Scientific Research Publishing

Open Journal of Gastroenterology, 2025, 15(8), 427-438
https://www.scirp.org/journal/ojgas
ISSN Online: 2163-9469
ISSN Print: 2163-9450

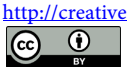
Safety Profile of Azathioprine in Inflammatory Bowel Disease

Rachid El Jim[1,2], Chaimae Maroute[1,2], Maria Lahlali[1,2], Asmae Lamine Séjai[1,2], Hakima Abid[1,2], Nada Lahmidani[1,2], Amine El Mekkaoui[1,2], El Yousfi Mounia[1,2], Dafr-Allah Bennajeh[1,2], Sidi Adil Ibrahimi[1,2], Mohamed El Abkari[1,2]

[1]Hepato-Gastroenterology Department, Hassan II University Medical Center, Fez, Morocco
[2]Faculty of Medicine, Dentistry and Pharmacy, Sidi Mohammed Ben Abdellah University, Fez, Morocco
Email: rachid.eljim@usmba.ac.ma

How to cite this paper: El Jim, R., Maroute, C., Lahlali, M., Séjai, A.L., Abid, H., Lahmidani, N., El Mekkaoui, A., Mounia, E.Y., Bennajeh, D.-A., Ibrahimi, S.A. and El Abkari, M. (2025) Safety Profile of Azathioprine in Inflammatory Bowel Disease. *Open Journal of Gastroenterology*, **15**, 427-438.
https://doi.org/10.4236/ojgas.2025.158039

Received: July 31, 2025
Accepted: August 22, 2025
Published: August 25, 2025



Abstract

Background: Azathioprine (AZA) remains a fundamental pharmacological agent in the treatment of chronic inflammatory bowel disease, particularly in resource-limited settings where biotherapies are less accessible. Despite its therapeutic efficacy, AZA is associated with significant adverse effects, necessitating rigorous monitoring. **Objective:** The main aim of our work is to assess the safety profile of azathioprine in Moroccan IBD patients by analyzing the incidence, nature, and temporality of adverse events in order to optimize its benefit-to-risk ratio in clinical practice. **Methods:** We conducted a retrospective, cross-sectional study over an 11-year period (2013-2024) at the Hassan II University Hospital in Fez, Morocco. A total of 250 patients with IBD treated with AZA were included in the analysis. Data were extracted from medical records and included demographic, clinical, and therapeutic variables. Adverse events were carefully recorded and analyzed according to frequency, patient profile, and time of onset. **Results:** Of the 250 patients included, 62 (24.8%) experienced adverse events requiring temporary or permanent discontinuation of AZA. Hematological toxicity was the most frequent complication, affecting 29 patients (46.8%), followed by digestive intolerance in 15 patients (24.2%), hepatotoxicity in 11 patients (17.7%), pancreatitis in 4 patients (6.5%), and allergic reactions in 3 patients (4.8%). A slightly higher incidence of adverse events was observed in women than in men (56.4% vs. 43.6%). The median time to onset of adverse events varied, with allergic reactions occurring most rapidly (5 days), followed by hematological toxicity (17 days), hepatotoxicity (28 days), and pancreatitis (36 days). A total of 29 patients were re-exposed to AZA, of whom 11 (37.9%) experienced a recurrence of adverse events. Of these, 6 developed hematological toxicity, 3 developed hepatotoxicity, and 2 developed digestive intolerance. In addition, 15 patients who had discontinued AZA were placed on 6-mercaptopurine (6-MP),

10 of whom tolerated this treatment well, while 5 developed new adverse events, mainly allergic reactions and hematological toxicity. **Conclusion:** AZA remains an essential therapeutic option for IBD in Morocco, but its narrow therapeutic index requires rigorous monitoring. Hematological toxicity emerged as the most frequent complication, underlining the need for an individualized approach to treatment. Future research should explore the value of genetic screening and alternative dosing strategies to reduce toxicity while maintaining therapeutic efficacy.

