Safety profile of azathioprine among inflammatory bowel disease patients in Addis Ababa University, College of Medicine and Health Science, School of Medicine, Department of internal medicine, Gastroenterology & Hepatology unit, Addis Ababa. Ethiopia.Two years retrospective study

Thesis

Safety profile of azathioprine among inflammatory bowel disease patients in Addis Ababa University, College of Medicine and Health Science, School of Medicine, Department of internal medicine, Gastroenterology & Hepatology unit, Addis Ababa. Ethiopia. Two year retrospective study

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SUMMARY

Back ground

Azathioprine, is the pro drug of 6-mercaptopurine which is a purine analogue. It inhibits cell growth by directly interfering with nucleic acid synthesis. It has long been a cornerstone in the management of inflammatory bowel disease (IBD), encompassing both Crohn's disease and ulcerative colitis. As with any potent medication, understanding its safety profile is paramount in optimizing patient care.

Objective

The objective of this study was to assess the safety profile Azathioprine among IBD patients in Tikur Anbessa Specialized hospital, Ethiopia, 2024.

Methodology

A retrospective cross-sectional study was conducted to assess the safety profile of Azathioprine among IBD patients in TASH, Ethiopia ,2024. A total of 123 patients who were on Azathioprine for the management of IBD were enrolled. Data was collected from electronic records. A structured questionnaire and checklist was used to collect data. Bivariate logistic regression was employed to look at the crude associations between the outcome variables and determinant variables. Multivariable analysis was done to show the association between Azathioprine side effect and other variables that had a p-value less than 0.05 within the bivariate analysis.

Result

Among the total 123 patient involved, the mean Age of the participants was 33.82 with SD (±10.24) with minimum of 18 years and a maximum of 67 years.Among the total participants the mean duration of Azathioprine treatment was 28.8 months ± SD (19.20) with minimum of 6 months and maximum of 118 months. The median time gap between side effect occurrence and Azathioprine initiation was 28.5 weeks; and the maximum and minimum dose of Azathioprine were 50 and 150 respectively. Of the total 123 participants involved in the study, 105(85.4%) had no comorbidity, 106(86.2%) of them had Crhon's disease. The prevalence of azathioprine side effect among IBD patient attending at TASH during the study period was 27.64% with 95%CI, (19.63%, 35.66%).According to the correlation of azathioprine side effect occurance low hemoglobin level before initiation of the azathioprine had statistically significant correlation with azathioprine drug with a p value of less than 0.05

Conclusion

The prevalence of azathioprine side effect among IBD patients seen at TASH was 27.64% The commonest azathioprine side effect was GI intolerance followed by myelosupression . There is a positive correlation between azathioprine side effects with patients' with base line low hemoglobin level .

Key words: Azathioprine, Inflammatory bowel disease

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ACRONYMS

ALP- Alkaline phosphatase

ALT – Alanine aminotransferase

AST - Aaspartate aminotransferase

AZA -Azathioprine

GI- Gastro entrology

IBD – Inflammatory bowel disease

TASH –Tikur Anbessa specialized hospital

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1. INTRODUCTION

1.1 Background

Inflammatory Bowel Disease (IBD) is a chronic inflammatory condition affecting the gastrointestinal tract, encompassing conditions such as Crohn's disease and ulcerative colitis. The management of IBD often necessitates long-term immunosuppressive therapy to control inflammation and maintain disease remission [1].

Azathioprine, is the prodrug of 6-mercaptopurine which is a purine analogue. It inhibits cell growth by directly interfering with nucleic acid synthesis. However the mechanism of immunomodulation is by inducing T cell apoptosis through modulating cell (Rac1) signalling[2]has long been a cornerstone in the management of inflammatory bowel disease (IBD), encompassing both Crohn's disease and ulcerative colitis. Its immunosuppressive properties make it a valuable asset in controlling disease activity and achieving long-term remission in patients. However, as with any potent medication, understanding its safety profile is paramount in optimizing patient care [2].

Over the years, extensive clinical experience and research have provided valuable insights into the safety profile of azathioprine, shedding light on its efficacy, adverse effects, and appropriate monitoring strategies. In the context of IBD management, clinicians are tasked with balancing the therapeutic benefits of azathioprine against potential risks, ensuring optimal patient outcomes while mitigating adverse events[3].

This introduction aims to explore the safety profile of azathioprine specifically in patients with IBD, highlighting key considerations such as common adverse effects, monitoring protocols, and strategies for risk minimization. By examining the existing literature and clinical guidelines, this overview seeks to provide clinicians with a comprehensive understanding of the safety landscape surrounding azathioprine therapy in the context of IBD, empowering them to make informed decisions in patient care.

