

### HLA B62 as a possible risk factor for drug reaction with eosinophilia and systemic symptoms to piperacillin/tazobactam



Krzysztof Rutkowski, MD, MRCP<sup>a</sup>,

Craig Taylor, PhD, FRCPath<sup>b</sup>, and Annette Wagner, MD<sup>c</sup>

#### Clinical Implications

- Piperacillin/tazobactam appears to be a frequent cause of drug reaction with eosinophilia and systemic symptoms. HLA typing revealed a high frequency (50%) of HLA B62, which could be a risk factor for this severe cutaneous reaction.

#### TO THE EDITOR:

Unpredictable adverse drug reactions (ADRs) (World Health Organization type B [bizarre]) make up 5% to 20% of all ADRs. Severe cutaneous reactions are very rare at 0.4 to 1.2 cases/million but more common in inpatients (1:1000).<sup>1</sup> Drug reaction with eosinophilia and systemic symptoms (DRESS) carries a mortality of 10% and is one of a spectrum of severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome and toxic epidermal necrolysis. Carbamazepine seems to be the most common trigger, but more than 44 drugs have been associated with DRESS.<sup>2</sup> The diagnosis can be made using the European Registry of SCAR (RegiScar) clinical and laboratory scoring criteria to rate cases as negative, possible, probable, or definite. Three of 4 criteria need to be met: an acute rash, temperature of more than 38°C, lymphadenopathy at 2 sites, involvement of more than 1 organ, and abnormalities in lymphocyte and eosinophil counts. Additional criteria include hospitalization and that the reaction is suspected to be drug-related. Japanese criteria overlap with RegiScar and include evidence of viral reactivation, for example, Herpesviridae.<sup>1,3,4</sup>

The underlying pathophysiology is only partially understood and may involve detoxification defects, viral reactivation, and a T-cell-dependent immune response.<sup>2,3,5</sup> Activation of T cells is dependent on the presentation of antigen as MHC-associated peptides to T-cell receptors. In the case of carbamazepine and abacavir, specific alleles (HLA-B\*15:02 and 57:01, respectively) carry a greatly increased risk of such an activation and SCARs. This has led to the recommendation of HLA typing of patients before administering these drugs.<sup>6</sup>

Beta-lactam antibiotics and nonsteroidal anti-inflammatory drugs account for the majority of all ADRs and have been described as the cause of SCARs.<sup>2</sup> In the last 12 months, 3175 doses of piperacillin/tazobactam (PT) were administered at Cambridge University Hospital. Over the last 7 years, this antibiotic was the probable cause of 74% of SCARs investigated in the local Department of Allergy (15 out of a total of 20 cases). Therefore, the ability to predict the risk of DRESS to PT would be of major benefit to patient safety.

Between 2009 and 2016, 3 definite and 3 probable cases of DRESS to PT (Tazocin, Pfizer Ltd, UK) were diagnosed in the

Department of Allergy in Cambridge. RegiScar score, skin testing, and HLA typing were undertaken (Table I).

Skin prick test with stock concentrations of benzylpenicilloyl octa-L-lysine, benzilpenicilloyl sodium, amoxicillin, benzylpenicillin, flucloxacillin, and PT were negative in all patients at 15 minutes. Intradermal tests with a 1:10 dilution of the antibiotics in 0.9% NaCl were read at 15 minutes and 24 (48) hours. In all patients, they were negative at 15 minutes. In 4 patients, there was a positive delayed intradermal test result to PT only; in 1 patient, to all penicillins with the strongest reaction (central blister) to PT. The result was not documented in 1 patient (Table I). RegiScar criteria do not recommend routine tests for viral reactivation. However, patients 4 and 6 had a negative cytomegalovirus, EBV, herpes simplex, hepatitis A, B, and C, and adenovirus serology.

Low-resolution (first field) HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DRB3/4/5, HLA-DQB1 typing was performed using PCR sequence-specific primers (PCR-SSO, LABType SSO, One Lambda, Canoga Park, Calif) and results converted to serological equivalents for the purposes of presentation (Table II). Three of the 6 white patients (50%) were HLA-B62 positive. Our own data calculated using HLA types of 10,000 consecutive deceased organ donors confirm a 12% frequency of B62 in the UK whites. The patient cohort sample size was however too small to perform meaningful statistical comparison.

