Thiopurine methyltransferase activity and adverse effects of azathioprine in at risk paediatric inflammatory bowel disease patients.

Introduction. Azathioprine is widely used for maintenance of steroid free remission in paediatric inflammatory bowel disease (pIBD). European consensus guidelines recommend testing for thiopurine methyltransferase (TPMT) activity prior to treatment to identify those at risk of early profound myelosuppression. [1,2] We aimed to determine the clinical impact of assessing TPMT activity on the incidence of adverse drug reactions (ADRs), including myelosuppression, in a large cohort of children from a tertiary level children's hospital.

Methods. Patients were identified through a department database, and cross referenced with active prescriptions for azathioprine. These data were then extracted from both paper and electronic health records. Patients whom never received azathioprine and/or had transitioned to adult care services were excluded.

Results. 108 patients were identified, with diagnoses of Crohn's Disease (n=79, 52 male), Ulcerative Colitis (n=24, 9 male) and IBD Unclassified (n=5, 3 male). Mean age at diagnosis: 10.2 years (range 2.5 – 16). Mean age at time of audit here??

For 85 (79%) patients azathioprine was used as primary maintenance therapy post induction of remission with either steroids or exclusive enteral nutrition. For the remaining 23 (21%) patients azathioprine was used as add-on therapy, most commonly following mesalazine therapy.

One hundred (93%) patients had TPMT activity measured. The majority of these (70%) had normal levels (reference range 68-150 mU/L). Twenty four (22%) patients had low levels (reference range 20-67 mU/L), and none were deficient (level <20 mU/L). One patient with a low TPMT level was formally genotyped and found to be heterozygous for TPMT normal/mutant allele.

Across the population, ADRs were recorded in 23 (21%) patients (Table 1), requiring cessation of therapy in 16/23 (70%). Chi-squared analysis did not reveal any significant difference in the rates of ADRs between the two groups at the 5% significance level.

Table 1. Adverse drug reactions reported in pIBD patients with normal and low TPMT activity

	ADR reported	No ADR reported
Normal TPMT	20	56
Low TPMT	3	21

Conclusions. pIBD patients with intermediate or low TPMT activity are at risk of azathioprine toxicity. However, through identification of TPMT activity we have been able to reduce ADRs in at risk pIBD patients to that of the wild type population.

References

[1] Ruemmele FM, Veres G, Kolho KL, et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. *J Crohns Colitis*. 2014;8(10):1179-1207.

[2] Turner D, Ruemmele FM, Orlanski-Meyer E, et al. Management of Paediatric Ulcerative Colitis, Part 1: Ambulatory Care-An Evidence-based Guideline From European Crohn's and Colitis Organization and European Society of Paediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2018;67(2):257-291.