1.2 STATEMENT PROBLEM

Inflammatory Bowel Disease (IBD), comprising Crohn's disease and ulcerative colitis, is a chronic inflammatory disorder of the gastrointestinal tract, characterized by periods of active disease and remission.[4] Azathioprine, an immunosuppressive agent, has been a cornerstone in the management of IBD due to its ability to induce and maintain remission. However, despite its efficacy, concerns persist regarding its safety profile.

While it is recognized for its therapeutic benefits, there are notable adverse effects associated with its long-term use, including myelosuppression, hepatotoxicity, pancreatitis, and increased risk of malignancies[5]. Furthermore, the variability in individual responses to azathioprine poses challenges in determining optimal dosing strategies to minimize adverse effects while ensuring therapeutic efficacy[6].

Additionally, the safety considerations extend beyond the drug's direct effects, encompassing issues such as drug interactions, patient adherence, and monitoring protocols. Azathioprine's interactions with other medications commonly used in IBD management necessitate a thorough understanding to prevent potential adverse outcomes. Moreover, ensuring patient compliance with treatment regimens and implementing robust monitoring protocols are vital aspects in mitigating risks associated with azathioprine therapy[7].

In light of these considerations, the primary objective of this proposal is to conduct a comprehensive assessment of the safety profile of azathioprine in the management of IBD. This involves elucidating the spectrum and incidence of adverse effects associated with its use, identifying factors contributing to inter-individual variability in response and toxicity, exploring strategies to mitigate risks, and reassessing its position in the contemporary landscape of IBD therapy.

Ultimately, addressing these aspects will provide clinicians with evidence-based insights to optimize the use of azathioprine in the management of IBD, ensuring a balance between therapeutic efficacy and safety considerations for improved patient outcomes

1.2 Significance of the study

Inflammatory Bowel Disease (IBD) poses a significant health burden globally, including in Ethiopia. Azathioprine, an immunosuppressive medication, is commonly used in the management of IBD to induce and maintain remission. However, the safety profile of azathioprine in Ethiopian populations remains inadequately studied. This proposal aims to investigate the safety profile of azathioprine in the context of managing IBD in Ethiopia, with a focus on its significance outlined as follows:

Understanding the safety profile of azathioprine in Ethiopian patients with IBD is crucial due to potential differences in genetic predispositions, environmental factors, and healthcare practices compared to other populations. This study will provide context-specific insights into the risks and benefits associated with azathioprine therapy in the Ethiopian setting.

Physicians managing IBD patients in most health settings often face challenges related to medication choices, including concerns about safety and adverse effects. Investigating the safety profile of azathioprine will equip healthcare providers with evidence-based information to make informed decisions regarding treatment options, ultimately improving patient care and outcomes.

Azathioprine is known to be effective in maintaining remission in IBD, but concerns about its safety, particularly regarding hematologic, hepatic, and gastrointestinal adverse effects, may deter its optimal utilization. By elucidating the safety profile of azathioprine in Ethiopian IBD patients, this study can contribute to optimizing treatment strategies, potentially increasing the use of this medication where appropriate.

Adverse events associated with azathioprine therapy can significantly impact patients' quality of life and adherence to treatment regimens. Assessing the safety profile of azathioprine will help identify strategies to mitigate adverse effects, thereby enhancing patient safety and improving their overall well-being. In conclusion, investigating the safety profile of azathioprine in the management of IBD in Ethiopia is significant for enhancing patient care, optimizing treatment strategies, informing healthcare decision-making, and contributing to the global understanding of IBD management. This study holds promise for improving the lives of IBD patients in Ethiopia and beyond.

2. LITERATURE REVIEW

2.1 Introduction

Inflammatory Bowel Disease (IBD), encompassing Crohn's disease and ulcerative colitis, represents a significant burden on global healthcare systems and profoundly impacts the quality of life of affected individuals.[8] IBD is Characterized by chronic inflammation of the gastrointestinal tract, IBD presents a complex therapeutic challenge requiring long-term management strategies to achieve and maintain disease remission[9]. Among the arsenal of pharmacological agents used in IBD treatment, azathioprine has emerged as a cornerstone therapy due to its potent immunomodulatory effects.[10]

Azathioprine, a purine analogue, exerts its therapeutic action by inhibiting DNA synthesis and suppressing immune-mediated inflammation[11]. Introduced decades ago, azathioprine has revolutionized the landscape of IBD management, offering an alternative to corticosteroids and enabling steroid-sparing strategies[12]. Despite its widespread use and established efficacy, concerns surrounding the safety profile of azathioprine persist, prompting on going scrutiny and re-evaluation[13].

