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# Evaluation of Therapeutic Drug Monitoring and Genotyping Services for the Optimisation of Thiopurine Therapy in Asian IBD Patients

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**Aims**: Thiopurine immunomodulators undergo complex metabolism which leads to the formation of active and potentially myelotoxic metabolite 6-thioguanine (6-TGN) and potentially hepatotoxic metabolite 6-methylmercaptopurine (6-MMPN). Therapeutic drug monitoring (TDM) of these metabolites has been recommended to improve safety and efficacy, with proposed therapeutic thresholds of 235-450 and <5,700pmol/8x108 erythrocytes, respectively. Variations in the TPMT and NUDT15 genes have also been associated with higher risks of thiopurine-induced myelotoxicity. This study sought to evaluate the clinical utility of TDM and genotyping services in optimising thiopurine therapy in Asian IBD patients.

**Methodology**: IBD patients who have been on stable thiopurine doses for at least four weeks were evaluated (N=139). Data on disease and treatment characteristics, efficacy and toxicity outcomes were prospectively collected. Intra-cellular 6-TGN and 6-MMPN concentrations were quantified using a validated LC-MS/MS assay. Variants in TPMT and NUDT15 were genotyped using a validated Pyrosequencing method. Statistical analyses were performed on SPSS v14.0.

**Result**: High 6-TGN levels (>450pmol/8x108 erythrocytes) was significantly associated with thiopurine-induced leukopenia [OR: 3.5, CI: 1.1–10.7; P=0.0253]. Significant association was also observed between 6-MMPN concentration above 5,700 pmol/8x108 with thiopurine-induced hepatotoxicity [OR: 25.3, CI: 2.6–246.4; P=0.0168]. TPMT variants were of minor relevance given their low frequencies (2.3%) in Asian IBD patients. However, variants in the NUDT15 gene, particularly c.415C>T (rs116855232), was significantly predictive of thiopurine-induced leukopenia, conferring a 22.9-fold higher risk in patients carrying the variant T allele [OR: 22.9, CI: 5.2-101.4; P=3.71 x 10-5]. Nadir WBC and ANC counts within 4 weeks, 8 weeks, 12 weeks and 6 months of thiopurine initiation were also significantly lower in patients carrying the T allele at the c.415C>T locus (overall P<0.05).

**Conclusion**: These findings highlight the critical roles of TDM of thiopurine metabolites and genotyping of NUDT15 variants in optimising thiopurine therapy in IBD patients, particularly those at risks of myelotoxicity and hepatotoxicity, as well as in guiding thiopurine dose adjustments.