Keywords

Inflammatory Bowel Disease, Crohn's Disease, Ulcerative Colitis, Azathioprine, Adverse Effects, Morocco

1. Introduction

The therapeutic arsenal for chronic IBD is vast and includes a variety of molecules, notably immunosuppressants, among which azathioprine has historically played a key role. Its efficacy has been widely documented through numerous clinical studies and Meta-analyses, making it a mainstay of treatment, particularly between 1980 and 2010 [1]. However, with the advent of biologic therapies and a more accurate assessment of the benefit-risk ratio, the use of immunosuppression as monotherapy has declined, and now concerns only 10% - 20% of IBD patients.

The choice of treatment depends on a number of factors, among which the therapeutic objectives are key to the therapeutic strategy.

Despite the increasing availability of biological agents, immunosuppressants such as azathioprine continue to play an important role, particularly in maintenance therapy. Because of its historic role in the management of IBD and its affordability, azathioprine remains an essential component of modern therapeutic strategies, particularly in settings where access to biological treatments is limited.

Azathioprine is an orally absorbed prodrug, metabolized to 6-mercaptopurine (6-MP), which follows three main metabolic pathways, producing active (6-TGN, effective but myelotoxic) and inactive (6-MMPR, hepatotoxic) metabolites. The activity of thiopurine S-methyltransferase (TPMT), influenced by a genetic polymorphism, determines treatment tolerance and requires dosage adjustment in deficient patients. Another polymorphism, affecting the NUDT15 gene, increases the risk of toxicity and may contraindicate AZA use in certain patients.

Despite its many advantages, AZA is associated with adverse effects ranging from simple gastrointestinal intolerance to severe complications such as pancreatitis, liver failure, and myelosuppression. The recommended dosage of AZA is 2 to 2.5 mg/kg. Its administration is recommended during meals to reduce side effects such as nausea or vomiting, an approach whose efficacy has been confirmed by several clinical studies and Meta-analyses.

In Morocco, available treatments for IBD include aminosalicylates, corticoster-

oids, and biological agents, with the progressive introduction of new molecules on the market. Given the persistent use of AZA, our study aims to assess the prevalence and characteristics of its adverse effects in Moroccan IBD patients, in order to optimize its benefit-to-risk profile in clinical practice.

2. Methods

This is a retrospective, descriptive, cross-sectional study conducted over an 11-year period (2013-2024), including all adult patients followed for IBD, as well as those initially managed in pediatrics before transfer to the gastroenterology department of the University Hospital Center Hassan II in Fez, Morocco. This university hospital covers a large population in the central region of Morocco, estimated at around 4,468,000 inhabitants, or 12.1% of the national population according to the 2024 census.

Patients with incomplete follow-up or other pathologies likely to interfere with the evaluation of adverse effects, such as chronic liver failure unrelated to AZA or underlying hematological pathologies, were excluded from the analysis.

Data were extracted from patient records via hospital registers and "Hosix" software. A standardized form was used to collect demographic, clinical, and therapeutic information. Basic characteristics such as age, sex, type of IBD, treatment regimen, complications, and duration of follow-up were recorded.

The definition of a patient with IBD was based on a combination of clinical signs suggestive of the disease and radiological, endoscopic, and pathological criteria.

Myelotoxicity was defined as leukopenia with a white blood cell count $< 3.0 \times 10^9$/L and/or thrombocytopenia (platelet count $< 100 \times 10^6$/L) resolving after treatment discontinuation or dose reduction. Anemia was defined as a hemoglobin level < 13 g/dL in men and < 12 g/dL in women.

Hepatotoxicity was defined as an increase in serum transaminases (ALAT) greater than twice the upper limit of normal, or an increase in bilirubin, with resolution after treatment discontinuation or dose reduction.

Pancreatitis was defined as upper abdominal pain associated with an elevation of pancreatic lipase levels greater than 3 times the upper limit of normal.

Digestive intolerance was defined as the onset of persistent gastrointestinal symptoms, notably nausea, vomiting, abdominal pain, or diarrhea occurring within the first weeks of azathioprine initiation, in the absence of alternative organic causes, and leading to dose reduction, temporary suspension, or permanent discontinuation of therapy. The symptoms were considered attributable to AZA if they resolved after discontinuation or dose adjustment.

We also evaluated signs of allergic reactions, such as skin rash, fever, or arthralgia, when no infectious or inflammatory cause was identified.

