*Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol13Issue2abst007P.pdf*

**The Role of HMGB1 in Drug-Induced Stevens Johnson Syndrome/ Toxic Epidermal Necrolysis**

Stevens Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are serious life threatening severe immune-mediated cutaneous reactions with mortality ranging from 10-30%. The commonest causes are drugs. SJS/TEN is characterised by widespread epidermal detachment predominantly due to keratinocyte apoptosis. The aim of this study was to identify a potential prognostic biomarker and determine its role in the pathogenesis of SJS/TEN.

Previous evidence has shown elevated cytotoxic molecules as potential serum biomarkers. However, to date, no mechanism based biomarker has been validated for diagnostic utility in this field. HMGB1 is a well validated biomarker of cell death and inflammation. This study investigated whether HMGB1 represents a valid, utilisable biomarker for drug-induced SJS/TEN.

Serum samples from nevirapine-treated Malawian HIV patients (27 maculopapular exanthema (MPE), 12 drug rash with eosinophilia and systemic symptoms (DRESS), 12 SJS/TEN cases and 114 matched tolerant controls) were analysed for HMGB1 by ELISA. Furthermore, mass-spectrometric protocols were used to analyse post-translationally modified forms of HMGB1. Additionally, an *in vitro* keratinocyte cell-line (HaCaT) model of cell death was developed to investigate the role of HMGB1 in mechanisms of keratinocyte cell death and SJS/TEN pathogenesis.

Serum elevation of HMGB1 was observed at the time of reaction in a pattern that correlated with disease severity. Interestingly, mass spectrometric data revealed distinct differences in the profile of post-translationally modified acetylated and non-acetylated molecular forms of HMGB1 in patients with MPE and DRESS when compared with SJS/TEN phenotypes. An *in vitro* models of Fas-mediated keratinocyte apoptosis resulted in an increase in secreted HMGB1 levels from cells treated with an apoptotic FasR agonist (NOC-18).

Taken together, our data suggest HMGB1 might play a key role in the pathogenesis of severe blistering cutaneous eruptions and further work using longitudinal sampling is required to determine whether it can serve as a prognostic biomarker of drug-induced SJS/TEN.