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Defining Regional Differences in Drug-Induced SJS/TEN: A tool to improve drug safety?

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Introduction

Regional differences exist in the epidemiology of immunologically mediated adverse drug events (IMIADRs) such as SJS/TEN but also in the way individual drugs are labeled. These differences are clues to the key drivers of these reactions which are HLA class I alleles. This knowledge can facilitate studies that will define genetic risk factors for IMADRs and maximize the efficiency of providing safer drug formularies and driving the translation of genetic screening into the clinic.

Definition of racial differences as a factor contributing to risk of serious immunologically mediated adverse drug reactions has provided important clues to motivate studies that have found genetic risk factors prevalent in specific populations. The first well established example was noted with abacavir hypersensitivity syndrome (AHS), where early in the post-marketing phase of drug development those of African ancestry were observed to be at lower risk of this hypersensitivity syndrome compared to those of European ancestry(1). The discovery of a strong association between HLA-B*57:01, an HLA class 1 allele prevalent in those of European ancestry but uncommon in those of African and Asian ancestry, 4 years following FDA approval of abacavir provided an explanation for the earlier epidemiological observation(2,3). Indeed, the recognition of the AHS in the pre-marketing phase of drug development was predicated on the study of abacavir in predominantly European ancestry individuals. Similarly, for aromatic anti-epileptic drugs such as carbamazepine it had been observed that those of Southeast Asian origin had at least 10 fold higher the risk of serious IM-ADR such as SJS/TEN compared to those of European ancestry. Carbamazepine was known to be associated with 25–33% of SJS/TEN cases in Southeast Asian populations compared to only 5–6% of European cases of SJS/TEN.(4) In 2004 a strong association between HLA-B*15:02, an HLA class 1 allele prevalent in those of Southeast Asian

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ancestry but uncommon (<1% prevalence) in those of European and African ancestry was reported that again provided an explanation for the initial epidemiological observation(4).

In an attempt to define the risk of medication related SJS/TEN more broadly across Asian populations *Wang et. al.* analyzed registration databases in eight Asian countries including seven in Southeast Asia and Japan, and compared this with medications labeled by the FDA as having a high risk for SJS/TEN. From patients treated between 1998–2017 they identified 1028 cases of SJS/TEN that met a minimum of a probable score on the ALDEN causality assessment scoring system for SJS/TEN and in 98% a single drug was implicated as having a probable or definite causality. Comparing the medications most commonly associated with SJS/TEN in Asian countries with those labeled by the FDA as carrying a risk for SJS/TEN, and the most common drugs associated with the EuroSCAR cohort of 237 published cases they found several key differences. In Asians more than half of SJS/TEN cases were associated with aromatic anticonvulsants which in the case of carbamazepine and phenytoin was driven by Southeast Asian countries, and in the case of lamotrigine was driven by high representation in Japan. This compared to 25% of cases associated with aromatic anticonvulsants in the EuroSCAR where lamotrigine was not represented and carbamazepine represented only 11% of SJS/TEN cases. Antibiotics were prevalent causes in both regions however oxcarbazepine, sulfasalazine, Cox-2 inhibitors and strontium ranelate were found to be new causes in the Asian region which are drugs either without representation of SJS/TEN in the FDA label or that are not FDA approved. Strontium ranelate SJS/TEN has more recently been associated with HLA alleles HLA-A*33:03 and HLA-B*58:01 which are part of a haplotype highly represented in Southeast Asians but uncommonly seen in Europeans. Not surprisingly this association was defined in a Singapore population and SJS/TEN has been a rare event in other populations where Strontium ranelate was approved such as Australia and Europe. Moreover, other drugs that were labeled as having a risk for SJS/TEN by the FDA were not identified amongst the Asian cases and common anti-infectives such as rifampicin, streptomycin and tetracycline without SJS/TEN in their FDA label were represented amongst the Asian cases.

There are several limitations to this study which cannot account for differences in approval times or prescription differences between countries. In addition, HLA-B*15:02 genetic screening and reduction of off-label use of carbamazepine was introduced in Taiwan in 2010, and HLA-B*15:02 screening programs were also introduced in Hong Kong and subsequently Singapore and Thailand. Table S1 and Figure S1 show annual usage of antiepileptic drugs in relation to the period prior to and following implementation of HLA-B*15:02 screening in Taiwan in 2010. This total drug consumption data suggests that carbamazepine use was displaced by oxcarbazepine, for which HLA-B*15:02 has a lower positive predictive value for SJS/TEN compared to carbamazepine, and also by valproic acid for which SJS/TEN is an uncommonly associated clinical phenotype that is not known to be associated with HLA-B*15:02. In the case of phenytoin although total consumption also decreased and the risk of SJS/TEN leveled off, it did not show a linear decrease in the years post HLA-B*15:02 screening, and from the data presented it remains unclear how phenytoin was prescribed in relation to known HLA-B*15:02 positivity, which is a weaker risk factor for phenytoin SJS/TEN in Han Chinese(5).