3. Result

A total of 250 individuals were enrolled in the study, having started or continued azathioprine treatment for the management of inflammatory bowel disease between

2013 and 2024. Among this cohort, 62 individuals (24.8%) experienced an adverse event that necessitated the cessation of treatment temporarily or permanently. The mean age of participants at the occurrence of the adverse reaction was 58 years (with an age range of 18 - 67 years). Regarding the distribution of the disease, 64% of the patients were diagnosed with Crohn's disease (CD), whereas 36% were diagnosed with ulcerative colitis (UC).

The various types and frequencies of adverse events are meticulously enumerated in Table 1. Hematological toxicity emerged as the most prevalent adverse event, representing 46.8% of cases (29 patients). Within this subset, 16 were male and 13 were female. Digestive intolerance was documented in 15 individuals (24.2%), comprising 9 females and 6 males. Hepatotoxicity was identified in 11 individuals (17.7%), exhibiting a higher incidence in females (7 females and 4 males). Ultimately, 4 individuals (6.5%) discontinued treatment as a result of pancreatitis, which included 3 females and 1 male. Additionally, 3 patients (4.8%) presented with allergic reactions (3 females).

Overall gender distribution (Table 2) showed a slight predominance of females (56.4%) among patients with adverse reactions. Nevertheless, marked disparities were observed for certain types of reactions. For example, allergic reactions were significantly more frequent in women. However, analysis of the relationship between gender and side effects did not reveal any statistically significant results.

Table 1. Types and frequencies of adverse effects leading to cessation of azathioprine.

Adverse Effect	Number of Patients	Percentage of Total (%)
Hematological Toxicity	29	46.8
Leukopenia	18	
Thrombocytopenia	7	
Anemia	4	
Digestive Intolerance	15	24.2
Hepatotoxicity	11	17.7
Pancreatitis	4	6.5
Allergic Reactions	3	4.8
Total	62	100

Table 2. Gender distribution of adverse effects.

Adverse Effect	**Male Patients**	**Female Patients**	**Total Patients**
Hematological Toxicity	16	13	29
Digestive Intolerance	6	9	15
Hepatotoxicity	4	7	11
Pancreatitis	1	3	4
Allergic Reaction	0	3	3
Total	27	35	62

The median interval between initiation of azathioprine therapy and the onset of an adverse event varied in our cohort, depending on the type of event observed. Allergic reactions occurred earliest, with a median delay of 5 days (extremes: 1 - 9 days), followed by hematological toxicity at 17 days (extremes: 7 - 29 days), elevated liver transaminases and/or bilirubin at 28 days (extremes: 14 - 42 days), and acute pancreatitis at 36 days (extremes: 5 - 76 days). The median duration of adverse events was 13.4 days, with extremes ranging from 1 to 76 days. No deaths related to azathioprine adverse events were reported in our cohort.

These findings are visually summarized in Figure 1.

