

COMPARISON BETWEEN THE MAXIMUM RECOMMENDED DOSE OF AZATHIOPRINE ACCORDING TO THE ENZYMIC ACTIVITY OF THIOPURINE METHYLTRANSFERASE AND 6-THIOGUANINE LEVELS WITH THE MAXIMUM TOLERATED DOSE

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Background and importance


Azathioprine (AZA) is an analog of purines used in the **inflammatory bowel disease (IBD)** treatment.

AZA is transformed by **thiopurine methyltransferase (TPMT)** into its metabolites; **6-methylmercaptopurine (6-MMP)** and **6-thioguanine (6-TGN)**.

Aim and Objectives

- 1 Analyze the prevalence of deficient, low, intermediate, moderate and high **TPMT activity**.
- 2 Evaluate the **MTD** and **6-TGN levels**
- 3 Compare the **maximum recommended dose of AZA** according to **thiopurine methyltransferase (TPMT) activity** and the **maximum tolerated dose (MTD)**

Results

 **131 patients**, 61 (46.6%) women, mean age 34.7 (17.4) years.

When analyzing the dosage according to the TPMT activity and MTD, it was observed that according **MTD**, it was:

- **Higher** in 30 (22.9%) patients.
- **Within the range** in 58 (44.3%) patients.
- **Lower** in 43 (32.8%) patients.

Recommended 6-TGN levels (target 300-550 pmol/0,2 mL) in the patients receiving the MTD were:

- **Higher** in 35 (26.7%) patients.
- **Within the range** in 72 (54.9%) patients.
- **Lower** in 24 (18.3%) patients.

Patients with **6-TGN levels <300 pmol/0,2 ml:**

Median 6-MMP/6-TGN ratio: 1.5.

3 (2.3%) patients had a 6-MMP/6-TGN ratio >4.

Mean serum creatinine: 0.70 (0.35) mg/dl.

Patients' renal function did not influence in the elimination of AZA metabolites.

Conclusion and Relevance

The phenotypes of intermediate and moderate activity of TPMT were the most prevalent. 6-TGN levels were high in some patients increasing the risk of toxicity. In most patients, the recommended dose based on TPMT activity was not coincident with MTD, suggesting the need to detect other genetic factors that might influence AZA metabolism.

Material and methods



Retrospective observational study

- From February 2017 to May 2021



Patients with IBD treated with AZA with a determination of enzymatic activity of TPMT

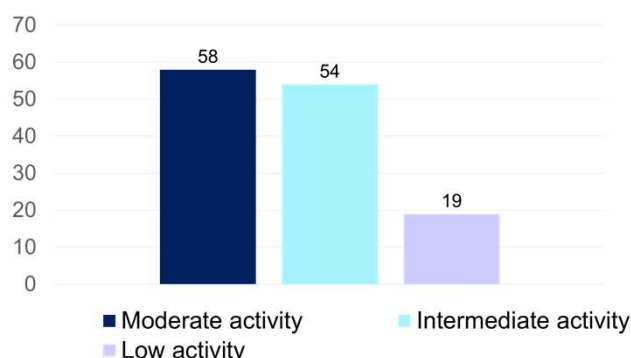
Demographic, clinical data, 6-TGN levels and phenotype [activity of TPMT (IU/ml), determined by HPLC] were collected.

AZA dosage according to TPMT activity

following the Vall d'Hebron Hospital protocol

- **Poor** activity; TPMT <5.0 U/mL RBC: AZA not recommended
- **Low** activity; TPMT 5.1-13.7 UI/ml: AZA 0.5 mg/kg
- **Intermediate** activity; TPMT 13.8-18 UI/ml: AZA 1.5 mg/kg
- **Moderate** activity; TPMT 18.1-26.0 UI/ml: AZA 2.5 mg/kg
- **High** activity; TPMT 26.1-40.0 UI/ml: AZA 3.0 mg/kg.

TPMT phenotype



No patients with poor or high TPMT activity were detected in the study population.

The **AZA posology** was:

- **Decreased** in 31 (23.7%) patients.
- **Withdrawn** in 22 (16.8%) due to adverse events.

Most frequently adverse events detected were:

- Digestive intolerance: 10 (7.6%) patients.
- Leukopenia: 7 (5.3%) patients.
- Lymphopenia: 5 (3.8%) patients.
- Hypertransaminasemia: 4 (3.1%) patients.
- Nausea: 3 (2.3%) patients.