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AZATHIOPRINE METABOLITES IN AUTOIMMUNE HEPATITIS:RELATIONSHIP WITH THERAPEUTIC EFFICACY

doi:10.1136/gut.2011.239301.482

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Introduction Long term azathioprine (AZA, 2 mg/kg/day) is used to maintain remission in Autoimmune Hepatitis (AIH). However 10–20% of patients are unresponsive to AZA. AZA is a pro-drug and formation of the active metabolite (thioguanine nucleotides-TGNs) varies between individuals. Competing with TGN formation is drug methylation, catalysed by the polymorphic enzyme thiopurine methyltransferase (TPMT), leading to formation of methyl mercaptopurine metabolites (MeMPs). In Inflammatory Bowel Disease (IBD), clinical response is associated with TGN concentrations of above 230–260 pmol/8×10^8 RBCs.[1] The study aim was to assess the relationship between TPMT activity, metabolite levels (TGN and MeMPs) and therapeutic response in AIH.

Methods The authors recruited 68 patients with AIH who had achieved biochemical remission (normalisation of ALT) and were taking maintenance AZA. Erythrocyte TGN, MeMPs and TPMT were measured on serial blood samples (median (range) 3 (1–7) per patient), at a constant AZA dose. Average metabolite concentration for each patient were analysed. Patients were divided into group 1: patients in remission on AZA monotherapy (n=49) and group 2, patients requiring prednisolone also (n=19, dose 5 (2.5–10 mg/day).

Results TGN concentration was (median (range) 207 (57–839) pmol/8×10^8 RBCs at a median dose 1.83 mg/kg/day. AZA dose (mg/kg/day) correlated positively with MeMPs concentration (r=0.414, p=0.000) but not with TGN (r=0.002, p=0.998). Between the two groups (see table 1), there was no difference in TGN or MeMPs concentrations, or in TPMT activity. Serum ALT was lower in group 1 (median difference 12, 95% CI 4 to 22). Serum ALT was negatively correlated with TGN concentration

Table 1 PTH-081

	Group 1: azathioprine n=49 median (range)	Group 2: AZA+prednisolone n=19 median (range)	p Value
Age at diagnosis	50 (19–89)	61 (19–81)	0.424
AZA dose (mg/kg/day)	1.8 (0.7–2.6)	1.9 (0.3–2.7)	0.316
TGN pmol/8×10^8RBC	208 (57–400)	198 (82–839)	0.581
MeMPs pmol/8×10^8RBC	1123 (0–23 798)	779 (0–20 044)	0.409
TPMT activity (U/ml RBC)	11.7 (5.8–15)	12.1 (6–17)	0.429
ALT (IU/l)	20 (10–66)	32 (12–106)	0.003

(r=−0.235, p=0.06) and positively correlated with TPMT activity (r=0.243, p=0.05), both of borderline significance.

Conclusion TGN concentrations were lower in our patients with AIH, than the therapeutic range for IBD. The authors were unable to identify a threshold associated with an adequate therapeutic response. However, lower TPMT activity and higher TGN concentration, tended to correlate with lower serum ALT. While further studies are needed, these results are consistent with a role for AZA metabolite formation in influencing the efficacy of AZA maintenance therapy in AIH.

Competing interests None.

Keywords autoimmune hepatitis, azathioprine.

REFERENCE

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