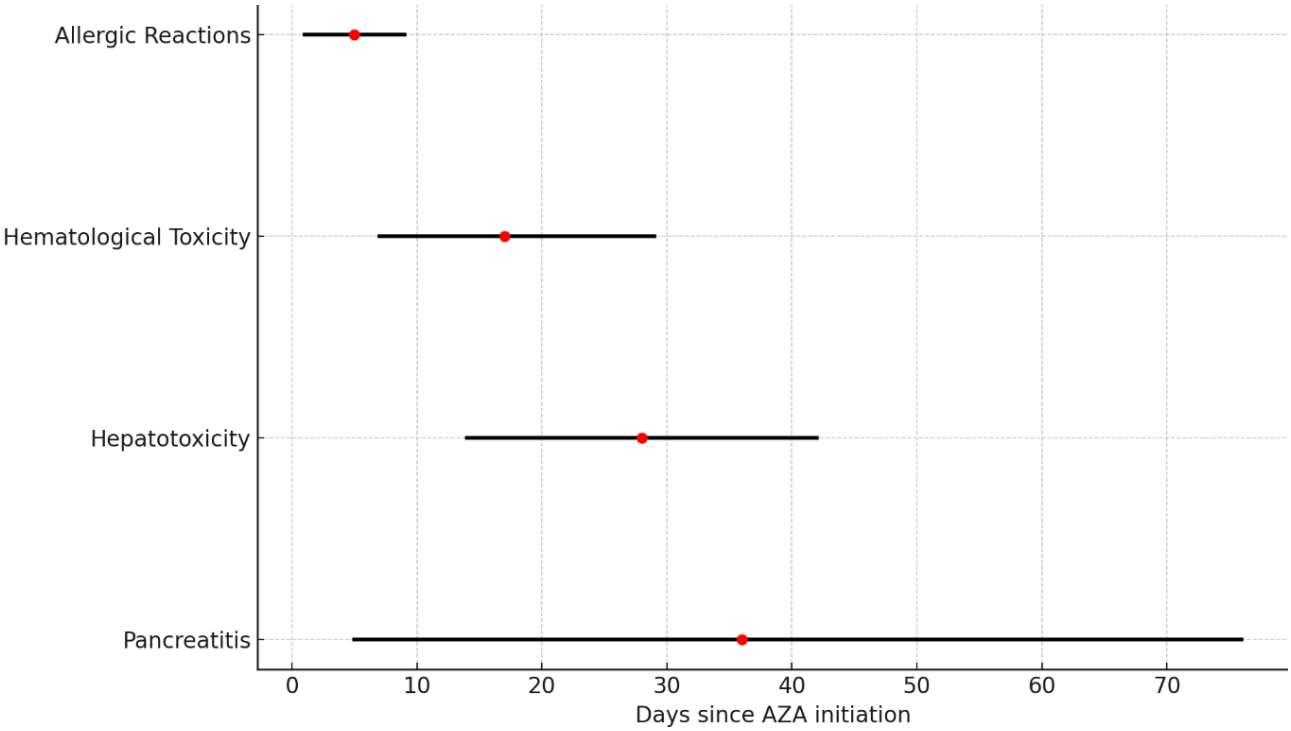


Figure 1. Time to onset of azathioprine adverse events.

A total of 29 patients were subsequently re-exposed to azathioprine, 11 of whom experienced a recurrence of adverse events. The decision to reintroduce AZA was based on the lack of effective therapeutic alternatives, the mild or transient nature of the initial adverse event, and the perceived benefit of maintaining immunosuppressive therapy. The most frequently observed adverse event was hematological toxicity (6 patients), followed by hepatic cytolysis (3 patients) and digestive intolerance with vomiting (2 patients).

In a cohort of 33 patients, azathioprine was discontinued and replaced by 6-mercaptopurine (6-MP) in 15 of them. Of these patients, 15 were re-evaluated: 10 showed good tolerance to 6-MP, while 5 developed adverse effects, mainly allergic reactions and hematological toxicity.

Two patients who developed allergic reactions to azathioprine were switched to 6-mercaptopurine. Initially, both tolerated the new treatment; however, they later

developed similar allergic reactions, leading to discontinuation of 6-MP.

The remaining patients, for whom treatment discontinuation was definitive, underwent either surgery or biotherapy.

4. Discussion

Azathioprine currently occupies an important place in the treatment of chronic inflammatory bowel disease. It is effective in maintaining remission in patients with moderate to severe Crohn's disease and ulcerative colitis, and in preventing immunization against certain biotherapies.

It is a molecule with a narrow therapeutic margin, associated with a risk of toxicity, particularly hematological and hepatic [2], which can sometimes lead to permanent discontinuation of treatment.

The complex metabolic pathways of this molecule are significantly influenced by genetic polymorphisms, resulting in inter-individual variability in treatment response and tolerability.

Comparative analysis of adverse events associated with azathioprine versus placebo showed an odds ratio (OR) of 2.11 (95% CI: 0.92 to 4.84), suggesting a propensity for decreased tolerance to pharmacological intervention when juxtaposed with placebo, though without reaching statistical significance [3].

4.1. Prevalence of Adverse Events

In our unit, the azathioprine monitoring protocol consists of several steps. Before initiating treatment, an initial assessment is performed, including a complete blood count (CBC) and a liver function test (ASAT, ALAT, gamma-GT, bilirubin). After initiation, biological monitoring involves a CBC and liver function test conducted weekly during the first month, then monthly for three months, and finally every three months thereafter.

Clinical monitoring includes the surveillance of digestive intolerance, acute pancreatitis, hypersensitivity reactions, and opportunistic infections, with increased vigilance during the first three months. In the long term, an annual dermatological assessment is performed, along with an annual gynecological follow-up, including a cervical smear for women.

