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Stevens-Johnson-syndrome and toxic epidermal necrolysis associated with carbonic anhydrase inhibitors: epidemiology, genetics and insights into mechanisms

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In this issue of the Journal of Allergy and Clinical Immunology: In Practice, Kim and colleagues present a Korean experience of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) resulting from the use of carbonic anhydrase inhibitors (CAIs), noting the extensive cutaneous manifestations and frequent ocular sequalae [1]. The authors impressively utilized a national retrospective cohort (n = 352) in Korea of 34 institutions to examine a known SJS/TEN drug-association that was previously only reported in the form of small case reports or series from Korea and Japan. Earlier reports of methazolamide induced SJS exist in the literature[2, 3]. Less frequently acetazolamide has been implicated [4]. Jachiet *et al.* reported cases of maculopapular exanthema and acute generalized exanthematous pustulosis to acetazolamide but interestingly no episodes of SJS/TEN[5]. In this letter by Kim *et al.* cases of SJS/TEN secondary to CAIs where infrequent in global terms (1.9%), with methazolamide the predominate CAI cause. Although cases of drug reaction with eosinophilia and systemic symptoms (DRESS) were part of the search criteria, CAIs do not appear to be associated with other forms of SCAR in this cohort. This highlights the importance of new and emerging regional data to inform local clinician drug causality assessments and disease phenotyping, that can be geographically specific and this may also be a major clue to a HLA association related to carriage of an HLA risk allele prevalent in the populations where the SCAR is seen but not in other populations . The most

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widely employed assessment tool to date, the Algorithm for Assessment of Drug Causality in Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (ALDEN)[6], was developed in a European context and places weight on drug probability, and as such the drug 'notoriety' field should reflect changing and region-specific epidemiology, such as that presented by Kim *et al*. Recently, Goldman *et al*. highlighted that ALDEN performed best of the available causality assessment tools, yet like all tools limitations and intra-rater reliability exist [7].

An interesting observation the authors make is the more extensive cutaneous involvement and ocular sequalae with CAI-induced SJS/TEN without differences in ICU admission or mortality. Limited by small study numbers, the mortality of CAI-induced diseases was very low (6.7%), compared to the 30% associated with anti-TB drugs in this and other antimicrobial-associated SCAR cohorts [8, 9]. The higher ocular sequelae may relate purely to propensity for CAI to distribute and concentrate at the site of tissue damage. Previous studies have supported that T-cell mediated severe cutaneous adverse drug reactions such as SJS/TEN are related to dose dependent activation of T cells and high ocular levels. [10, 11]. The presence of effector memory resident T cells in the epidermis and ocular surface may also play a key role in immune activation and antigen recognition. Some evidence supports the role of tissue-resident memory T (T_{RM}) cells in SJS and TEN[12], and disease distribution may relate to their site-predominance. T-cell dose-dependency both *in vitro* and *ex vivo* has been clearly demonstrated with drugs associated with severe T-cell mediated hypersensitivities and this is highlighted by dose-dependent activation of T cells and *in vivo* responses in the skin with abacavir hypersensitivity syndromes and increased *in vitro* responses, mortality and granulysin levels associated with oxypurinol levels in the setting of allopurinol SJS/TEN [13, 14]. Further, in relation to the extensive cutaneous involvement seen with CAI SJS/TEN compared with other drugs, carbonic anhydrases have been shown to be expressed in the epidermis and papillary dermis and play a significant role in wound healing and re-epithelialization.

A key finding in this study and supported by the already published literature is that CAI-induced SJS/TEN may in fact be predictable phenomenon in South and East Asians based on a strong class I HLA association. The role of HLAs as key regulators in T-cell mediated drug hypersensitivity is increasingly known.[15] Previous work has suggested that HLA-B*59:01 is strongly associated with methazolamide induced SJS/TEN in patients of Korean and Japanese origin,[16] later also in Han Chinese [17]. A meta-analysis of these two studies confirmed such a finding and recommended screening in Asian populations prior to utilization [18]. HLA-B59 has been reported in association with acetazolamide SJS/TEN in two Korean patients suggesting the potential for cross-reactivity between acetazolamide and methazolamide which are structurally similar non-antibiotic sulfonamide CAI [19]. Impressively HLA-B*59 was carried in 34/36 individuals with CAI reported in the literature to-date [1]. Of these HLA-B59 carriers 32 were methazolamide associated SJS/TEN, 2 were acetazolamide associated SJS/TEN, and one did not have HLA-B typing completed [1]. Of interest the only case of methazolamide associated SJS/TEN that had HLA-B typing and where HLA-B59 was not present, carried HLA-B*52:01 which shares peptide binding specificities with HLA-B*59:01 (Figure 1). Although methazolamide and acetazolamide have the potential to interact with HLA-B*59:01 (Figure 1), the drugs are not predicted to