The safety profile of azathioprine in IBD management is a topic of paramount importance, as clinicians strive to balance therapeutic efficacy with the risk of adverse events. Adverse events associated with azathioprine therapy range from mild and reversible to severe and life-threatening, encompassing hematologic toxicity, hepatotoxicity, infectious complications, and gastrointestinal intolerance. Additionally, rare but serious adverse events, including malignancies and hypersensitivity reactions, underscore the need for vigilant monitoring and risk mitigation strategies[14].

As the landscape of IBD management continues to evolve with the advent of novel therapeutic agents and personalized treatment approaches, understanding the safety profile of azathioprine remains imperative[15].

2.2 Historical Background

Inflammatory Bowel Disease (IBD) represents a group of chronic inflammatory conditions of the gastrointestinal tract, predominantly comprising Crohn's disease and ulcerative colitis[16]. IBD is characterized by a dysregulated immune response against luminal antigens in genetically predisposed individuals, resulting in mucosal inflammation, tissue damage, and a myriad of clinical manifestations[16].

The global prevalence of IBD has been steadily rising over the past few decades, with significant variations observed across geographic regions and ethnic populations[17]. The etiology of IBD remains multifactorial, encompassing genetic susceptibility, environmental triggers, alterations in gut microbiota, and dysregulated immune responses[18].

The management of IBD is multifaceted and requires a tailored approach based on disease severity, phenotype, and patient-specific factors[19]. While the goals of therapy include achieving and maintaining clinical remission, minimizing disease-related complications, and improving quality of life, the therapeutic landscape of IBD has evolved significantly over time[20]. Conventional treatment modalities, such as corticosteroids, immunomodulators, and amino salicylates, have been supplemented by the advent of biologic agents targeting specific cytokines and immune pathways implicated in IBD pathogenesis[20].

Azathioprine, a purine analogue, was first introduced in the 1960s as an anti-cancer agent and later repurposed for the treatment of autoimmune conditions, including IBD. Azathioprine exerts its immunosuppressive effects by inhibiting DNA synthesis and interfering with lymphocyte proliferation, thereby modulating the aberrant immune response characteristic of IBD. Over the years, azathioprine has become an integral component of the therapeutic armamentarium for IBD, offering an effective alternative to corticosteroids and enabling steroid-sparing strategies.[21]

Despite its established efficacy in inducing and maintaining remission in IBD, the use of azathioprine is tempered by concerns regarding its safety profile[21]. Adverse events associated with azathioprine therapy encompass a broad spectrum, ranging from mild and reversible to severe and life-threatening.[22] Hematologic toxicity, hepatotoxicity, infectious complications, and gastrointestinal intolerance are among the most commonly reported adverse events, necessitating vigilant monitoring and individualized risk assessment. Additionally, rare but serious adverse events, including malignancies and hypersensitivity reactions, underscore the need for comprehensive risk-benefit assessment and shared decision-making between patients and healthcare providers[22].

Given the evolving landscape of IBD management and the emergence of novel therapeutic options, understanding the safety profile of azathioprine remains a critical priority. While azathioprine continues to play a pivotal role in the management of IBD[23] .

2.3 Mechanism of Action and Pharmacokinetics

Azathioprine is a prodrug that undergoes extensive metabolism to its active metabolites, primarily 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine (6-MMP)[24]. These metabolites exert immunosuppressive effects by inhibiting DNA synthesis and interfering with the proliferation of activated

lymphocytes, thereby modulating the aberrant immune response characteristic of inflammatory conditions such as Inflammatory Bowel Disease (IBD). Specifically, 6-TGNs are incorporated into DNA during replication, leading to impaired DNA synthesis and cell proliferation, particularly in rapidly dividing cells such as lymphocytes. This mechanism ultimately results in the suppression of inflammatory responses and the induction of immune tolerance, contributing to the therapeutic efficacy of azathioprine in IBD management [24].

Pharmacokinetics

Following oral administration, azathioprine is rapidly and extensively metabolized in the liver by the enzyme thiopurine S-methyltransferase (TPMT) into its active metabolites, 6-TGN and 6-MMP. TPMT is a key enzyme involved in the metabolism of thiopurine drugs, and genetic polymorphisms affecting TPMT activity can influence individual responses to azathioprine therapy. While 6-TGNs are primarily responsible for the immunosuppressive effects of azathioprine, 6-MMPs are associated with potential hepatotoxicity and myelosuppression, necessitating careful monitoring of metabolite levels in clinical practice[25].

The pharmacokinetics of azathioprine exhibit interindividual variability, influenced by factors such as genetic polymorphisms, concomitant medications, and hepatic function. Azathioprine and its metabolites are extensively distributed throughout the body, with peak plasma concentrations typically reached within 1 to 2 hours following oral administration. The elimination half-life of azathioprine ranges from 3 to 5 hours, with metabolites excreted primarily via the renal route[26].