In our cohort consisting of 250 patients, 24.8% encountered adverse events that necessitated the suspension of AZA therapy. This frequency is consistent with prior research indicating adverse event rates between 15% and 43.6% among individuals with IBD undergoing AZA treatment. For example, a systematic review conducted by Loutas *et al.* analyzing the side effects of azathioprine in patients with Crohn's disease reported the presence of side effects in 43.6% of patients, with 23.6% discontinuing therapy due to intolerance [4]. Another Meta-analysis and systematic review has estimated the rate of adverse events associated with this molecule to be around 9% [5] [6].

Polymorphisms in the TPMT gene are recognized to significantly influence the concentrations of thiopurine toxic metabolites, specifically 6-MMP, along with 6-

TGN levels; consequently, these genetic variations are systematically assessed before the initiation of AZA therapy, particularly in Western nations [7]-[11].

Similarly, polymorphisms in the NUDT15 gene have emerged as critical determinants of thiopurine intolerance, particularly in East Asian populations, where the frequency of risk alleles is significantly higher. Several studies have shown that NUDT15 variants are strongly associated with early-onset leukopenia and severe myelosuppression, even in patients with normal TPMT activity [12] [13].

Although the prevalence of NUDT15 polymorphisms in North African or Moroccan populations remains unknown, their potential clinical relevance should not be overlooked. Incorporating NUDT15 genotyping into pre-treatment assessments could be particularly beneficial in cases of early hematologic toxicity or when TPMT testing is inconclusive. Further studies are needed to assess the feasibility and cost-effectiveness of implementing NUDT15 screening in the Moroccan context.

In our unit, the prescription of metabolite assays, in particular thiopurine methyltransferase (TPMT), is rarely carried out prior to prescription due to the difficulty of accessing this biological analysis. Its availability in Morocco is limited due to its high cost. As an alternative, clinicians may consider empirical dose reduction in patients at higher risk of toxicity, such as those with low baseline WBC counts or a history of drug intolerance.

4.2. Types of Adverse Events

Hematological toxicity emerged as the most frequently observed adverse event in our investigation, constituting 46.8% of the cases analyzed. This observation aligns with the prevailing literature that recognizes myelotoxicity as a prevalent side effect associated with azathioprine. Guerra *et al.* documented myelotoxicity in 7% of the patient population studied [14]. Another study, Connell *et al.* reported myelosuppression in 5% of patients [15], with leukopenia occurring in 3.8% and thrombocytopenia in 2% of cases. Similarly, Fousekis *et al.* noted leukopenia in 2.7% of patients [16].

Gastrointestinal intolerance is frequently reported, with incidences ranging from 8.6% to higher percentages in various studies [3] [14]. It was documented in 24.2% of our patient cohort, which is consistent with earlier findings that indicated gastrointestinal adverse effects in 11.4% of instances [4].

Hepatotoxicity occurred in 17.7% of our patients, which is higher than the 11.7% reported by Loutas *et al.* [4] and 5.4% in some cohorts [14]. This is consistent with the extensive body of literature that recognizes hepatotoxicity as a significant concern, albeit occurring less frequently than hematological complications [15].

Pancreatitis was one of the least frequent side effects, affecting 6.5% of our cohort. This slightly higher prevalence compared with previous studies (4.8%) suggests the potential influence of demographic or genetic factors on susceptibility [4].

Allergic reactions were rarely observed, occurring in 4.8% of patients, with a

significant predominance in women. This observation is in line with the literature, which reports a higher incidence of hypersensitivity reactions in female patients.

The notable discrepancy between our results and those reported in previous studies may be attributed to several factors: demographic differences between the study populations, azathioprine administration protocols, criteria used to define hematological toxicity, limited availability of thiopurine methyltransferase (TPMT) screening tests, as well as poor adherence to scheduled follow-up examinations, which may also influence these observed disparities.

4.3. Gender Distribution

The examination of the prevalence of azathioprine-associated adverse reactions in IBD patients, stratified by gender, indicates a slight female predominance, with 56.4% of documented adverse reactions occurring in women. This observation is in line with numerous studies showing gender-related differences in the frequency and characteristics of adverse reactions to IBD treatments. Current literature suggests that women may have a higher incidence of certain adverse reactions due to underlying biological and psychosocial determinants.