All patients required topical steroids (bethamethasone, clobetasol, or mometasone) and oral (fexofenadine) or intravenous antihistamines (chlorphenamine). Only patient 3 received 5 days of 100 mg intravenous hydrocortisone twice a day followed by 5 days of 30 mg prednisolone once a day.

The understanding of the pathophysiology of the immune response in DRESS has improved since its first description in 1950 (phenytoin). It is a Gell-Coombs type IV (T-cell-mediated) reaction.<sup>7</sup> Activation of T cells requires binding of MHC-associated peptides to specific T-cell receptors. In delayed drug hypersensitivity, novel HLA-binding peptides are derived from drug-hapten protein adducts or direct binding of a drug to the peptide sequences displayed by the MHC molecules, altering their specificity. Specific alleles seem to predispose to this. So far most associations have been identified within the HLA class I and more specifically the HLA B locus.<sup>5,8</sup>

For carbamazepine and abacavir, there is a clear association with HLA-B\*15:02 and HLA-B\*57:01, respectively. Indeed, absence of these has a 100% negative predictive value for a severe hypersensitivity reaction, allowing patient selection before treatment. However, their presence has only a 50% positive predictive value.<sup>6</sup> Other risk or protective factors may play a role in addition to the immunological response.

Identifying predictive factors for the development of DRESS to PT faces a number of difficulties. There is no simple diagnostic test due to the heterogeneity of the patient group. Although piperacillin is thought to be the allergenic moiety in PT, tazobactam-specific immune response cannot be ruled out. Moreover, commercially, these 2 agents are not separately available for testing. In addition, *in vitro* experiments suggest that under certain circumstances, for example, high concentration of the drug, a less restricted and more promiscuous T-cell response

**TABLE I.** Clinical characteristics and laboratory investigations

| Age (y)<br>& sex | Indication for PT                   | Onset (day<br>of course) | T (°C) | Skin                                     | Laboratory investigations  |                            |              |                            |                                                |                                 | RegiScar<br>score |
|------------------|-------------------------------------|--------------------------|--------|------------------------------------------|----------------------------|----------------------------|--------------|----------------------------|------------------------------------------------|---------------------------------|-------------------|
|                  |                                     |                          |        |                                          | Neu<br>( $\times 10^9/L$ ) | Lym<br>( $\times 10^9/L$ ) | ALT<br>(U/L) | Plt<br>( $\times 10^9/L$ ) | Eos ( $\times 10^9/L$ )<br>(maximum<br>on day) | IDT: size (mm)<br>and delay (h) |                   |
| 61, F            | Perforated sigmoid                  | 31                       | 39.2   | Severe MPR                               | 13.08                      | 2.76                       | 27           | 490                        | 2.68 (9)                                       | 9 $\times$ 10; 24               | 7: definite       |
| 29, M            | Osteomyelitis                       | 18                       | 39.7   | Severe MPR trunk                         | 1.85                       | 0.59                       | 30           | 222                        | 1.64 (20)                                      | 7; 10                           | 4: probable       |
| 54, F            | Infection after<br>wrist surgery    | 4 post course            | 39.8   | Severe MPR; facial<br>angioedema         | 4.21                       | 1.03                       | 39           | 320                        | 0.9 (3)                                        | Not read at 24 h                | 4: probable       |
| 12, M            | Chemotherapy for<br>medulloblastoma | 14                       | 40     | Severe MPR                               | 2.37                       | 1.20                       | 1099         | 30                         | 0.79 (11)                                      | (+); 24                         | 6: definite       |
| 69, F            | Esophageal<br>perforation           | 18                       | 38.3   | Severe MPR                               | 8.88                       | 2.8                        | 52           | 329                        | 1.47 (8)                                       | (+); 24                         | 5: probable       |
| 53, M            | Infected calcaneal<br>fracture      | 25                       | 39.8   | Severe MPR;<br>generalized<br>angioedema | 0.1                        | 0.41                       | 212          | 213                        | 2.6 (14)                                       | (+); 24<br>(central blister)    | 8: definite       |

ALT, Alanine aminotransferase; Eos, eosinophils; F, female; IDT, intradermal test; Leu, leukocytes; M, male; MPR, maculopapular rash; Neu, neutrophils; Plt, platelets.

