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Prevention and Diagnosis of Severe T-Cell-Mediated Adverse Drug Reactions: ARE We There Yet?

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Severe cutaneous adverse reactions (SCARS), such as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), are T-cell-mediated delayed reactions that are associated with significant short-term morbidity and mortality. A sequela of SCAR that affects both patients and their health care providers is the threat and uncertainty of future safe treatment choices.[1] This is particularly relevant in the developing world, in the setting of antimicrobial treatment, and treatment of diseases of high global importance such as HIV, tuberculosis, and leprosy where multiple drugs implicated in SCAR are prescribed concurrently, and where the risk of rechallenge morbidity and mortality has to be balanced against the risk of morbidity and mortality of the underlying infectious disease that may be both inadequately treated and have significant public health implications.[1,2]

The discovery of strong human leukocyte antigen (HLA) class I associations with T-cell-mediated drug hypersensitivity syndromes represented a significant advance in our understanding of the immunopathogenesis of SCAR with significant translational potential.[3] In the case of abacavir hypersensitivity and HLA- B*57:01, this most notably led to the routine use of HLA- B*57:01 screening before abacavir use, which has eliminated true immunologically mediated abacavir hypersensitivity.[4] A crucial part of the translational pathway was widespread provision of a quality-assured screening test that could be reproduced in different treatment settings.[5] An important downstream effect of HLA-B*57:01 screening was that the possibility of abacavir hypersensitivity was eliminated, meaning that false-positive clinical diagnoses were significantly reduced and efforts could be placed on making a correct diagnosis of an underlying infectious disease, immune restoration syndrome, or alternative drug hypersensitivity syndrome.[4,6] A similar translational pathway has been successful for HLA-B*15:02 and carbamazepine SJS/TEN where successful screening strategies in many Southeast Asian countries reduced morbidity and mortality from this disease.[7,8] The discoveries of HLA-B*57:01-associated abacavir hypersensitivity and HLA-B*15:02-associated carbamazepine SJS/TEN, in addition to their

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significant contribution to prevention of T-cell-mediated adverse drug reactions, have fuelled our understanding of the immunopathogenesis of these diseases.[3]

Despite these advances, there are key gaps that still exist in our ability to prevent and ascertain with certainty the implicated drug in SCAR and other T-cell-mediated adverse drug reactions. Notably, in terms of screening and prevention, this includes the fact that for most SCARs only a small portion (<5%) carrying an HLA risk allele will develop disease and the presence of a strong association and HLA-B risk allele in one population will not necessarily be globally generalizable across all racial groups and ethnicities.[1] In this issue of the *Journal of Allergy and Clinical Immunology: In Practice*, Klaewsongkram et al[9] present a prospective study of 160 probable/definite Thai patients with SCAR recruited by dermatologists from 6 university hospitals with the objective of retrospectively determining the utility of HLA-B screening for SCAR prevention coupled with IFNg-release Enzyme Linked ImmunoSpot (ELISpot) analysis for causative drug determination. HLA A B C typing was performed, and results from HLA B typing were analyzed on 151 patients with extracted DNA and SCAR (SJS/TEN [74], DRESS [59], and acute generalized exanthematous pustulosis [AGEP] [18]). Of these patients, 41 (27.2%) developed SCAR after taking drugs with known HLA-B risk alleles (HLA-B*13:01, HLA- B*15:02, HLA-B*35:05, and HLA-B*58:01 for dapsone, carbamazepine/oxcarbazepine, nevirapine, and allopurinol SCAR, respectively). Prescreening this cohort would have protected 78% of patients carrying a known risk allele. Not surprisingly, the majority of those reactions prevented (92%) would have been HLA-B*15:02-associated carbamazepine SJS/TEN and HLA-B*58:01-associated allopurinol DRESS and SJS/TEN. Prescreening benefit would not have been realized where the HLA-B*15:02 association has been much weaker or other genetic factors have been implicated such as phenytoin SCAR.[10] Looking at all potentially implicated drugs together, screening would also not have been effective for AGEP, not surprisingly because AGEP is a SCAR for which strong HLA class I associations have not been described yet. Overall, using HLA-B as a screening and preventative tool in these 151 patients, only 21.1% would have expected to have had SCAR prevented through identification of a known HLA-B risk allele.

In addition to the retrospective examination of HLA-B and its potential role in SCAR prevention in this cohort, the authors examined IFNg ELISpot as a tool to aid causality assessment. IFNg ELISpot was most useful for ascertaining the most likely implicated drug for DRESS>SJS/TEN>AGEP cases. Culprit drug determination was 50% of DRESS, but only 31.3% for AGEP. However, the utility of IFNg ELISpot for causative drug assignation for each SCAR phenotype is difficult to disentangle from the class of drug. IFNg ELISpot was poor at determining causality for beta-lactams, and in this study, beta-lactam use was the major cause of AGEP. IFNg ELISpot was most effective in assigning causality for anticonvulsants, antituberculosis agents, and to a lesser extent allopurinol and antimicrobial sulfonamides/ sulfones, all drugs most commonly associated with DRESS and SJS/TEN.