Although empirical evidence regarding the gender-specific effects of azathioprine remains limited, much research into therapeutic interventions for IBD suggests that female patients may be more vulnerable to certain adverse drug reactions. For example, it has been documented that women have a higher prevalence of hypersensitivity reactions to anti-TNF agents, which are also used in the therapeutic management of IBD [16]. This phenomenon could also apply to azathioprine, given the similar immunomodulatory mechanisms involved.

Genetic research has highlighted gender-specific genetic correlations in IBD, which may influence pharmacokinetics and therapeutic responses to drugs. For example, gender-dimorphic genetic loci have been identified, which may explain the observed differences in treatment efficacy and adverse effects between men and women [17].

These empirical observations underline the importance of adopting a personalized approach in the management of patients treated with azathioprine, taking into account variations in pharmacological response and gender-specific adverse effects. They also highlight the need for increased monitoring of this pharmacological agent in female patients, particularly with regard to the occurrence of allergic reactions.

Therefore, although the female predominance observed in our study may appear modest, it aligns with existing evidence suggesting that gender may influence both the pharmacodynamics and the immunological response to azathioprine. This underlines the importance of adopting a personalized approach and reinforces the need for increased monitoring of female patients, particularly regarding allergic or hypersensitivity reactions.

4.4. Timing of Adverse Events

The onset of azathioprine-associated adverse events in IBD patients can vary con-

siderably depending on the specific type of side effect. Our findings are consistent with the existing literature, which also reports disparities in the time to onset of different adverse effects. Allergic reactions generally occur rapidly, while other effects, such as hematological toxicity, hepatotoxicity, and pancreatitis, tend to manifest themselves over a longer period. This variability has major clinical implications that practitioners must take into account when monitoring patients on azathioprine.

In our study, allergic reactions had a median time to onset of 5 days, which is in line with the existing scientific literature, suggesting that these reactions may occur early during follow-up [18]. This rapid onset underlines the importance of rigorous monitoring from the outset of patient follow-up. After allergic reactions, hematological toxicity appeared later, with a median delay of 17 days in our study. This result is consistent with literature data indicating that hematological adverse effects, such as leukopenia and anemia, can occur within the first few weeks of initiation of azathioprine therapy [19] [20].

As treatment continues, liver toxicity may become a concern, with a median time to onset of 28 days in our cohort. This finding is corroborated by studies indicating that liver enzyme abnormalities can occur within the first month of follow-up. This underlines the importance of regular liver function tests from the very first weeks of observation [21] [22]. In contrast, pancreatitis occurred later, with a median time to onset of 36 days. This result is in line with previous studies indicating that azathioprine-induced pancreatitis (AIP) generally manifests itself within the first few weeks to a few months of clinical follow-up. Various risk factors, including smoking and concomitant pharmacological treatments, can significantly influence both the time to onset and the prevalence of AIP [23].

Variability in both the onset and intensity of adverse effects associated with azathioprine can be modulated by many factors. Genetic polymorphisms, particularly those affecting thiopurine methyltransferase (TPMT), significantly influence AZA metabolism and may make some patients more vulnerable to early onset or more marked adverse effects [24] [25]. Pharmacological interactions with concomitant treatments, such as aldehyde oxidase inhibitors, may alter azathioprine metabolism, thus influencing both the onset and severity of adverse effects [21]. To reduce these risks, it is essential to implement dosing and monitoring strategies, including TPMT screening and dosage adjustments based on individual metabolic capacity. These measures are crucial for preventing severe toxicities and optimizing patients' clinical outcomes [25].

5. Conclusions

Azathioprine is a fundamental component in the therapeutic management of chronic inflammatory bowel disease, particularly in resource-constrained healthcare environments where access to biologic therapies may be restricted. Our study, conducted over a period of 11 years, highlights a considerable incidence of adverse events associated with AZA, with hematological toxicity appearing as the predominant com-

plication. The variability observed in the onset of side effects, ranging from immediate hypersensitivity reactions to later hepatotoxicity and pancreatitis, underlines the need for personalized patient monitoring strategies.

Although AZA's efficacy is well established, its narrow therapeutic index calls for rigorous monitoring, including blood tests and regular assessment of liver function, particularly during the first few months of treatment. The absence of systematic TPMT screening in our clinical setting could accentuate the variability of toxic risk, reinforcing the need for heightened vigilance and early dose adjustments.

