

<p>Institution: UNIVERSITY OF LIVERPOOL and LIVERPOOL SCHOOL OF TROPICAL MEDICINE</p>
<p>Unit of Assessment: UOA1 - Clinical Medicine</p>
<p>Title of case study: HLA alleles as genetic predictors for drug-induced hypersensitivity reactions</p>
<p>1. Summary of the impact</p> <p>The University of Liverpool (UoL) research has had health impact on immune-mediated drug hypersensitivity reactions, which can be severe and life-threatening. It has shown that predisposition to hypersensitivity reactions caused by abacavir, nevirapine, carbamazepine and flucloxacillin is due to specific HLA genes on chromosome 6. This has led to changes in the drug label and guidelines for abacavir, increased <i>HLA-B*57:01</i> gene testing in the NHS through a University spin-out company, and a reduction in the incidence of hypersensitivity from 7% to <1%. The more recent demonstration of <i>HLA-A*31:01</i> and predisposition to carbamazepine hypersensitivity, has led to drug label changes for carbamazepine.</p>
<p>2. Underpinning research</p> <p>The research described was all undertaken at the UoL after 1993 and led by Professors Munir Pirmohamed and Kevin Park and Dr Ana Alfirevic (Snr Lecturer).</p> <p>Adverse drug reactions (ADRs) account for 6.5% of all hospital admissions (Pirmohamed et al, <i>BMJ</i>. 2004; 329:15-9). Immune-mediated ADRs (also called hypersensitivity reactions) are not predictable from the pharmacology of the drug and can lead to fatalities. The reactions are mediated by antigen-specific T cells interacting with HLA-restricted antigen presenting cells, providing a functional rationale to the potential role of the major histocompatibility complex (MHC), and the HLA alleles contained therein, as markers of susceptibility. The research in this area began in 2000, with our first publication in 2001 showing the importance of genes within the MHC, including HLA alleles, in carbamazepine-induced hypersensitivity [1].</p> <p>Abacavir is an antiretroviral that can cause life threatening hypersensitivity in 5-7% of patients, with rechallenge leading to severe and fatal reactions. Work undertaken in Australia in 2002 showed that <i>HLA-B*57:01</i> predisposed to abacavir hypersensitivity. UoL research undertaken between 2002 and 2004, which included the identification and recruitment of abacavir hypersensitivity patients and controls [2], showed that not only was <i>HLA-B*57:01</i> associated with the reaction, but in addition, it was the first study to demonstrate the cost effectiveness of pre-treatment testing for <i>HLA-B*57:01</i> in preventing hypersensitivity.</p> <p>Carbamazepine, an anticonvulsant, can cause a wide range of hypersensitivity reactions including dangerous or even fatal skin reactions. In 2004, a Taiwanese group reported that all Han Chinese patients who experienced carbamazepine-induced Stevens-Johnson syndrome (SJS) were positive for <i>HLA-B*15:02</i>. UoL research showed that this allele was not important in patients of European ancestry because of its low prevalence [3], and it did not predispose to another type of hypersensitivity reaction called DRESS (drug reaction with eosinophilia and systemic symptoms). A recent UoL systematic review has shown that <i>HLA-B*15:02</i> is important in Chinese, Thai, Malay and Indian populations, but not in Caucasians or Japanese [4].</p> <p>In March 2011, UoL research showed that <i>HLA-A*31:01</i> is associated with CBZ-hypersensitivity reactions in Caucasians [5]. <i>HLA-A*31:01</i>, unlike <i>HLA-B*15:02</i>, is associated with all forms of hypersensitivity reactions to CBZ (including maculopapular eruptions, hypersensitivity syndrome and SJS). The same finding has also been demonstrated in Japanese patients. The finding is particularly important given the <u>wider</u> worldwide distribution of <i>HLA-A*31:01</i> compared with <i>HLA-B*15:02</i> which is found predominantly in South East Asia.</p> <p>The research has investigated other hypersensitivity reactions: e.g. it has shown that <i>HLA-B*57:01</i> is a predisposing factor for flucloxacillin hepatitis (Daly et al; <i>Nat Genet</i> 2009;41:816-9) and <i>HLA-C*04:01</i> is a predisposing factor nevirapine-induced SJS in Malawians [6].</p>
<p>3. References to the research</p> <ol style="list-style-type: none"> 1. Pirmohamed M, Lin K, Chadwick D, Park BK (2001). TNF-α promoter region gene polymorphisms in carbamazepine-hypersensitive patients. <i>Neurology</i>, 56, 890-896 (PMID:

Impact case study (REF3b)

11294926) Citations: 96 Impact Factor: 8.249

2. **Hughes DA, Vilar FJ, Ward CC, Alfirevic A, Park BK, Pirmohamed M.** (2004). Cost-effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity. *Pharmacogenetics*, 14, 335-342 (PMID: 15247625) Citations: 147 Impact Factor: 3.608
3. **Alfirevic A, Jorgensen AL, Williamson PR, Chadwick DW, Park BK, Pirmohamed M.** (2006). HLA-B locus in Caucasian patients with carbamazepine hypersensitivity. *Pharmacogenomics*, 7, 813-818 (DOI: 10.2217/14622416.7.6.813) Citations: 122 Impact Factor: 3.857
4. **Yip VL, Marson AG, Jorgensen AL, Pirmohamed M, Alfirevic A.** (2012). HLA genotype and carbamazepine-induced cutaneous adverse drug reactions: a systematic review. *Clin Pharmacol Ther*, 92, 757-765 (DOI: 10.1038/clpt.2012.189) Citations: 5 Impact Factor: 6.846
5. McCormack M, **Alfirevic A**, Bourgeois S, Farrell JJ, Kasperaviciute D, Carrington M, **Sills GJ, Marson T**, Jia X, De Bakker PI, Chinthapalli K, Molokhia M, Johnson MR, O'connor GD, Chaila E, Alhusaini S, Shianna KV, Radtke RA, Heinzen EL, Walley N, Pandolfo M, Pichler W, **Park BK**, Depondt C, Sisodiya SM, Goldstein DB, Deloukas P, Delanty N, Cavalleri GL, **Pirmohamed M.** (2011). HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *N Engl J Med*, 364, 1134-1143 (DOI: 10.1056/NEJMoa1013297) Citations: 156 Impact Factor: 51.658
6. **Carr DF, Chaponda M, Jorgensen AL, Castro EC, Van Oosterhout JJ, Khoo SH, Laloo DG, Heyderman RS, Alfirevic A, Pirmohamed M.** (2013). Association of human leukocyte antigen alleles and nevirapine hypersensitivity in a Malawian HIV-infected population. *Clin Infect Dis*, 56, 1330-1339 (DOI: 10.1093/cid/cit021) Citations: 0 Impact Factor: 9.374

Key research grants

2007-2013. **The Department of Health.** Department of Health Chair in Pharmacogenetics, £3.3m (£33,000 supplement; 2009), PI **M Pirmohamed**, Col **BK Park**

2008-2013. **Wolfson Foundation.** Wolfson Centre for Personalised Medicines, £2m, PI **M Pirmohamed**

2008-2013. **MRC.** MRC Centre for Drug Safety Sciences, £3.7m, Director **BK Park**, Deputy Director **M Pirmohamed**

2006-2009. **The Wellcome Trust.** The Pharmacology of Nevirapine in Malawian Patients: Implications for Dosing and Understanding of Hypersensitivity Reactions, £438,229. (Clinical Training Fellowship for Chaponda, **Pirmohamed** primary supervisor)

2010-2013. **EU FP7 Initial Training Network.** Priorities and Standards in Pharmacogenomic Research: Opportunities for a Safer and More Efficient Pharmacotherapy, €3.2m (£936,049 to Liverpool), PI **M Pirmohamed**

2010-2013. **Serious Adverse Event Consortium.** Development of the International Consortium on Drug Hypersensitivity, £300k, PI **M Pirmohamed**

2010-2016. **MRC** (and Industry partners including GSK, AZ, ICON). **North West England MRC Fellowships in Clinical Pharmacology and Therapeutics**, £3,012,100, Programme Leader **M Pirmohamed**

4. Details of the impact

Research at the University of Liverpool has collectively improved understanding of the genetic basis of drug-induced hypersensitivity and provided “proof of principle” for the clinical use of genetic testing before prescribing drug therapy. UoL research has contributed to changes in the prescribing information for two widely used drugs, carbamazepine and abacavir. The prescribing information has been revised to include information on the genetic predisposing factors to hypersensitivity reactions caused by these two drugs; clinical guidelines have also been changed for abacavir to reflect the need for genotyping prior to drug administration. The research has impacted on the clinical care and lives of patients with chronic diseases such as epilepsy, bipolar

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disorder, neuropathic pain and AIDS. Therapy has been optimised by individualising drug prescription to a patient based on key characteristics such as genetic factors. This reduces the risk of severe and potentially fatal ADRs.