The quest to examine approaches to prevent and ascribe drug causality for SCAR in this study has several limitations. Notably, although HLA-B associations are still most likely to be relevant to SCAR, other HLA class I associations have been increasingly described including HLA-A and -C.[11–13] Although the authors list putative HLA haplotypes, it is still

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most likely that there is a biological interaction with a single HLA class I allele and a drug, and the haplotypes described by the authors can only be imputed rather than truly determined (without family studies). In keeping with the proposed biological model for delayed T-cell-mediated drug hypersensitivity that drugs may activate T cells through different mechanisms and noncovalently bind to peptide, HLA, and/or T-cell receptor, it is possible that interactions with HLA class I alleles with shared peptide binding specificities may explain the fact that a single HLA-B allele could not identify those at risk for a specific drug SCAR.[13] In addition, the IFNg ELISpot test has not been validated across large populations of drug hypersensitivity patients over different time points from their acute reaction. Areas of uncertainty include whether this is the most sensitive technique for all clinical phenotypes or whether IFNg as the readout is appropriate for all phenotypes, what the optimal timing of the test is in relation to the acute SCAR, whether both the drugs and their active metabolites are needed in the assay, optimal drug concentrations in relation to Cmax and other pharmacokinetic parameters, the impact of steroids and other immunosuppressants used in acute treatment on sensitivity, imperfect specificity considering false positives noted with control specimens, and the risk for false positives or erroneous results with extended incubation (>24 hours).[14]

Despite its limitations, the study by Klaewsongkram et al both highlights key unmet needs and foreshadows future approaches that may contribute to the prevention and diagnosis of SCAR. It seems clear, for instance, that exemplary phenotyping of SCAR facilitated by clinical causality assessment *ex vivo* and *in vivo* testing will aid in the discovery of new HLA risk alleles. In addition to IFNg ELISpot, *in vivo* techniques such as delayed intradermal and patch testing have shown promise in identification of implicated drugs in SCAR, and similar to IFNg ELISpot, show different sensitivity amongst specific drugs and SCAR phenotypes with DRESS>AGEP>SJS/TEN.[15] The future may in fact lie in the combined role of *ex vivo* and *in vivo* testing in combination with genetic risk factors and other biological markers to improve sensitivity and specificity of SCAR diagnosis. It is also possible that *ex vivo* testing during both the acute reaction and a follow-up time point may provide a higher sensitivity and specificity, and potentially better highlight the durability of T-cell responses. Recent work suggests that the kinetics and time course of *ex vivo* versus *in vivo* approaches may differ and that when used correctly these may provide complementary approaches to drug causality ascertainment.[14]

Abacavir hypersensitivity appeared to be a unique example where the 55% positive predictive value and 100% negative predictive value and generalizability of the HLA-B*57:01 association across racially disparate different populations meant that <30 cases would need to be tested to prevent one case of clinically diagnosed abacavir hypersensitivity.[3] This meant that HLA-B*57:01 screening could effectively eliminate abacavir hypersensitivity as a clinical entity. However, for most drugs from less than 1% to 6% of those carrying an HLA risk allele will develop SCAR and the implicated HLA allele may vary according to the drug, the phenotype, and the population, making screening as the universal and only approach impractical.[1] *Ex vivo* approaches such as IFNg ELISpot show promise for the diagnosis of SCAR; however, these tests also clearly have significantly less than 100% sensitivity and specficity, and considerable research and development will be

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needed to get these up to a standard where they could be quality assured, reproducible tests of acceptable precision and accuracy for use in the clinical setting.

Ultimately, in the near future, the safest and most pragmatic approach, particularly for the complicated patient treated with multiple potentially implicated drugs, and where drug cross- reactivity is also likely to be relevant, may be application of a decision analytic approach that combines clinical causality assessment utilizing validated phenotyping tools, HLA typing, and *ex vivo* and *in vivo* testing approaches for implicated and potentially cross-reactive drugs to define the most likely implicated drug(s). Given the severity of SCAR, the need for future treatment options in many of these patients, and the potential morbidity and mortality implications for drug rechallenge, it is promising to consider approaches that will be able to define drugs that are safe to use in the future. The discovery and study of multidimensional approaches to prevent, diagnose, and treat SCAR will be the future of precision approaches to T-cell- mediated drug allergy.

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