Netherlands
The Journal of Medicine

LETTER TO THE EDITOR

High TPMT activity as a risk factor for severe myelosuppression during thiopurine therapy

M.L. Seinen[1]*, A.A. van Bodegraven[1], A.B.P. van Kuilenburg[2], N.K.H. de Boer[1]

[1]Department of Gastroenterology and Hepatology, VU University Medical Centre, Amsterdam, the Netherlands, [2]Laboratory Genetic Metabolic Diseases, Academic Medical Center, Amsterdam, the Netherlands, *corresponding author: tel.: +31 90)20-4440613, fax: +31 (0)20-4440554, e-mail: ml.seinen@vumc.nl

Dear Editor,

The methylating enzyme thiopurine S-methyl transferase (TPMT) plays a crucial role in the metabolism of the thiopurines, azathioprine (AZA) and mercaptopurine (MP). Diminished or absent TPMT activity, leading to elevated levels of the pharmacologically active 6-thioguanine nucleotide (6-TGN), is associated with an increased risk of myelotoxicity. An increased activity of TPMT, which may lead to grossly elevated levels of methylated metabolites (e.g. 6-methylmercaptopurine (6-MMP)), has not been associated with bone marrow suppression.[1] We report a case of an ulcerative colitis (UC) patient who developed a severe pancytopenia due to high TPMT activity.

A male patient, diagnosed with pancolitis ulcerosa, was treated with intravenous cyclosporine, after failure of mesalazine and prednisolone therapy, followed by maintenance treatment with AZA (200 mg). Thiopurine metabolite concentrations were repeatedly low during treatment, without compliance problems. After years, his disease became active again and in attempt to achieve higher 6-TGN levels, AZA was switched to MP (150 mg). After four weeks he developed complaints of gastrointestinal discomfort and general malaise. Laboratory tests showed a severe myelosuppression (leucocyte count 1.0 x 10^9/l and haemoglobin 3.2 mmol/l) and an increased C-reactive protein level of 138 mg/l. Thiopurine metabolites now demonstrated grossly elevated levels of 6-MMP (19,000 mmol/8 x 10^8 RBC) and low 6-TGN concentration (73 mmol/8 x 10^8 RBC). Mercaptopurine therapy was discontinued and he received blood transfusions. Standard viral causes for pancytopenia were ruled out. Endoscopy showed a severely active pancolitis, for which intravenous prednisolone was started and subsequently anti-TNF-α therapy. After ten days, his bone marrow suppression resolved. After discharge, combination therapy with low-dose MP (25 mg) and 100 mg allopurinol was started alongside infliximab. TPMT activity was determined twice, one month after admission (80 nmol/gram protein/hour (reference values: 34-94)) and four months later (121 nmol/g/h). His colitis remained in clinical remission without haematological abnormalities.

In contrast to the well-known association between low TPMT activity and myelosuppression, our case illustrates that high TPMT activity with extremely elevated 6-MMP levels may also induce bone marrow suppression and should be considered a potential risk factor for myelosuppression. 6-Methylmercaptopurine and its ribonucleotides can inhibit the *de novo* purine synthesis leading to a depletion of purines which are essential elements for DNA and RNA formation.[2]

Our case also demonstrates the pitfall of measuring TPMT activity too early after blood transfusions. After one month, the TPMT activity was within normal ranges, while four months later his TPMT activity was found to be elevated. This phenomenon is most likely due to the blood transfusions our patient received during hospitalisation. During the first TPMT measurement donor erythrocytes were still present so the outcome of the test was influenced by the TPMT activity of the donor.

Interestingly, we observed that thiopurine metabolism can change dramatically after switching from AZA to MP with the potential risk of developing severe toxicity, underlining the necessity to strictly monitor patients after modification of thiopurine therapy. Patients displaying grossly elevated 6-MMP and low 6-TGN levels are at risk to develop hepatic transaminitis and may experience therapeutic inefficacy.[3] Combination therapy of allopurinol and low-dose thiopurine can optimise thiopurine therapy in these patients, leading to a steep decrease in 6-MMP levels.[4,5] Our case demonstrates the potential beneficial use of combination therapy as no myelotoxicity reoccurred, indicating that the high 6-MMP levels due to high TPMT activity probably caused the myelosuppression.

REFERENCES

1. van Egmond R, Chin P, Zhang M, et al. High TPMT enzyme activity does not explain drug resistance due to preferential 6-methylmercaptopurine production in patients on thiopurine treatment. Aliment Pharmacol Ther. 2012;35:1181-9.
2. Dervieux T, Blanco JG, Krynetski EY, et al. Differing contribution of thiopurine methyltransferase to mercaptopurine versus thioguanine effects in human leukemic cells. Cancer Res. 2001;61:5810-6.
3. Dubinsky MC, Yang H, Hassard PV, et al. 6-MP metabolite profiles provide a biochemical explanation for 6-MP resistance in patients with inflammatory bowel disease. Gastroenterology. 2002;122:904-15.
4. Ansari A, Elliott T, Baburajan B, et al. Long-term outcome of using allopurinol co-therapy as a strategy for overcoming thiopurine hepatotoxicity in treating inflammatory bowel disease. Aliment Pharmacol Ther. 2008;28:734-41.
5. Hoentjen F, Seinen ML, Hanauer SB, et al. Safety and effectiveness of long-term allopurinol-thiopurine maintenance treatment in inflammatory bowel disease. Inflamm Bowel Dis. 2012;16:1541-9.