**HLA and immune-mediated adverse drug reactions: another hit with vancomycin**

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Serious cutaneous adverse reactions (SCAR) are an important clinical problem caused by a variety of drugs1. The most serious clinical manifestations are DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) and SJS/TEN (Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis). DRESS, a multi-system hypersensitivity syndrome, is immune-mediated and can be associated with mortality rates up to 10%. Antibiotics are amongst the most common drugs to cause DRESS. A recent analysis of a large electronic healthcare record database showed the prevalence of DRESS to be 2.18 per 100,000, with antibiotics responsible for 74% of cases2. The antibiotics most commonly implicated were vancomycin (39%), β-lactams (23%), fluoroquinolones (4%), tetracyclines (4%) and sulfonamides (3%).

There has been increasing interest in antibiotics recently because of the rise in the incidence of antimicrobial resistance (AMR), which has led to grave warnings that this may result up to 10 million deaths a year by 20503. While AMR is largely driven by the over-use of antibiotics in man and in animals, other factors also play a role. In many infections, multiple antibiotics are administered concomitantly. If a patient develops a hypersensitivity reaction, the clinician will not know definitively which antibiotic was responsible for the reaction. Using the precautionary principle, the patient will be labelled as “allergic” to all the administered antibiotics, and for subsequent infections, the patient will be treated with alternative antibiotics, which may have a higher risk of AMR, may be more costly, and may not be the most effective antibiotics. This has been a particular problem with penicillin allergy, which is over-diagnosed (falsely reported to occur in approximately 10% of patients), and leads to the use of more broad-spectrum antibiotics. A recent UK based cohort study showed that documented penicillin allergy led to a higher risk of methicillin-resistant *S. aureus* (MRSA) and *C. difficile* infection4.

Vancomycin is a glycopeptide antibiotic that is active against Gram-positive microbes, including MRSA. DRESS caused by vancomycin often manifests as rash, fever, eosinophilia, and renal dysfunction – a recent retrospective case review suggested that the likelihood of renal involvement was at least 2-fold higher than seen with DRESS caused by other drugs5. In this issue of the *Journal,* Konvinse *et al* have an undertaken a genetic analysis of the HLA region in 23 patients with vancomycin-associated DRESS6. They show that 82.6% of cases carried *HLA-A\*32:01* compared with 6% of the population from Vanderbilt’s biorepository (BioVU), a highly significant finding underlined by their calculations that (a) 19% of the positive group developed DRESS within 4 weeks, and (b) 70 patients would need to be tested to prevent one case of DRESS associated with vancomycin. It is interesting to note that most patients were taking other antibiotics concomitantly, which as discussed above, can lead to problems in identifying the culprit drug. The authors have not provided information on renal involvement in their DRESS cases, and it would be interesting to undertake a comparison of the HLA predisposition in patients with vancomycin DRESS ± renal involvement. As with any genetic association, the finding needs to be replicated in independent cohorts. However, given the effect size shown, it is likely that this will be a true positive association. Future studies should also determine whether the same HLA association is observed in patients with hypersensitivity to teicoplanin, another glycopeptide antibiotic, which has been reported to cross-react with vancomycin7.

The HLA association identified with vancomycin DRESS is another addition to the striking number of associations that have been identified with hypersensitivity reactions caused by drugs. Indeed, about 30 such HLA associations have been identified since the beginning of this century8 – the drugs implicated have had a wide variety of therapeutic indications (including anti-infectives such as flucloxacillin, co-amoxiclav, dapsone, abacavir and nevirapine), have disparate structures and have affected different organ systems (figure 1). Some of these associations have been implemented into clinical practice with positive benefits including *HLA-B\*57:01* genotyping prior to the use of abacavir, *HLA-B\*15:02* before carbamazepine prescription in SE Asian patients, and *HLA-B\*58:01* before allopurinol, again in some Asian countries8.