**TABLE II.** HLA typing results

| Patient | HLA-A     | HLA-B           | HLA-C     | HLA-DR       | HLA-DRB3/4/5 | HLA-DQ     |
|---------|-----------|-----------------|-----------|--------------|--------------|------------|
| 1       | 11, 24(9) | 39(16), 62(15)~ | 7, 9(3)   | 8, 13(6)     | 52, —        | 4, 6(1)    |
| 2       | 1, 2      | 44(12), 64(14)  | 2, 8      | 15(2), 16(2) | 51, —        | 5(1), 6(1) |
| 3       | 1, 2      | 8, 62(15)       | 7, 10(3)  | 4, 17(3)     | 52, 53       | 2, 8(3)    |
| 4       | 2, —      | 39(16), 62(15)  | 10(3), 12 | 4, 11(5)     | 52, 53       | 7(3), 8(3) |
| 5       | 1, 2      | 8, 57(17)       | 6, 7      | 7, 17(3)     | 52, 53N      | 2, 9(3)    |
| 6       | 2, 24(9)  | 7, 27           | 2, 7      | 15(2), —     | 51, —        | 6(1), —    |

HLA typing was performed using PCR sequence-specific primers. HLA typing results were converted to serological equivalent specificities with "split" antigen specificities in parentheses. The en dash means homozygosity.

is possible.<sup>9</sup> This might explain the lack of association with a single specific HLA allele in our patients.

It seems remarkable that a relatively infrequent allele B62 should cluster in a small group of patients, all suffering from a rare adverse drug reaction. Because of the size of the cohort, there are caveats: all B62 alleles are associated with DRB 52 and DQ6 is also present at the same rate as B62. Patient number in this study was too small to distinguish the importance of one over the other. However, B62, a rare haplotype, had a much higher frequency than in the control population. Understandably, large multicentre studies are required to confirm the validity of our observation and investigate other HLA associations. Until then it might be impossible to predict SCARs to PT. Another important and practical finding is that in the hands of an allergist/immunologist experienced in drug allergy, *in vivo* intradermal testing is a safe method of confirming a T-cell-mediated reaction during DRESS. This could be used in addition to patch tests and *in vitro* studies.

Corresponding author: Krzysztof Rutkowski, MD, MRCP, Department of Allergy, Guy's and St Thomas' NHS Foundation Trust, Great Maze Pond, 2nd Fl, Bermondsey Wing, London SE1 9RT, UK. E-mail: [chris.rutkowski@gstt.nhs.uk](mailto:chris.rutkowski@gstt.nhs.uk). 2213-2198

© 2016 American Academy of Allergy, Asthma & Immunology  
<http://dx.doi.org/10.1016/j.jaip.2016.10.008>

## REFERENCES

- Roujeau J, Stern R. Severe adverse cutaneous reactions to drugs. *N Engl J Med* 1994;331:1272-85.
- Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, et al. The DRESS syndrome: a literature review. *Am J Med* 2011;124:588-97.
- Kardaun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Response to variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 2007;156:609-11.
- Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among Herpes viruses and antiviral and antidrug immune responses. *Allergol Int* 2006;55:1-8.
- Choudhary S, McLeod M, Torchia D, Romanelli P. Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome (literature review). *J Clin Aesthet Dermatol* 2013;6:31-7.
- Brent Ferrell P Jr, McLeod HL. Carbamazepine, HLA\*B1502 and risk of Stevens-Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations. *Pharmacogenetics* 2008;9:1543-6.
- Walsh SA, Creamer D. Drug reaction with eosinophilia and systemic symptoms (DRESS): a clinical update and review of current thinking. *Clin Exp Dermatol* 2010;36:6-11.
- Pavlos R, Mallal S, Ostrov D, Pompeu Y, Phillips E. Fever, rash, and systemic symptoms: understanding the role of virus and HLA in severe cutaneous drug allergy. *J Allergy Clin Immunol Pract* 2014;2:21-33.
- Al-Attar Z, Faulkner L, Farrell J, Whitaker P, Peckham D, Park K, et al. Characterization of the TCR V repertoire of piperacillin-specific T-cells. *Clin Trans Allergy* 2014;4:P39.

<sup>a</sup>Department of Allergy, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom

<sup>b</sup>Tissue Typing Laboratory, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom

<sup>c</sup>Department of Allergy, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication July 25, 2016; revised October 3, 2016; accepted for publication October 12, 2016.

Available online November 30, 2016.

Reproduced with permission of copyright owner.  
Further reproduction prohibited without  
permission.