Optimal dosing strategies for azathioprine in IBD management aim to achieve therapeutic concentrations of 6-TGNs while minimizing the accumulation of potentially toxic metabolites such as 6-MMPs. Individualized dosing regimens based on patient characteristics, disease severity, and TPMT genotype can help optimize therapeutic outcomes and mitigate the risk of adverse events associated with azathioprine therapy[27].

2.4 Safety Profile of Azathioprine

The definition for AE was adopted by Jha rap et al, that is, any new symptom or sign, any significant laboratory abnormality, or worsening of a preexisting condition or abnormality that occurred after initiation of thiopurines was considered anAE[28].According to several studies, myelotoxicity, pancreatitis, infection, flulike symptoms, rash myelosuppression, liver toxicity, and systemic toxicity were the top azathioprine adverse effects.

AZA caused side effects in 60 people worldwide, or 23% of the total patient population. The most common reactions were pancreatitis (31 patients, or 12% of the entire population), hepatotoxicity (n = 5, 2%), myelotoxicity (n = 5, 2%), and gastrointestinal intolerance (nausea/vomiting/diarrhea, 10 patients, 4%)[29].

White blood cell counts< 4000 in two or more assessments were considered myelotoxic. Liver enzymes more than 1.5 times higher than the upper limit of normal is defined as hepatotoxic Abdominal symptoms along with an increase in lipase and/or amylase were used to diagnose pancreatitis. Any one of the following indications or symptoms was indicative of systemic toxicity: fever, rash on the skin, arthralgias, myalgia, asthenia, diarrhea, nausea, and abdominal pain [30][24].

Myelosuppression

It is the most frequent dose-dependent side effect of azathioprine. Leukopenia with a count of fewer than 4000 is the most common side effect, occurring in approximately 5–15% of cases. Thrombocytopenia can occur alone or in conjunction with leukopenia, and additional research is required if the thrombocytopenia does not improve with medication reduction or discontinuation [24].

Hepatotoxicity

Thiopurines appear to have a range of effects on the liver, despite the fact that the precise processes are still unknown. A certain percentage of patients may see slight increases in transaminase levels.There may be a biological basis for this type of liver damage, as recent research indicates that this mild toxicity is dosage dependent[24].

It is unusual that therapy needs to be stopped for most of these patients because they respond well to dosage reduction. Furthermore, it has been proposed that the liver enzymes will often return to normal without the need for dose adjustments. The long-term effects are uncertain for patients whose enzymes do not return to normal over time[24]. While the precise cause of thiopurine-induced nodular regenerative hyperplasia is still unknown, several theories suggest that it is more idiosyncratic than metabolite- or dose- dependent [24].

Potential for Malignancy

A cohort of 755 patients treated over a 30-year period did not show an increased risk of cancer over that expected, according to Connell et al. 55. According to Present et al., the incidence and kind of tumors were comparable to those anticipated in the background population, and the rate of malignant lymphoma was recorded at 3%. Using a fictitious Markov model, Lewis et al.56 initially suggested that thiopurines have

more advantages than disadvantages, including the possibility of cancer[24]. The same group then used the General Practice Research Database UK database to conduct a retrospective cohort research, and they came to the conclusion that there did not seem to be a higher risk of lymphoma among IBD patients who used 6-MP.57 Studies on the population raise the potential that those with CD may have a slight elevated risk of developing cancer[24].

Pregnancy consideration

Study done in London enrolled 16 pregnancies in 14 women on azathioprine for inflammatory bowel disease were retrospectively analyzed. Hepatitis B virus infection was the only infectious pregnancy complication; the children did not have any congenital defects or subsequent health issues. According to this exploratory study, individuals with inflammatory bowel disease who are pregnant can safely take azathioprine, and women who become pregnant while taking the medication do not necessarily need to stop their pregnancies[31].AZA are found in breast milk, and in most cases nursing is not recommended because of unknown risk of long term immunosuppression and carcinogenesis to the child[24].

Drug discontinuation

Study done in china showed that drug withdrawal happened in 76 out of 276 patients (28.44)% in the whole study population .Drug discontinued happened in 39 (14.6%) patients due to drug side effect [28].

Predictors of Therapy Discontinuation

Study done in south China ,Multivariate analysis revealed that higher odds of stopping thiopurine treatment were linked to lower body mass index (BMI) (<18 kg/m2) (HR, 1.59; 95% CI, 1.04–2.46), extraintestinal manifestation at CD diagnosis (HR, 1.85; 95% CI, 1.18–2.88), and leucopenia incidence (HR, 1.76; 95% CI, 1.05–2.97)[28].