Abacavir hypersensitivity

The study showed that it would be cost-effective to undertake pre-treatment screening for *HLA-B*57:01* to predict susceptibility to abacavir hypersensitivity [2]. This has led to the following impacts.

- Clinical guidelines from societies, e.g. the British HIV Association, were changed in 2008 to recommend testing for *HLA-B*57:01* before the use of abacavir [7]. This is now well established in NHS practice.
- The drug labels (i.e. prescribing information) were changed in the US, EU and Australia after 2008 to recommend the use of *HLA-B*57:01* genotyping prior to the use of abacavir [8-10].
- The evidence from the UoL study was used by the NHS to implement the use of the *HLA-B*57:01* testing in HIV clinics from 2006. This has led to a marked reduction of the incidence of abacavir hypersensitivity (from 7.8% to 2% [11]). It is now rare to see any cases of abacavir hypersensitivity in clinical practice to the benefit of patients – this has been demonstrated in a publication from the Chelsea and Westminster HIV clinic which showed that the incidence of hypersensitivity had gone down from 7.8% to 2% [11]
- The number of *HLA-B*57:01* genetic tests undertaken in the NHS rose sharply after 2006, and at the same time the use of abacavir also increased (see figure), and continues to the present day.

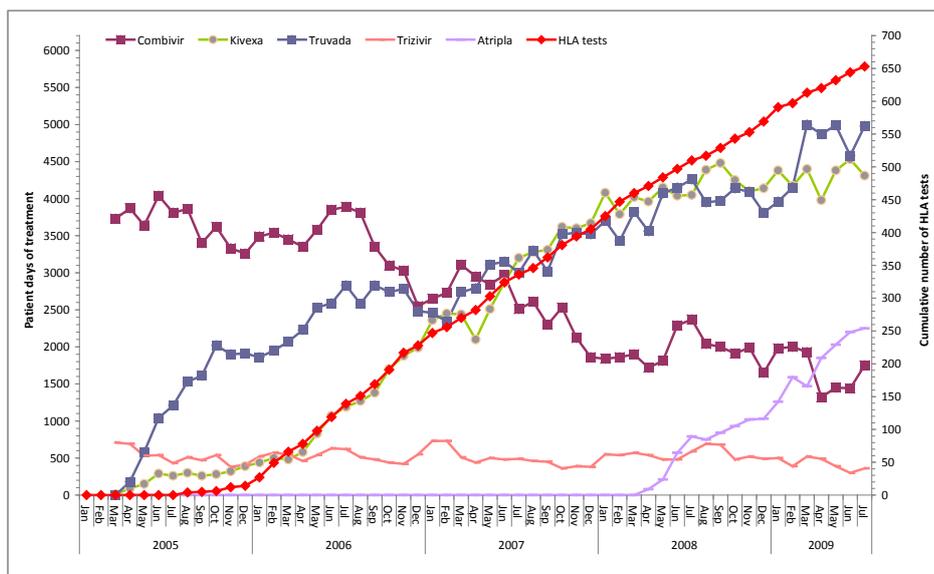


Figure: The increase in HLA testing and at the same time, the rise in the use of abacavir (kivexa)

- Most of the *HLA-B*57:01* testing was provided by Delphic Diagnostics, a University of Liverpool spin-out company (co-founders were Prof Khoo and Back, Dept of Pharmacology, UoL). Delphic was

bought out by Lab21 in 2009. Total number of tests in 2007-08 and 2008-09 were 3,493 (revenue £186,850) and 1,908 (£100,630) respectively.

The importance of this work is confirmed by a case study by The Academy of Medical Sciences in 2012 [12]. Pre-prescription genotyping for *HLA-B*57:01* is now used in most countries and has also been shown to improve clinical outcomes (i.e. reduce hypersensitivity) in Australia and France, and has been shown to be cost-effective in several countries including the US and Germany.

