

EVIDENCE OF AN INCREASE OF THE ACTIVE METABOLITES OF THIOPURINES INDUCED BY AMINOSALICYLATES IN INFLAMMATORY BOWEL DISEASE

Marino S.^{1,2}, Stocco G.^{1,2}, Pozzi E.³, Martellosi S.², Lionetti P.³, Malusà N.⁴, Decorti G.^{1,2}
Bartoli F.¹, Ventura A.²

¹ Department of Biomedical Sciences, University of Trieste

² Department of Paediatrics, I.R.C.C.S. Burlo Garofolo Trieste

³ Research Children's Hospital 'Meyer', Florence

⁴ Department of Prevention, Azienda Sanitaria 1, Trieste

Thiopurine antimetabolites, 6-mercaptopurine and its prodrug azathioprine, and aminosaliclates, like mesalamine, are often administered in combination in inflammatory bowel disease (IBD), particularly to maintain remission in patients with refractory disease. Aminosaliclates cause an increase in the concentration of the active 6-thioguanine nucleotide metabolite (6TGN) of thiopurines, through an inhibition of their metabolism. The aim of this study was to measure the concentration of thiopurine metabolites after mesalamine interruption and to evaluate the role of genetic polymorphisms of enzymes involved in drug metabolism on this phenomenon. A number of genetic polymorphisms can influence the therapeutic efficacy and toxicity of AZA. 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 and that polymorphism in the gene encoding the inosine triphosphate pyrophosphatase (ITPA) enzyme also predicts azathioprine toxicity in particular flu-like symptoms, rash and pancreatitis. Other enzymes that might influence azathioprine metabolism and toxicity are the glutathione-S-transferases (GST); azathioprine is converted to 6-mercaptopurine mainly through a reaction with glutathione (GSH) and, although this reaction is considered to be a non-enzymatic conversion, some studies have shown that GST might be involved. Moreover, the cytotoxic effects of azathioprine have been related to oxidative stress and GSH depletion. N-acetyltransferases are involved in the metabolism of aminosaliclates and these enzymes also exhibit a number of genetic polymorphisms.

Concentrations of 6TGN and methymercaptopurine (MMP) metabolites of thiopurines were measured by HPLC in 13 patients with IBD treated with a thiopurine and mesalamine. Blood samples were collected one month before and one month after the interruption of mesalamine. DNA was extracted and genotyping of GST-M, GST-T, ITPA, NAT2 and TPMT genes was performed using PCR assays. The median 6TGN concentrations before and after mesalamine interruption were 288 U (range 210-841) and 218 U (range 101-405) respectively, displaying a significant reduction ($p < 0.05$); the selected genotypes had no effect on this phenomenon; however, the number of patients enrolled so far is small. Mesalamine and thiopurines association could lead to higher incidence of adverse events but hypothetically even to an improved response to therapy, depending on the entity of the increase of 6TGN concentration; studies on larger patient's populations are in progress to assess the role of genetic factors on the clinical effects of this drug combination.