

Two papers on carbamazepine-induced hypersensitivity and its relationship to HLA status

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TITLE Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan

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TITLE HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans

AUTHORS McCormack M, Alfirovic A, Bourgeois S et al.

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SUMMARY

In 1995 a report in the *New England Journal of Medicine* on medication use and risk of Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) identified carbamazepine as a drug with a higher excess risk than most other drugs known to be associated with this severe muco-cutaneous drug reaction.³ Since then, pharmacogenomics (the study of the role of inherited and acquired genetic variation in drug response) has emerged as a new discipline, which is increasingly impacting on routine clinical practice.⁴ Perhaps the best known example of pharmacogenomics is variable thiopurine methyl transferase (TPMT) activity and the effect it has on azathioprine metabolism. Indeed, it is now the norm in the UK to measure TPMT activity before prescribing azathioprine in order to detect patients at risk of toxicity from conventional doses of this widely used drug. More recently, clinically relevant pharmacogenomic features have been identified for warfarin⁵ and clopidogrel.⁶

These two papers from the 24 March 2011 issue of the *New England Journal of Medicine* concern the same topic: pharmacogenomics of human leukocyte antigen (HLA)-related susceptibility to hypersensitivity reactions to carbamazepine. Two teams of researchers have used genome-wide association studies to identify HLA alleles that predict susceptibility to carbamazepine-induced SJS/TEN. In Taiwan, previous research established HLA-B*1502 as an important susceptibility marker for carbamazepine-induced Stevens Johnson syndrome.⁷ This led to a prospective study aimed at assessing HLA-B*1502 prior to carbamazepine prescribing. The result was a dramatic reduction in SJS and TEN, preventing an

estimated 10 cases of this potentially life-threatening complication of carbamazepine. The second study concerns HLA-typing to identify potential susceptibility markers for carbamazepine-induced SJS/TEN in European populations. McCormack et al reported HLA-A*3101 as a susceptibility marker for carbamazepine-induced hypersensitivity reactions in subjects of Northern European ancestry.

OPINION

These two studies are important because they represent the most important component of biomedical research: the translation of research into patient benefit. In a relatively short period of time the Taiwanese group have made the leap from careful study of a serious clinical problem to the introduction of a simple test which they have proved can save lives. Their research started by focusing on a clinical problem that was more common in their local population than elsewhere in the world. They subsequently identified HLA-B*1502 to be strongly associated with risk of developing SJS induced by carbamazepine. They then applied this knowledge to the local population, saving an estimated 10 cases of this severe complication of carbamazepine therapy.

McCormack et al are on a similar journey: the identification of HLA-A*3101 as a susceptibility marker for carbamazepine-induced hypersensitivity reactions in Europeans raises the prospect of using this knowledge prospectively, as in Taiwan, to reduce the risk of this life-threatening drug reaction in this population.

How should this research be used to improve patient safety? Among persons of Han Chinese descent,

carbamazepine-induced SJS/TEN almost never occurs in non-carriers of the HLA-B*1502 allele.¹ Thus, genotyping to prevent carbamazepine-induced SJS/TEN in routine practice seems to be warranted. All doctors who prescribe carbamazepine should consider testing for HLA-B*1502 when prescribing this drug in patients of Han Chinese descent. It is currently too soon to make a similar recommendation for pre-carbamazepine testing for HLA-A*3101 in Europeans, as clinical research study to confirm the merit of such an approach has yet to be done. However, doctors who prescribe carbamazepine

for large numbers of patients may wish to discuss such testing with their European patients (and with their colleagues in the relevant service laboratory). Additionally, all prescribers should be made aware of the pharmacogenomic implications of this research by appropriate alerts in the British National Formulary, Monthly Index of Medical Specialties (MIMS) and the carbamazepine drug data sheet.

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