In light of these observations, our study highlights the importance of individualized risk assessment and enhanced monitoring protocols to improve treatment safety. Future research should explore the feasibility of genetic screening and alternative dosing strategies to reduce toxicity while preserving the therapeutic benefits of AZA.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Axelrad, J.E., Roy, A., Lawlor, G., Korelitz, B. and Lichtiger, S. (2016) Thiopurines and Inflammatory Bowel Disease: Current Evidence and a Historical Perspective. *World Journal of Gastroenterology*, **22**, 10103-10117. https://doi.org/10.3748/wjg.v22.i46.10103

[2] Bianchetti, D., Salvador Nunes, L., André, P., Schoepfer, A., Moradpour, D. and Chtioui, H. (2022) Métabolisme et suivi thérapeutique de l'azathioprine en gastroentérologie et hépatologie. *Revue Médicale Suisse*, **18**, 1588-1593. https://doi.org/10.53738/revmed.2022.18.793.1588

[3] Sander, B.Q., Nunes, R.M., Cardoso, P.D., *et al.* (2023) Effects of Azatioprine in Patients with Diagnosis of Intestinal Inflammatory Disease: A Systematic Review. *Acta Scientific Gastrointestinal Disorders*, **6**, 4-10. https://doi.org/10.31080/asgis.2023.06.0553

[4] Loutas, T., Moutou, A. and Theodosopoulou, E. (2016) Side Effects from the Use of Azathioprine in Crohn's Disease: A Systematic Review. *Progress in Health Sciences*, **6**, 1-10. https://doi.org/10.5604/01.3001.0009.5135

[5] Pearson, D.C., May, G.R., Fick, G.H. and Sutherland, L.R. (1995) Azathioprine and 6-Mercaptopurine in Crohn Disease. *Annals of Internal Medicine*, **123**, 132-142. https://doi.org/10.7326/0003-4819-123-2-199507150-00009

[6] Pearson, D.C., May, G.R., Fick, G., and Sutherland, L.R. (2000) Azathioprine for Maintaining Remission of Crohn's Disease. *Cochrane Database of Systematic Reviews*, No 2, CD000067.

[7] Derijks, L.J.J., Gilissen, L.P.L., Hooymans, P.M. and Hommes, D.W. (2006) Review Article: Thiopurines in Inflammatory Bowel Disease. *Alimentary Pharmacology & Therapeutics*, **24**, 715-729. https://doi.org/10.1111/j.1365-2036.2006.02980.x

[8] Cuffari, C., Hunt, S. and Bayless, T. (2001) Utilisation of Erythrocyte 6-Thioguanine Metabolite Levels to Optimise Azathioprine Therapy in Patients with Inflammatory Bowel Disease. *Gut*, **48**, 642-646. https://doi.org/10.1136/gut.48.5.642

[9] Deshpande, A.R. and Abreu, M.T. (2010) Optimizing Therapy with 6-Mercaptopurine and Azathioprine: To Measure or Not to Measure? *Therapeutic Advances in Gastroenterology*, **3**, 275-279. https://doi.org/10.1177/1756283x10376121

[10] Ansari, A., Hassan, C., Duley, J., Marinaki, A., Shobowale-Bakre, E.-M., Seed, P., *et al.* (2002) Thiopurine Methyltransferase Activity and the Use of Azathioprine in Inflammatory Bowel Disease. *Alimentary Pharmacology & Therapeutics*, **16**, 1743-1750. https://doi.org/10.1046/j.1365-2036.2002.01353.x

[11] Dong, X., Zheng, Q., Zhu, M.-M., Tong, J.-L. and Ran, Z.-H. (2010) Thiopurine S-Methyltransferase Polymorphisms and Thiopurine Toxicity in Treatment of Inflammatory Bowel Disease. *World Journal of Gastroenterology*, **16**, 3187-3195. https://doi.org/10.3748/wjg.v16.i25.3187

[12] Moriyama, T., *et al.* (2016) NUDT15 Polymorphisms Alter Thiopurine Metabolism and Hematopoietic Toxicity. *Nature Genetics*, **48**, 367-373.