3. Objectives

3.1 General Objective

To assess the safety profile among IBD patients taking Azathioprine in Tikur Anbessa Tertiary hospital.

3.2 Specific Objectives

- Evaluate the prevalence and types of adverse events associated with azathioprine therapy in patients with IBD.
- Investigate the relationship between azathioprine dosage and the occurrence of adverse events in IBD patients.
- To assess Factors associated with higher risk of Azathioprine adverse events.

Conceptual framework

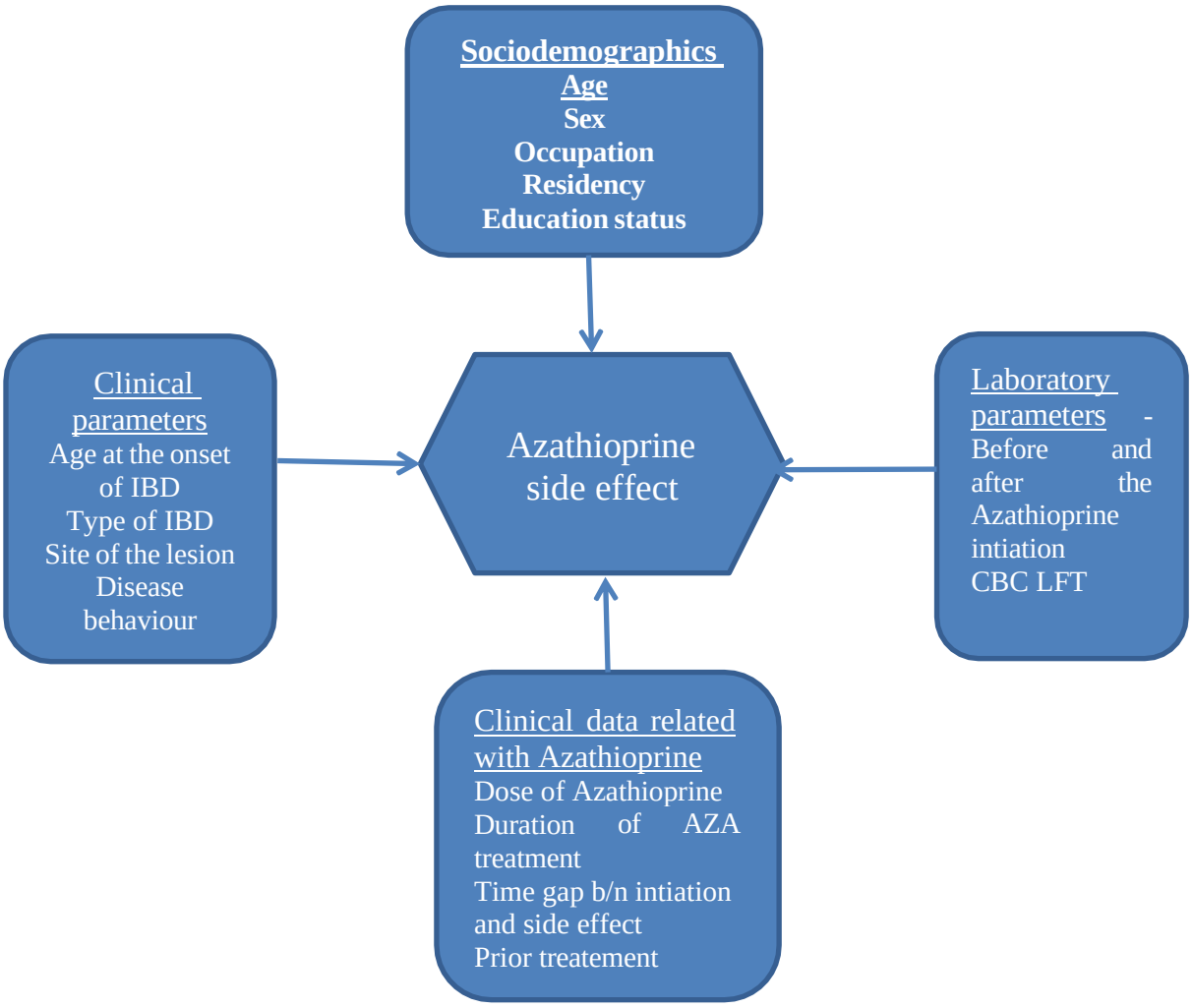

Figure 1 Conceptualof participants who was on azathioprine in the treatment IBD from 2022 to 2024 GC at TASH Addis Ababa, Ethiopia, (n=123)

4. METHODOLOGY

4.1 Study area

The study was conducted at TASH, which is the largest and oldest teaching hospital situated in Addis Ababa, Ethiopia . In addition to offering various clinical services, the hospital's gastrointestinal and hepatology division trains medical residents, GI and hepatology fellows, and undergraduate students. Along with inpatient and outpatient clinical treatments, the unit also provides diagnostic and therapeutic Gastroenterology endoscopy scope services. The Gastroenterology and hepatology unit has about eight faculties, seven fellows and seven nurses and serving for patients come from all regions of the country.