Given the many advances in the pharmacogenetics of adverse drug reactions (ADRs) over the last two decades, a framework for how these tests can be used to improve clinical practice has been proposed9. While pharmacogenetic tests have largely been used for prediction and prevention of ADRs, perhaps they can also be used for exclusion of ADRs, stratification of monitoring and diagnosis, as well as pre-emptively and to understand mechanisms. This framework is consistent with the suggestion by Kovince *et al*6 that HLA testing could be used for risk stratification after starting vancomycin but before the development of DRESS. In order to facilitate the implementation of HLA testing for ADRs, an HLA-gene panel has been developed, which aims to have a turnaround time of 48 hours (Pirmohamed, unpublished), and which has been shown to be cost-effective10. In the context of AMR, pharmacogenomic tests (in combination with other tests such as the IFN-γ ELISpot as used by Kovince et al6) could be used to identify the culprit drug (when multiple drugs are started in combination) and/or exclude a suspected drug9, and therefore enable patients to receive antibiotics in the future which may otherwise not have been available if the patient is wrongly labelled as being allergic.

In summary, the important finding that *HLA-A\*32:01* predisposes to vancomycin-associated DRESS adds to the growing evidence of the importance of the HLA region in predisposing to drug hypersensitivity reactions. It also provides an opportunity to prevent these serious ADRs, and/or improve their clinical management, which in the case of antibiotics may have unintended benefits in the fight against AMR.

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**References**

1. Duong TA, Valeyrie-Allanore L, Wolkenstein P, Chosidow O. Severe cutaneous adverse reactions to drugs. Lancet 2017; 390:1996-2011.

2. Wolfson AR, Zhou L, Li Y, Phadke NA, Chow OA, Blumenthal KG. Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome Identified in the Electronic Health Record Allergy Module. J Allergy Clin Immunol Pract 2019; 7:633-40.

3. O'Neill J. Review on Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations. Review on Antimicrobial Resistance. London, 2014. Available from: https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations\_1.pdf.

4. Blumenthal KG, Lu N, Zhang Y, Li Y, Walensky RP, Choi HK. Risk of meticillin resistant *Staphylococcus aureus* and *Clostridium difficile* in patients with a documented penicillin allergy: population based matched cohort study. BMJ 2018; 361:k2400.

5. Madigan LM, Fox LP. Vancomycin-associated Drug-Induced Hypersensitivity Syndrome (DIHS). J Am Acad Dermatol 2019.

6. Konvinse KC, Trubiano JA, Pavlos R, James I, Shaffer CM, Bejan CA, et al. HLA-A\*32:01 is strongly associated with vancomycin-induced drug reaction with eosinophilia and systemic symptoms. J Allergy Clin Immunol 2019.

7. Miyazu D, Kodama N, Yamashita D, Tanaka H, Inoue S, Imakyure O, et al. DRESS Syndrome Caused by Cross-reactivity Between Vancomycin and Subsequent Teicoplanin Administration: A Case Report. Am J Case Rep 2016; 17:625-31.

8. Pirmohamed M, Ostrov DA, Park BK. New genetic findings lead the way to a better understanding of fundamental mechanisms of drug hypersensitivity. J Allergy Clin Immunol 2015; 136:236-44.

9. Alfirevic A, Pirmohamed M. Genomics of Adverse Drug Reactions. Trends Pharmacol Sci 2017; 38:100-9.

10. Plumpton CO, Pirmohamed M, Hughes DA. Cost-Effectiveness of Panel Tests for Multiple Pharmacogenes Associated With Adverse Drug Reactions: An Evaluation Framework. Clin Pharmacol Ther 2018 [Epub].

**Legend**

**Figure 1**: HLA associations described with some of the anti-infective agents, including antibiotics and antivirals. The boxes around the genetic associations refer to the genetic testing framework reported in reference 9, while the lowermost part of the figure refers to the potential clinical benefits of using genetic testing in patients exposed to the agents, before, during or after drug administration. SCAR: serious cutaneous adverse reaction; DRESS: drug reaction with eosinophilia and systemic symptoms.