[13] Yang, S., Hong, M., Baek, J., Choi, H., Zhao, W., Jung, Y., *et al.* (2014) A Common Missense Variant in NUDT15 Confers Susceptibility to Thiopurine-Induced Leukopenia. *Nature Genetics*, **46**, 1017-1020. https://doi.org/10.1038/ng.3060

[14] Guerra, I., Algaba, A., Serrano, Á., Aulló, C., Alcalde, D., de Lucas, M., *et al.* (2014) P504 Effectiveness and Adverse Events of Azathioprine in Inflammatory Bowel Disease: 9-Year Follow-Up Study. *Journal of Crohn's and Colitis*, **8**, S277-S278. https://doi.org/10.1016/s1873-9946(14)60624-3

[15] Connell, W.R., Kamm, M.A., Ritchie, J.K. and Lennard-Jones, J.E. (1993) Bone Marrow Toxicity Caused by Azathioprine in Inflammatory Bowel Disease: 27 Years of Experience. *Gut*, **34**, 1081-1085. https://doi.org/10.1136/gut.34.8.1081

[16] Fousekis, F., Kourtis, G., Saridi, M., Albani, E., Katsanos, K. and Christodoulou, D. (2022) P368 Safety Issues of Azathioprine in Patients with Inflammatory Bowel Disease: Clinical Experience from a Referral Center. *Journal of Crohn's and Colitis*, **16**, i372-i372. https://doi.org/10.1093/ecco-jcc/jjab232.495

[17] Siramolpiwat, S. and Sakonlaya, D. (2017) Clinical and Histologic Features of Azathioprine-Induced Hepatotoxicity. *Scandinavian Journal of Gastroenterology*, **52**, 876-880. https://doi.org/10.1080/00365521.2017.1311936

[18] Zelinkova, Z. (2012) Sex-Dimorphic Adverse Drug Reactions to Immune Suppressive Agents in Inflammatory Bowel Disease. *World Journal of Gastroenterology*, **18**, 6967-6973. https://doi.org/10.3748/wjg.v18.i47.6967

[19] Khrom, M., Li, D., Naito, T., *et al.* (2023) Sex-Dimorphic Analyses Identify Novel and Sex-Specific Genetic Associations in Inflammatory Bowel Disease. *Inflammatory Bowel Disease*, **29**, 1622-1632.

[20] Avallone, E.V., Pica, R., Cassieri, C., Zippi, M., Paoluzi, P. and Vernia, P. (2014) Azathioprine Treatment in Inflammatory Bowel Disease Patients: Type and Time of Onset of Side Effects. *European Review for Medical and Pharmacological Sciences*, **18**, 165-170,

[21] Mishra, K., Pramanik, S., Sandal, R., *et al.* (2021) Safety and Efficacy of Azathioprine in Immune Thrombocytopenia. *American Journal of Blood Research*, **11**, 217-226,

[22] Fuggle, N.R., Bragoli, W., Mahto, A., Glover, M., Martinez, A.E. and Kinsler, V.A. (2015) The Adverse Effect Profile of Oral Azathioprine in Pediatric Atopic Dermatitis, and Recommendations for Monitoring. *Journal of the American Academy of Dermatology*, **72**, 108-114. https://doi.org/10.1016/j.jaad.2014.08.048

[23] Ueda, H., Narumi, K., Asano, S., Saito, Y., Furugen, A. and Kobayashi, M. (2023) Comparative Study on the Occurrence of Adverse Effects in the Concomitant Use of Azathioprine and Aldehyde Oxidase Inhibitors. *Expert Opinion on Drug Safety*, **23**, 89-97. https://doi.org/10.1080/14740338.2023.2295976

[24] van Liere, E.L., Bayoumy, A.B., Mulder, C.J., *et al.* (2021) Azathioprine with Allopu-

rinol Is a Promising First-Line Therapy for Inflammatory Bowel Diseases. *Digestive Diseases and Sciences*, **67**, 4008-4019.

[25] Freitas, M., Lima Capela, T., Macedo Silva, V., Arieira, C., Cúrdia Gonçalves, T., Dias de Castro, F., *et al.* (2022) Finding Predictors of Azathioprine-Induced Pancreatitis in Patients with Inflammatory Bowel Disease. *Pancreas*, **51**, 288-294. https://doi.org/10.1097/mpa.0000000000002012