ADVERSE EFFECTS OF AZATHIOPRINE IN PEDIATRIC PATIENTS WITH INFLAMMATORY BOWEL DISEASE AND MULTILOCUS GENOTYPES OF ENZYMES INVOLVED IN THE METABOLISM OF THIOPURINES

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Introduction: Azathioprine is widely used as an immunosuppressive agent in inflammatory bowel disease (IBD); its efficacy in maintaining remission in IBD is largely accepted but adverse drug reactions to this agent occur in 15-38% of patients and often require the withdrawal of therapy. Genetic polymorphisms of enzymes involved in azathioprine metabolism influence the therapeutic efficacy and toxicity of this drug. It has been shown that patients homozygous for thiopurine-S-methyl-transferase (TPMT) mutations have an increased risk of bone marrow toxicity during treatment with azathioprine, but the most frequent forms of adverse effects cannot be related to a mutated TPMT genotype. Even a polymorphism in the gene encoding for inosine-triphosphate-pyrophosphatase (ITPA) enzyme was shown to be associated with azathioprine adverse events. Among other enzymes that might influence azathioprine metabolism and toxicity glutathione-S-transferases (GST) seem likely candidates since azathioprine is converted to 6-mercaptopurine mainly through a reaction with glutathione (GSH) and recent studies have shown that GST might be involved in this transformation.
Aim: To evaluate retrospectively the association between the genetic polymorphisms of TPMT, ITPA, GST-M1, GST-P1 and GST-T1 and the occurrence of adverse effects in IBD patients treated with azathioprine.
Patients and Methods: 70 pediatric IBD patients (median age 16.2 years, 41 with Crohn's disease and 29 with ulcerative colitis) treated with azathioprine were enrolled and the incidence of adverse effects was retrospectively determined. Genotyping of TPMT, ITPA, GST-M1, GST-T1 and GST-P1 genes was performed by PCR assays.
Results: Fifteen patients (21.4 %) developed azathioprine related adverse effects. There were a significant under-representation (O.R. 0.18, $p<0.05$) of the GST-M1 null and a significant over-representation (O.R. 58.1, $p<0.01$) of ITPA94CA genotype in patients developing adverse effects. The multi-locus genotype ITPA/GST-M1 was significantly associated ($p<0.001$) with the development of azathioprine adverse events, allowing to divide patients in three groups of risk: low probability (genotype ITPA94CC/GST-M1 null, O.R. 1, 39 patients), intermediate probability (genotype ITPA94CC/GST-M1 normal, O.R. 8, 26 patients) and high probability (genotype ITPA94CA/GST-M1 null or normal, O.R. 165, 5 patients).
Conclusion: subjects with an ITPA94CA genotype or with a wild-type GST-M1 genotype have an increased probability of adverse effects during treatment of IBD with azathioprine.