4.2 Study period

Study was conducted from August1- 30, 2024 GC

4.3 Study design

A Retrospective study conducted to determine the Safety profile of Azathioprine among IBD patients at TASH

4.4 Study population

4.4.1 Source Population

The source population were All IBD patients on Azathioprine had follow up at TASH in the past two years.

4.4.2 Sample population

All IBD patients on Azathioprine for more than 6 months and had follow up in TASH .

4.4.3 Inclusion criteria

-Adults age >=18 years diagnosed with IBD and On Azathioprine for a minimum of 6 months

4.4.4 Exclusion criteria’s

A patient on other immuno modulater

Incomplete medical records

4.5 Sample size

$$n = \frac{z^2 * P(1 - P)}{W^2}$$

- n is the sample size.
- Z is the Z-value (the number of standard deviations from the mean) for the desired confidence level. For a 95% confidence level, Z is 1.96.
- p is the estimated proportion (0.10 in this case).
- E is the margin of error (0.05 in this case).

Sample size was of approximately 139 IBD patients as per the inclusion criteria we found 123 patients eligible for the study .

4.6 Sampling procedure

We included consecutive patients based on the inclusion criteria ., and we used the EMR system to identify all IBD patients treated with azathioprine over the past 2 years. Then a total of 123 patients with complete medical records were enrolled in the study.

4.7 Data collection procedures

Electronic medical records of eligible patients were reviewed at their progress note during their follow up visit for demographic information, disease characteristics, dosage and duration of azathioprine therapy and adverse events. Laboratory parameters like CBC, LFT were taken before azathioprine initiation and after on azathioprine treatment at the side effect occurrence for those who developed the side effect and for those didn't develop side effect at 24weeks of the treatment .

4.8 Study variable

Dependent variable

Azathioprine side effect

Independent variables

Patient demographics

Lab parameters

Disease behaviour

Dosage of Azathioprine

Duration of Azathioprine Therapy

Concomitant Medications

Comorbidity

4.9 Operational definition

Mylosupression – is defined as white blood cell < 3000mm^3 and/or platlates < 100,000mm^3 and /or Haemoglobin < 10g/dl after initiation of azathioprine treatment

Lymphopenia -defined as lymphocyte count < 1000 cells per microliter after the initiation of Azathioprine

Hepatotoxicity- elevation of liver enzymes (AST, ALT,ALP) >1.5 times in the last two repeated measurements after initiation of azathioprine

Clinical hepatitis- characterized by a combination of symptoms such as jaundice ,fatigue right upper quadrant pain ,dark urine and elevated liver enzymes(ALTASTALP) after initiation of azathioprine

Asymptomatic transaminatitis –defined as elevation of liver enzymes (ALTASTALP) with out clinical symptom of Liver disease(nausea ,vomiting Right upper quadrant pain, jaundice and dark urine) after initiation of azathioprine

GI intolerance – the occurrence of vomiting, nausea, abdominal pain diarrhea after Azathioprine initiation

4.10 Data processing and analysis

After being verified to be accurate, coded, and transferred to SPSS version 26, the obtained data examined critically. Results reported using conventional descriptive techniques (means/percentage and standard Deviations). Statements, tables, and figures used to display the results. of the relationship between the independent and dependent variables. The study conducted bivariate analysis and multivariable analysis incorporating all explanatory variables associated with the outcome variable at p-value less than 0.05. The multivariable analysis utilized an AOR with 95% CI and a P-

value of 0.05 to determine whether or not the independent variables are statistically significant with respect to the outcome variable.

4.11 Data quality management

The investigator provided appropriate training for data collectors and conduct routine supervision to ensure the quality of the data to be collected was maintained. The primary investigator performed a pre-test for one week before the actual data collection to ensure that the data was accurate, consistent, and free of any ambiguities. Issues found in the pre-test was fixed before the final data was gathered. Every day, the accuracy and completeness of the data was verified.

4.12 Ethical consideration

The study conducted after the proposal has been approved by the Addis Ababa University College of Health Sciences' ethical review committee of the department of internal medicine.

