

INFLUENCE OF THIOPURINE METHYLTRANSFERASE GENOTYPE AND PHENOTYPE ON ADVERSE EVENTS AND EFFICACY OF AZATHIOPRINE IN RHEUMATOLOGIC AND GASTROENTEROLOGIC PATIENTS

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Introduction. Severe adverse events (AEs) and therapeutic failure are serious problems in the management of azathioprine (AZA) therapy in patients with chronic inflammatory diseases. AZA is metabolized into inactive derivatives by thiopurine methyltransferase (TPMT), the enzymatic activity of which is affected by four gene single nucleotide polymorphisms (SNPs). In this study the influence of TPMT genotype and phenotype on AEs and efficacy were evaluated in a cohort of patients with chronic inflammatory diseases under treatment with AZA. **Methods.** One hundred and four patients (M=32, F=72, median age 40 years, range 17-76 years) affected by Crohn disease (n=15), ulcerative colitis (n=12), systemic connectivities (n=35), vasculitis (n=28) and other immune diseases (n=14) were analysed for TPMT *2,*3A,*3B,*3C SNPs by PCR (restriction fragment length polymorphism or allele-specific methods) and TPMT erythrocyte activity (HPLC assay of 6-thioguanine conversion into 6-methyl-thioguanine, 6MTG). **Results.** Single or multiple AEs occurred in 40 patients (38.5%): leukopenia (10.6%), serious infections (5.8%), liver dysfunction (13.5%), pancreatitis (2.9%), digestive (8.7%) and systemic symptoms (7.7%). Median time to AE onset was 7 months (range 0.5-80). TPMT polymorphisms were detected in 4 patients: 3 heterozygous for TPMT*3A (2.9%) and 1 homozygous *3C/*3C (0.9%). Among them, 3 patients developed AEs. AZA was effective in 89 (n=87 WT, n=2 *1/*3A) and ineffective in 4 patients (n=2 WT, n=1 *1/*3A, n=1 *3C/*3C), the WT genotype being predictive of treatment success (RR 1.74, CI 0.65-4.65, p<0.04). Median TPMT activity, analysed in a subgroup of 27 patients (n=26 WT, n=1 *1/*3A) was 54.2 nmol 6MTG/gHb/h (range 32.4-106.8). According to a validated cut off (46 nmol 6MTG/gHb/h), a low enzymatic activity was detected in 3 WT and 1 heterozygous patients. Values of TPMT activity in the remaining WT subjects (n=23) fell in the normal range. Among these patients, 9/23 subjects developed AEs and 18/23 subjects experienced a good control of disease activity. **Conclusions.** Detection of TPMT polymorphisms may predict the occurrence of AEs in AZA-treated patients. The presence of WT genotype seems a good predictor of AZA effectiveness, but it does not exclude the risk of AEs. Assessment of TPMT phenotype suggests that a favourable disease control can be expected in patients with a normal TPMT enzymatic activity. Overall, the evaluation of both TPMT genotype and phenotype may support an accurate clinical management of patients under chronic therapy with AZA.