Association between HLA-B*5801 and Allopurinol-Induced Cutaneous Adverse Reaction: A Case-control Study

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Background: Allopurinol, a uric acid lowering drug commonly used for gout, has been reported as a cause of severe cutaneous adverse drug reactions (SCAR) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). Previous studies reported that HLA-B*5801 has negative predictive value (NPV) of 100%. Whereas, patients are found with allopurinol induced SCAR with negative HLA-B*5801.

Objective: The aim of this study was to investigate the association between different types of allopurinol-induced cutaneous adverse drug reactions (CADR).

Methods: A retrospective case-control study was conducted. Eighteen patients with allopurinol-CADR and 36 allopurinol-tolerant patients were enrolled. Demographic data, co-morbidity, dose of allopurinol, co-medication, baseline renal function, uric acid, creatinine, Naranjo score, and HLA-B*5801 were collected. Odds ratio, sensitivity, specificity, NPV, and positive predictive value (PPV) were analyzed using SPSS version 22.

Results: Of 18 patients with CADR (1 TEN, 3 SJS, 10 DRESS, 4 maculopapular eruption (MPE), only 12 patients (66.7%) had tested positive for HLA-B*5801. Of these 12 patients tested positive for HLA-B*5801, there were 3 SJS, 8 DRESS, 1 MPE. One patient with TEN and two patients with DRESS had tested negative for HLA-B*5801. Of 36 patients with allopurinol tolerance, only one patient (2.7%) had tested positive for HLA-B*5801. The risk of allopurinol-induced CADR and allopurinol-induced SCAR was significantly greater in patients with HLA-B*5801 when compared with those who did not carry this allele, with an Odds ratio of 70.0 (95% confidence interval (CI) =7.6-642.1, p <0.001) and 69.7 (95% CI=10.3-470.0, p < 0.001), respectively. The sensitivity, specificity, NPV, and PPV of HLA-B5801 for prediction of allopurinol-induced CADR and allopurinol-induced SCAR were 66.6%, 97.2%, 85.4%, 92.3% and 78.6%, 95.0%, 96.7%, 84.6%, respectively.

Conclusion: There are strong associations of allopurinol-induced CADR and SCAR, similar to previous studies. However, NPV is only 85.4%. The findings should be emphasized in patients without HLA-B5801 for the monitoring of allopurinol-induced CADR.

Keywords: HLA-B5801, Allopurinol hypersensitivity, Cutaneous adverse drug reaction, Severe cutaneous adverse reaction, SJS, TEN, DRESS