4.13 Dissemination plan

Ultimately, copies of the results will be distributed to the appropriate authorities, such as the Addis Ababa University, College of Health Sciences. The hospital's quality assurance team will discuss the findings. It will be submitted to reputable journals. A copy of the research will be added to the library's reference collection. Additionally, findings will also be presented in medical conferences.

5. Result

There were 144 patients eligible during the study period among them 21 patients were excluded from the study .The exclusion criteria s were,14 patients having incomplete data, 6 patients started Azathioprine treatment in less than 6 months and one patient was on Dazatinib**.**

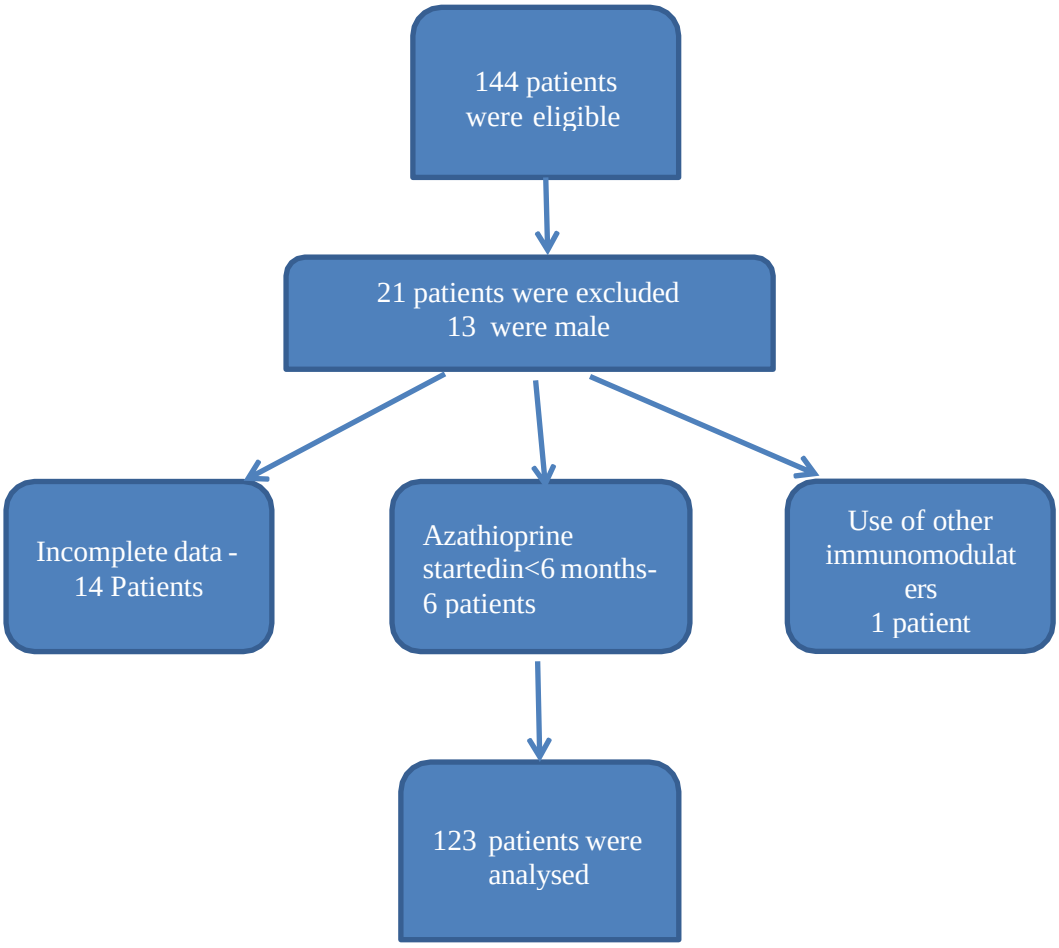

Figure 2. Consort form of participants who was on azathioprine in the treatment IBD from 2022 to 2024GC at TASH Addis Ababa, Ethiopia, (n=123)

5.1. Socio-demographic characteristics of participants

Among the total 123 patient involved, the mean Age of the participants was 33.82 with SD (±10.24) with minimum of 18 years and a maximum of 67 years. Of all participants, most of them 118(95.9%) participants lived in urban, and more than half 72(58.5%) of the participants were female. Regarding education level majority of them 56(45.5%) were college and above education level, and 68(55.3%) were married. Of all participants, most 51 (41.5%) were Unemployed (Table 1)

Table 1.Socio-demographic characteristics of participants who was on azathioprine in the treatment IBD

from 2022 -2024GC at TASH Addis Ababa, Ethiopia, (n=123)

