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Comment on: Safety of thiopurines in Inflammatory Bowel Diseases: Neither so good, nor so bad

Francisca Carvajal[1], Rodrigo Quera[1], Gonzalo Pizarro[1], Christian von Mühlenbrock[2], Paulina Núñez[1]

Universidad de los Andes, Clínica Universidad de Los Andes, [1]Programa Enfermedad Inflamatoria Intestinal, [2]Neurogastroenterología, Santiago Chile.

ORCID Register:

Francisca Carvajal: 0009-0007-4947-2024

Rodrigo Quera: 0000-0001-5854-0526

Gonzalo Pizarro: 0009-0006-9991-9616

Christian von Mühlenbrock: 0000-0001-5285-1147

Paulina Núñez: 0000-0003-3727-1851

Corresponding author: Rodrigo Quera, Clínica Universidad de los Andes. La Plaza Avenue 2501, Santiago de Chile, e-mail rquera@clinicauandes.cl

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To the Editor:

We have read with interest the article by Frisancho LE et al. titled 'Serious adverse events associated with thiopurine therapy in Inflammatory Bowel Disease: A retrospective cohort study from a tertiary center' (1). In this study, the authors demonstrate that serious adverse reactions to thiopurines are a significant cause of treatment failure, confirming the risks of thiopurine use in both the short and long term, as well as the need for close monitoring

Although we concur with these findings, we believe these drugs remain a viable treatment, especially in countries like Chile, where access to advanced therapies is limited by their high cost. Consequently, thiopurines are part of the therapeutic armamentarium, both as monotherapy and concomitant with anti-TNF, in what is known as combination therapy. The effect of these drugs is mediated by their intracellular conversion into 6-thioguanine nucleotides, which interfere with DNA mismatch repair, leading to apoptosis and the suppression of lymphocyte proliferation. To achieve their pharmacological activity, they undergo metabolism involving multiple enzymes, the primary ones being thiopurine methyltransferase (TPMT) and nudix hydrolase 15 (NUDT15). Among the most serious adverse effects is myelosuppression, which can reach up to 30% in Asian cohorts due to a higher prevalence of TPMT and NUDT15 variants (2). In a study conducted in Chile, von Mühlenbrock et al. (3) analyzed 253 patients with autoimmune pathologies treated with azathioprine, observing that 47 presented NUDT15 polymorphisms. The presence of this polymorphism was three times more frequent TPMT variants. Pre-treatment monitoring for both polymorphisms would allow for determining the feasibility of thiopurine use and the initial dosage of these drugs. However, performing these two tests does not exempt patients from follow-up with hematologic and liver profiles according to the protocols of each center.

In addition to myelosuppression, hepatotoxicity and gastrointestinal intolerance often lead to treatment discontinuation. In a retrospective study of 112 patients who discontinued azathioprine for these reasons, it was observed that after switching to

mercaptopurine, more than 50% were able to tolerate and maintain the therapy (4). Therefore, transitioning to mercaptopurine is a valid strategy before abandoning thiopurines

Therapeutic drug monitoring (TDM) of plasma metabolites serves as a biomarker for safety and efficacy. It has been established that 6-TGN concentrations > 450 pmol constitute a risk factor for myelosuppression, while 6-MMP levels exceeding 5,700 pmol pose a risk of hepatotoxicity. During this process, metabolic alterations may occur, resulting in excessive production of 6-MMP metabolites at the expense of 6-TGN levels, which often remain below the therapeutic range. These patients are at a particular risk of poor treatment response and the development of adverse events. In a study published by Kreijne et al., which included 221 patients, it was observed that combination therapy using low-dose azathioprine (25% to 50% of the standard dose) combined with allopurinol allowed for therapy continuity in the face of treatment failure (5). Allopurinol is a xanthine oxidase inhibitor that redirects thiopurine metabolism toward the formation of 6-TGN.

Finally, a second scenario for thiopurine use is combination therapy with anti-TNF agents, primarily infliximab. This strategy allows for the optimization of the biologic's serum levels and reduces its immunogenicity. In these cases, using doses aimed at achieving 6-TGN levels greater than 125 pmol is sufficient to reach this objective.

In conclusion, although the use of thiopurines carries a risk of adverse events, current knowledge of pharmacogenomics (TPMT and NUDT15) and regular metabolite monitoring allow these risks to be minimized. In regions with limited access to biologics, optimizing thiopurines remains a valid, effective, and safe strategy for IBD management (Figure 1).

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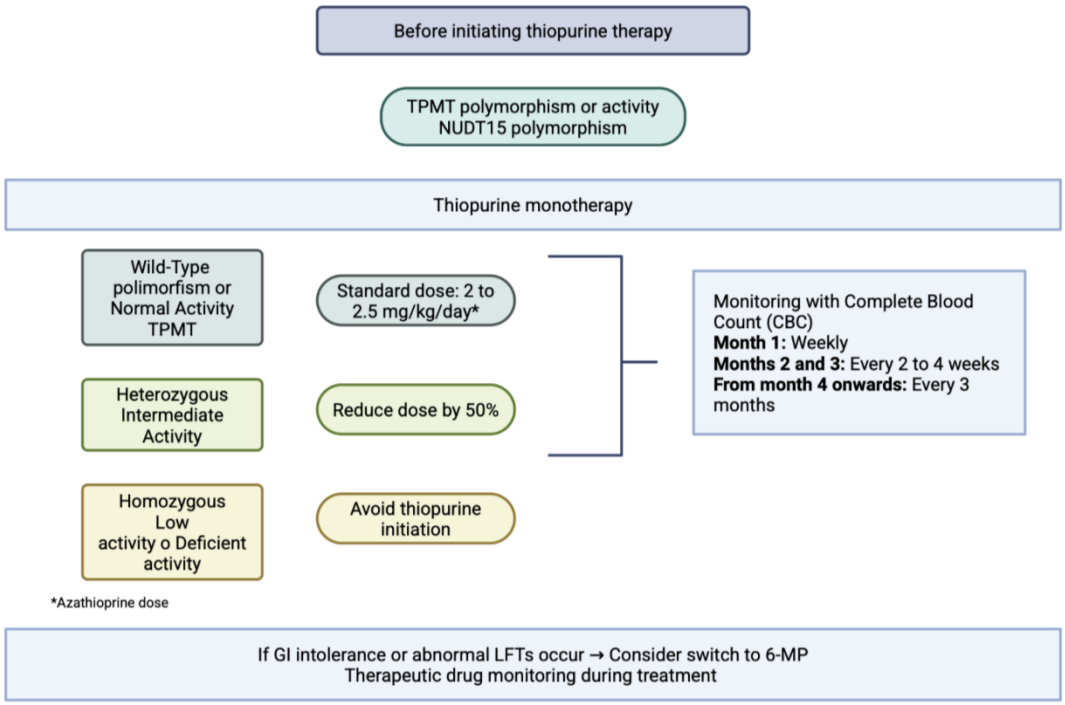
Figure 1. Figure 1. Personalized treatment of thiopurines in patients with inflammatory bowel disease.



GI: Gastrointestinal, LFT: Liver Function Tests

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