Carbamazepine hypersensitivity

UoL research showed susceptibility to carbamazepine hypersensitivity reactions in Caucasian patients was localised to the MHC, but that the risk factor in Caucasians was distinct to that demonstrated in Chinese patients [3]. Thus, in Caucasians, *HLA-B*1502*, is not a risk factor for SJS/TEN and for hypersensitivity syndrome, two distinct phenotypes associated with carbamazepine treatment. This publication was utilised by the FDA, who in December 2007, recommended that patients of Asian ancestry, but not Caucasians, should be tested for *HLA-B*1502* prior to the start of carbamazepine therapy [13]. The drug label was also changed in the

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EU in 2008, again recommending the use of testing in Asian patients, but not in Caucasians [14].

The continuing work of UoL in this area has recently identified *HLA-A*31:01* as a genetic risk factor for carbamazepine-induced hypersensitivity reactions in Caucasians [5]. The prescribing information for carbamazepine has been changed in Japan, in the EU and in the US since 2011 making prescribers aware of the association between this allele and carbamazepine hypersensitivity in Caucasians [15].

In 2010, the UoL became the global co-ordinating centre for the International Consortium on Drug Hypersensitivity (ITCH), sponsored by the International Serious Adverse Events Consortium (iSAEC) (<http://www.saeconsortium.org/>). We have now recruited 1500 patients with hypersensitivity reactions from 12 international centres, and 50 UK centres.

In 2013, we were awarded an i4i grant from the NIHR in collaboration with MC Diagnostics to develop a HLA-testing biomarker panel which can simultaneously test for multiple HLA alleles at a low cost (<£20) with turnaround time of <48h.

5. Sources to corroborate the impact

Each source listed below provides evidence for the corresponding numbered claim made in section 4 (details of the impact).

Abacavir

7. BHIVA prescribing guidelines for antiretrovirals (2008)
<http://www.liv.ac.uk/hiv/BHIVATreatmentGuidelines2008.pdf>
8. FDA abacavir warning on abacavir hypersensitivity and HLA testing (2008 onwards)
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm094302.htm>
9. EMEA warning for products containing abacavir (2008 onwards)
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000581/human_med_000878.jsp&murl=menus/medicines/medicines.jsp&jsenabled=true
10. WHO Collaborating Centre for International Drug Monitoring, Uppsala Sweden, newsletter (2008) <http://www.who.int/medicines/publications/newsletter/2008news3.pdf>
11. WATERS LJ, MANDALIA S, GAZZARD B, NELSON M. (2007). Prospective HLA-B*5701 screening and abacavir hypersensitivity: a single centre experience. *AIDS*. 21:2533-4 [academic article demonstrating how screening for abacavir reduces the occurrence of abacavir hypersensitivity. Although demonstrated in 2007, the impact of the testing to prevent hypersensitivity continues to the present day].
12. Case study on abacavir hypersensitivity and HLA-B*57:01 testing (including mention of Delphic) in the Academy of Medical Science report on stratified medicine.
http://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&frm=1&source=web&cd=8&ved=0CFgQFjAH&url=http%3A%2F%2Fwww.acmedsci.ac.uk%2Fdownload.php%3Ffile%3D%2Fimages%2Fproject%2FCasestud.pdf&ei=Q-1NUs3UFeah0QW9oIGgAw&usq=AFQjCNHAI0ubLPdOdLJfNGSfQQNLCwgzA&sig2=s0w_g6KKm-hmyiTmeOiFw (see case study 2)

Carbamazepine

13. FDA carbamazepine warning instructing prescribers to test for HLA-B*15:02 in certain ethnic groups but not in Caucasians (December 2007) (citing [3])
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124718.htm>
14. MHRA carbamazepine warning article *Drug Safety Update April 2008; Vol 1, Issue 9: 5*:
<http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON084888>
15. Summary of product characteristic (drug label) for carbamazepine with the warnings about HLA-A*31:01 and risk of carbamazepine hypersensitivity in Caucasians.
<http://www.medicines.org.uk/emc/medicine/24201/SPC/Tegretol+Prolonged+Release+200mg+and+400mg+Tablets+%28formerly+Tegretol+retard%29/>