under Warnings and Precautions and Adverse Reactions (32) SJS/TEN: • listed under Boxed Warning; Warnings and Adverse Reactions (32) Other sources: • SJS/TEN: 1.4/10,000 (35) • rash: 4–11% (27)	2
Lamotrigine	Package insert: • rash: epilepsy trials = 4.5–10% in adults, 4.4–14% in pediatric cases; bipolar trials: adults = 7–11% (32) • rash listed under Boxed Warning; Warnings and Precautions; Adverse Reactions (32) SJS/TEN: • 0.3% adults with epilepsy; 0.8% in pediatric patients with epilepsy (<16 years); 0.08% adults with bipolar disorder (using current titration schedules) (32) • listed under Boxed Warning; Warnings and Precautions; Adverse Reactions (32) Other sources: • 2.5/10,000 (35) • 10% (27)	2
Oxcarbazepine	Package insert: • rash: adults = 1.4–4%; pediatrics = 1.3–5.3% (32) • rash listed under Warnings and Precautions and Adverse Reactions (32) SJS/TEN: "Rare" (32) • listed under Warnings and Precautions (32) Other sources: • 2.5% (27)	2
Phenytoin	Package insert: • rash: rate not given (32) • rash listed under Warnings and Precautions and Adverse Reactions (32) SJS/TEN: •rate not given • listed under Warnings (32) Other sources: • 5–10% (33)	2
Primidone	Package insert: • rash listed as a possible side effect (32) SJS/TEN: • not mentioned Other sources: • contraindications: patients who are hypersensitive to phenobarbital (36)	2
Gabapentin	Package insert: • rash: adults = 1.2–1.3% (32)• listed under Adverse Reactions (32) SJS/TEN: • not mentioned Other Sources: • 1% (27)	3
Levetiracetam	Package Insert: • rash: adults: 0% (32) SJS/TEN: • not mentioned Other Sources: • not available	3
Topiramate	Package insert: • rash: adults = 1%; 2–4% in migraine; pediatrics = 2% (32)• listed under Adverse Reactions (32) SJS/TEN: • not mentioned Other sources: • 1% (27)	3
Vigabatrin	Package insert: • rash: adults: 0% (32) • rash listed under Adverse Reactions (32) SJS/TEN: • listed under Adverse Reactions (32) Other sources: • not available	3
Felbamate	Package insert: • rash: (1.2%) (32) • rash listed under Adverse Reactions (32) SJS/TEN: • not mentioned	4

SJS Stevens-Johnson syndrome, *TEN* toxic epidermal necrolysis, *BDDCS* Biopharmaceutics Drug Disposition Classification System

and valproate induced by the screening policy, such as the risk of teratogenicity (28), which is higher for valproate compared with carbamazepine may have exerted a negative effect on population health. Our analysis shows that there was no major shift in the BDDCS classes 2 and 1 prescription pattern, and this potentially explains the lack of reduction in SJS incidence.

The Food and Drug Administration (FDA) currently recommends that phenytoin, fosphenytoin, and lamotrigine should be avoided as an alternative for carbamazepine patients positive for HLA-B*15:02 (10,29). HLA-B*15:02 is largely absent in individuals not of Asian origin (e.g., Caucasians, African-Americans, Hispanics, and Native Americans); nonetheless, we observe a strong correlation between the drugs associated with cutaneous adverse reactions across different populations. Other HLA-B alleles such as HLA-A*31:01 (30) and HLA-B*15:11 (31) have been associated with carbamazepine-associated SJS but no *in vitro* assay has been performed as yet with these other alleles. BDDCS class 2 AEDs appear to be more reactive than other BDDCS classes.

Through a review of FDA package labels, in contrast to the 2% or less incidence of SJS/TEN for the BDDCS class 3 drugs listed in Table II, the values for the BDDCS class 2 drugs phenytoin (5–10%), lamotrigine (10%), carbamazepine (4–11%), and oxcarbazepine (2.5%) are often much higher (see Table III). As seen in the data presented here, patient exposure to BDDCS classes 2 and 1 AEDs is much higher (see Figure S2). For clinicians to be able to reduce the number of patient suffering from drug hypersensitivity reactions, they should understand that continual high prescription exposure of BDDCS class 2 and certain class 1 drugs may contribute to the reported adverse cutaneous reactions in patients who are at risk.

Use of BDDCS in the FDA Guidance for Drug Hypersensitivity Reactions

The previous discussion of BDDCS and AEDs in the literature was related to generic equivalence and interchangeability of AEDs. In that work, Bialer and Midha (37) contrasted the aspects of the FDA guidance of waiver of bioequivalence studies based on the Biopharmaceutics Classification System (BCS) (38) and the clinician's interchangeability of brand *versus* generic AED prescriptions. It is important to understand the distinction between BCS, which is based on the *extent* of drug permeability/absorption, *versus* BDDCS, which is based on the *rate* of drug permeability/absorption. In the BCS system, levetiracetam, gabapentin, and vigabatrin are classified as BCS class 1 drugs (39). These compounds are completely absorbed, with the exception of gabapentin that is about 70% absorbed in humans (40), although quite slowly. These three drugs, in contrast, are classified as BDDCS class 3 (see Table S2). Thus, the predictability of hypersensitivity reactions for AEDs is based on BDDCS, not BCS, classification, since BCS does not predict whether drugs will be extensively metabolized or not.

CONCLUSIONS

Drug-induced CARs constitute the most frequent idiosyncratic reactions confronting clinicians treating patients with epilepsy. Unfortunately, there is no reliable way to determine early in the clinical course of a rash if it is going to remain as a benign maculopapular rash or evolve into a severe skin reaction. Therefore, the drug should be discontinued as soon as possible in most cases. Our analysis concludes that BDDCS classes 2 and 1 AEDs are more prone to cutaneous toxicity and BDDCS class 3 AEDs have the lowest cutaneous rash incidence across the studied ethnic groups. We propose that, if possible, BDDCS class 3 AEDs should be preferentially dosed to patients of East Asian ancestry who most predominantly exhibit the HLA-B*15:02 allele (i.e., Han Chinese, Thai, and Malaysian populations), where an association between HLA-B*15:02 and carbamazepine-induced SJS and TEN has been demonstrated (4–9). We believe that categorizing drugs by BDDCS classification adds to the understanding of idiosyncratic reactions. We plan to further test other AEDs in the HLA-B *in vitro* assay. Other toxicity models using BDDCS such as the Torsade de Pointes (41) and drug-induced liver injury (DILI) (42) are starting to emerge. BDDCS may help characterize and predict drugs having the potential for greater toxicity.

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COMPLIANCE WITH ETHICAL STANDARDS

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