Despite the limitations, the study by Wang et al has provided important insights into regional differences of medication induced SJS/TEN across Asia, and highlights key differences between Asia and Europe. Indeed in countries and regions where there is little or less migration and population admixture, studies to define the epidemiology of uncommon but life-threatening adverse drug reactions such as SJS/TEN provide an opportunity to define key regional differences in risk for immunologically mediated adverse drug reactions and provide important clues to a potential genetic basis. This combined with differences in drug usage patterns across populations will also provide important information as to population specific differences in immunologically mediated adverse drug reactions which provide the basis for prioritization of genetic discovery and region specific drug formularies. For type A, on-target and pharmacologically predictable reactions the risk of an adverse drug reaction may be titrated in an individual on the known pharmacology of the drug and ecological and/or genetic factors in the individual. For Type B or immunologically mediated reactions the risk of such off-target reactions may lie in the population prevalence of the genetic risk factor that may be necessary but not sufficient for the development of the hypersensitivity reaction(6).

How might understanding the epidemiology of drug-induced SJS/TEN and other serious immunologically mediated adverse drug reactions across different regions improve drug safety globally? There are important insights to be gained that could potentially guide how drug utilization and drug formularies should be managed. This is directly relevant to regions subject to high racial admixture such as North America and Europe where genetic risk of immunologically mediated adverse drug reactions may not have been yet defined. In North America and Europe in particular, defining the epidemiology of SJS/TEN in racial minorities such as African and Asians, where SJS/TEN may be actually over-represented compared to Caucasians can be challenging and utilizing drug labeling information for the most highly represented sectors of the population therefore potentially misleading. Immunologically mediated reactions related to abacavir, carbamazepine and allopurinol have provided clear examples illustrating that racial differences in the epidemiology of the respective adverse drug reactions provided important clues that were springboards for the genetic discovery that explains these population differences (Figure 1)(6). In the case of abacavir the story was simple in that HLA-B*57:01 to-date has been the only HLA risk factor associated with AHS and HLA-B*57:01 has a high positive predictive value (PPV) (55%) for AHS compared with other drug HLA-pairs where the PPV has been consistently <5%. In addition, the structural, biochemical and functional basis for AHS has now been defined through mechanistic studies that followed the original genetic association and genetic screening licensing studies(7–9). For all other drugs it appears the prevalence of the strongest genetic association appears to be the most predictive risk factor defining regional differences in SJS/TEN. The associations between HLA-B*15:02 and carbamazepine SJS/TEN and HLA-B*58:01 and allopurinol serious cutaneous adverse drug reactions are important examples where the strong association between an HLA class 1 risk allele enhances our understanding of the global epidemiology of medication-induced SJS/TEN (Figure 1). Indeed, based on the four-fold higher carriage rate of HLA-B*58:01 in those of African ancestry compared with European ancestry it would be predicted that serious immunologically mediated adverse reactions associated with allopurinol would be over-

represented in those of African European and African American ancestry and this has been supported by recent studies (Figure 1) (10). On the other hand, in the case of carbamazepine SJS/TEN, a second allele HLA-A*31:01 has been the main HLA risk factor identified in European and Japanese populations where the prevalence of HLA-B*15:02 carriage is very low. This is in contrast to Southeast Asia where both the high population carriage rate and higher positive predictive value of HLA-B*15:02 for carbamazepine SJS/TEN compared with HLA-A*31:01 completely overshadow any measurable association with HLA-A*31:01. The association between HLA-A*31:01 with severe cutaneous adverse drug reactions associated with carbamazepine is in fact only detectable in populations such as Europeans and Japanese where the carriage rate of HLA-B*15:02 is less than 1%. The ability to assign causality or to detect an association between an HLA risk allele and drug-induced SJS/TEN in a given population largely relates to the number needed to treat to detect one case. For HLA class I restricted SJS/TEN the number needed to treat to detect one case is related to the prevalence of SJS/TEN associated with that specific drug, the carriage rate of the risk allele in the population, and the positive predictive value of the risk HLA allele for develop of SJS/TEN with that specific drug. For instance for HLA-B*15:02 and carbamazepine SJS/TEN where we now know that only 3% of those carrying HLA-B*15:02 develop carbamazepine SJS/TEN, it is not surprising that this association was discoverable in densely populated Southeast Asia where the carriage rate of HLA-B*15:02 is up 10–20% and approximately 300 individuals would need to be treated with carbamazepine to detect a single case of SJS/TEN. This compares to European populations where the carriage rate of HLA-B*15:02 is <1% and the number need to treat with carbamazepine to identify a single case would exceed 3000.

Ultimately it appears that for most drugs understanding the regional epidemiology of drug hypersensitivity reactions will be key to appropriately powering and prioritizing genetic discovery studies in specific populations, to studying the generalizability of genetic associations across different populations and ultimately to providing guidance on the feasibility and translation of genetic screening and safer drug formularies.

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Figure 1:

Map showing the global epidemiology of HLA-associated serious cutaneous adverse drug reactions in relation to carriage rate of the relevant HLA alleles. (Modified with permission from JACI:IP; Peter JG, Lehloeny R, Dlamini S, Risma K, White KD, Konvinse KC, et al. Severe Delayed Cutaneous and Systemic Reactions to Drugs: A Global Perspective on the Science and Art of Current Practice. J Allergy Clin Immunol Pract. 2017;5(3):547–63.). The geographic representation of the serious immune mediated adverse drug reactions such as abacavir hypersensitivity, carbamazepine SJS/TEN and allopurinol severe cutaneous adverse drug reactions is directly associated not only with regional drug use but the prevalence of the HLA risk allele in the region in question. This explains the dominance of allopurinol and carbamazepine SJS/TEN in Southeast Asia in relation to HLA-B*58:01 and HLA-B*15:02

respectively and the initial prevalent representation of abacavir hypersensitivity in European populations prior to the onset of widespread HLA-B*57:01 screening

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