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Letter to the Editor

Explaining the unexplained leucopenia in azathioprine treatment

K.H. Katsanos, E.V. Tsianos

TO THE EDITOR:

Sir, leucopenia represents a major adverse event during azathioprine (AZA) therapy in inflammatory bowel disease (IBD). The frequency of leucopenia has been reported up to 10% in AZA-treated IBD patients.[1] Leucopenia is usually reversible after AZA dose reduction but in some patients AZA has to be withdrawn.

Leucopenia occurs when 6-TGN, the active product of AZA, is highly accumulated in tissues, including bone marrow tissue.[2] AZA after its ingestion can follow three competitive metabolic routes: the first is the route to 6-TGN catalyzed by TPMT and the other two routes are S-methylation to methylmercaptopurine (6-MMP pathway) catalyzed also by TPMT or oxidation to thiouric acid via the enzyme xanthine oxidase (XO).[3]

Although some leucopenia cases can be explained by using thiopurine-methyltransferase (TPMT) gene genotyping or TPMT activity measurements, in the majority of cases leucopenia cannot be attributed to usual TPMT variants (TPMT*2, TPMT*3A and TPMT*3C) which account for 80-95% of indermediate or low TPMT enzyme activity cases.[4] In addition, TPMT enzyme activity measurement is not always predictive and is influenced by drug interactions and blood transfusion.[5]

Thus, in patients diagnosed with leucopenia under AZA treatment, after excluding other clinically obvious causes (i.e optimal AZA dosage, hematologic or other comorbidity, viral infection etc) we have to consider other reasons. Some additional cases can be explained by the presence of unfrequent TPMT variants. In the remaining cases we have to exclude increased activity of the TPMT-6-TGN route by either 6-MMP or XO inhibition induced by sulfasalazine, mesalamine, allopurinol, cotrimoxazole and diuretic co-administration.[6]

Finally, it is of interest that other enzymes and their coding genes with their variants which are involved in AZA metabolization steps and alter the 6-TGN flow to target cells have not so far been widely investigated [Table]. These enzymes may prove of importance in explaining many of the unexplained cases of leucopenia in patients with inflammatory bowel disease treated with azathioprine.

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Key words: Azathioprine, leucopenia, inflammatory bowel disease.

[1] *1st Department of Internal Medicine (Hepato-Gastroenterology Unit), University Hospital of Ioannina, Greece*

Author for correspondence:

Dr Epameinondas V. Tsianos, Professor of Internal Medicine, 1st Department of Internal Medicine, Medical School,University of Ioannina, Leoforos Panepistimiou, 451 10 Ioannina, Greece, Tel: 0030-26510-097501, Fax: 00-30-26510-097016, e-mail: etsianos@cc.uoi.gr

Table. Other than TPMT enzymes and their coding genes involved in azathioprine metabolization

ENZYME	NAME	FUNCTION	GENE SNPs	REFERENCES	COMMENTS
XO/XDH	Xanthine oxidase/xanthine dehydrogenase	-purine metabolism: catalyzes oxidation of hypoxanthine to xanthine and subsequently to uric acid -iron uptake & transport -antimicrobial defense	-Not studied -Post-transcriptional studies not available in humans	*-Su Y et al. J Chromatogr 1999;732:459-68* *-Xu P, et al. J Biol Chem 2000;275:5918-26* *-Graziewicz MA,Mutat Res 1999;434:41-52* *-Doyle WA,et al. Eur J Biochem 1996;239:782-5* *-Scazzocchio C,et al. Eur J Bioch 1973;36:428-45*	-multiple molecular forms of the enzyme -allopurinol resistance -use of allopurinol in azathioprine ineffectiveness
HPRT (HGPRT)	Hypoxanthine guanine phosphoribosyl transferase	-6-MP t o 6-TIMP -6-TIMP to PPRP (purine synthesis)	-chemically induced or spontaneous mutants in rats -SNPs in paroxysmal nocturnal hemoglobinuria	*-Horikawa K, et al. Blood 2002;99:24-9* *-Ding GR, et al. Life Sci 2001;68:1041-6* *-Miyakosi J, et al. Mutat Res 1996;349:109-14* *-Armel P, et al. Mutat Res 1988;202;147-53*	-T-cell colonies with mutated gene are resistant to 6-TG -Mutations after exposure to electric or magnetic fields
IMPDH (6-MeTIMP) [Type I and II]	6-methyl thioinosinic monophosphatase	-Catalyzes the rate-limiting step in de novo GTP synthesis	-Asp226Asn -Hamster V79 cell line with altered IMPDH activity is resistant to MMF	*-Bowne SJ, et al. Invest Opthalmol Vis Sci 2006; 47:34-42* *-Hyle J, et al. J Biol Chem 2003;31: 28470-28478* *-Zhou S, et al. Virology 2003;310:333-42* *-Collart F, Mol Cell Biol 1987:7:3328-3331*	-Mutations lead in inherited retinitis pigmentosa -V79 cell line resistant to MMF -Inhibition of IMPDH enzyme by ribavirin or VX-497 results in reduction to intracellular GTP
Rac1	Rac1	Rac1 is a GTPase regulating cellular functions by cycling through GDP and GTP states -GTP/GDP exchange (inactive GDP/active GTP) -signal transduction pathways with Cdc42	Activated forms/SNPs -Rac1b -Rac1 L61D38 -Inactivated forms/SNPs -Rac1 N17	*-Schnelzer A, et al. Oncogene 2000;19:3013-20* *-Matos et al. Exp Cell Res 2005;305:292-299*	-The role of Rac1b remains unknown, probably it is related to signal transduction and cytoskeletal reorganization and polarization -Rac1b stimulates G1/S progression and survival via NFkB

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