bind with high affinity (based on molecular docking) in the absence of specific peptides. These data raise the potential that either methazolamide, acetazolamide or their metabolites generate drug-altered carbonic anhydrase derived peptides that bind to HLA-B*59:01 and lead to an HLA-B*59:01 restricted CD8+ T-cell response in the skin, eye and other tissues. Currently SJS/TEN associated with CAI has not been prevalently described outside those of South and East Asian ancestry which could relate both to drug usage patterns and the low carriage rate (<0.1%) of HLA-B*59:01 in European and African populations.

This paper progresses our understanding of drug-induced SJS/TEN, but also highlights some limitations including the retrospective design and relatively small case numbers. Prospective data or data with population ascertainment would enable calculation of the prevalence of CAI associated SJS/TEN which would enable calculation of an approximate positive predictive value of HLA-B*59:01 for CAI associated SJS/TEN and the feasibility for implementation. Given the severity of SJS/TEN and the presence of alternative therapies to manage intraocular pressure and ocular disease such as glaucoma, based on current knowledge it would seem logical to consider targeted screening approaches for HLA-B*59:01.

This study very clearly highlights the ongoing need and challenges with both defining the epidemiology and genomic predispositions of SJS/TEN. Peter *et al.* provides a global perspective on the broader group of SCAR, reflecting drug access and utilization in addition to genomic predisposition are likely key to be key –SJS/TEN related to drugs used in TB and HIV/TB co-infection secondary to high utilization in Africa, which are infrequently seen in higher income countries due to low prevalence of TB and uptake of newer antiretroviral therapies. [20] Regional networks are important to developing local causality assessments and risk-prediction and more recently they have been essential in providing important clues as to HLA associations. However, it can be acknowledged that regional network findings may not be generalizable to other populations where drug-utilization and pharmacogenomics differ. A recent review by Manolio *et al.* demonstrates clearly the variations in global distribution of three well described alleles associated with abacavir hypersensitivity, allopurinol hypersensitivity and carbamazepine SJS/TEN, HLA-B*57:01, HLA-B*58:01 and HLA-B*15:02 and urges clinicians to seize the opportunity to translate these findings into clinical practice.[21] A recent multi-national multi-site collaboration (Australia and United States) was able to identify a strong association with vancomycin DRESS and HLA-A*32:01 in patients of European origin utilizing only a small number of cases (n = 23), providing a roadmap for future discoveries in SCAR.[22] Combining multiple prospective networks is likely to drive the most impactful discoveries with greatest potential for translation and disease prevention. White *et al.* published the meeting proceedings from the 2017 SJS/TEN meeting highlighting the need for “multidisciplinary networks to drive science and translation”.[23] *Kim et al.* highlight the significant and unnecessary attributable morbidity and mortality associated with SJS/TEN [1]. Despite many unknowns in SJS/TEN there is a consensus of unmet needs and that it will be key to develop strategies to fuel efforts for prevention and earlier diagnosis.

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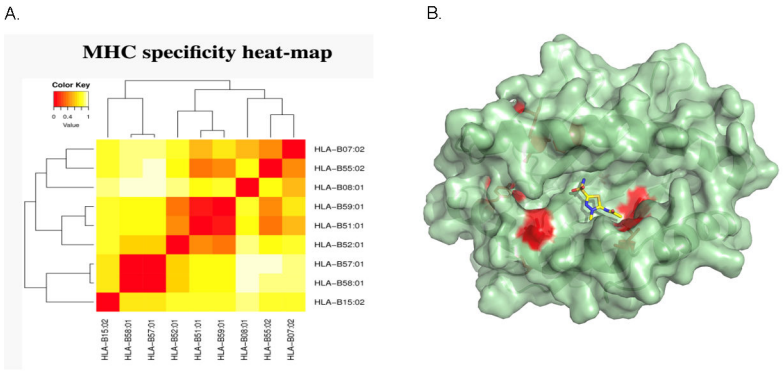

Figure 1.

A. Heatmap of HLA-B alleles showing shared peptide binding specificities between HLA-B*59:01, HLA-B*52:01 and HLA-B*51:01. (NetMHC-Pan2.8, http://www.cbs.dtu.dk/services/MHCcluster/) B. Molecular docking of methazolamide in a structural model of HLA-B*59:01 suggesting low prediction of HLA binding in the absence of peptide. The residues that differ between HLA-B*59:01, HLA-B*51:01 and HLA-B*52:01 are highlighted in red.