Variables	Category	Frequency	Percentage
Residency	Rural	5	4.1
	Urban	118	95.9
Sex	Female	72	58.5
	Male	51	41.5
Education level	No formal education	1	0.8
	Only read and write	5	4.1
	Primary education	20	16.3
	Secondary education	41	33.3
	College and above	56	45.5
Marital status	Single	54	43.9
	Married	68	55.3
	Widowed	1	0.8
Occupation	Unemployeed	51	41.5
	Private workers	34	27.6
	Merchanet	8	6.5
	Governmental employee	30	24.4

5.2. Clinical characteristic of participants

Among the total participants the mean duration of Azathioprine treatment was 28.8 months ± SD (19.20) with minimum of 6 months and maximum of 118 months. The median time gap between side effect occurrence and Azathioprine initiation was 28.5 weeks; and the maximum and minimum dose of Azathioprine were 50 and 150 respectively. Of the total 123 participants involved in the study, 105(85.4%) had no comorbidity, 106(86.2%) of them had Crhon's disease . None of them had history of substance use . Among the total participants attending the facilities, 117(95.1%) of them had no history of appendectomy; and 59(48.0%) and 39(31.7%) of participants had ileocecal and ileum as a site of lesion respectively. The mean age at the onset of IBD was 30.2 year with SD (± 10.90) with minimum of 20 years and maximum of 64 years. Regarding disease behavior, 42(34.1%) had structuring, and 40(32.5%) had non-penetrating and non-structuring. Of the total participants, 76(61.8%) of them had prior treatments for

IBD before Azathioprine, and 52(42.3%) of them took steroid with azathioprine. After the side effect of azathioprine had occurred ,12(42.86%)were continued and 7 (25.0%) were temporally withdrawn (Table 2 Fig 1and Fig 2 ,).

Table 2 Clinical characteristics of participants who was on azathioprine in the treatment IBD from 2022 to 2024 GC at TASH Addis Ababa, Ethiopia, (n=123)

Variables	Category	Frequency	Percentage
Comorbidity	No	105	85.4
	Yes	18	14.6
Substance use	No	123	100.0
History of appendectomy	No	117	95.1
	Yes	4	3.3
	Unknown	2	1.6
Types of IBD	Crhon's	106	86.2
	Ulcerative colitis	16	13.0
	Both	1	0.8
Disease behavior	Non penetrating non structuring	40	32.5
	Penetrating	24	19.5
	Stricturing	42	34.1
	Both penetrating and structuring	2	1.6
	Collitis	12	9.8
	Proctitis	3	2.4
Prior treatments for IBD before Azathioprine	No	47	38.2
	Yes	76	61.8
Concomitant drugs used with azathioprine	None	67	54.5
	Steriod	52	42.3
	Allopranol	1	0.8

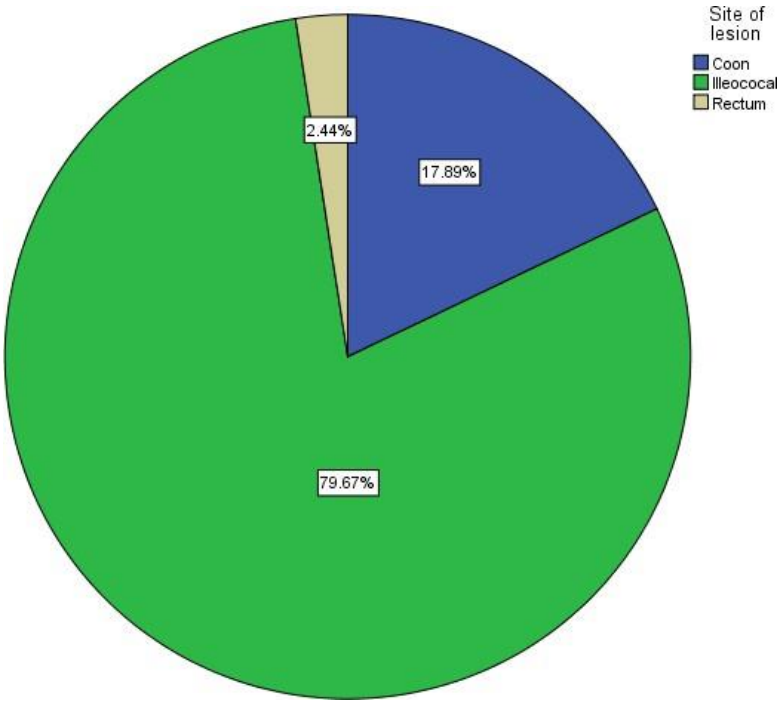

Figure 3 Site of the lesion of IBD of participants who was on azathioprine in the treatment IBD from 2022 to 2024 Gc at TASH Addis Ababa, Ethiopia, (n=123)

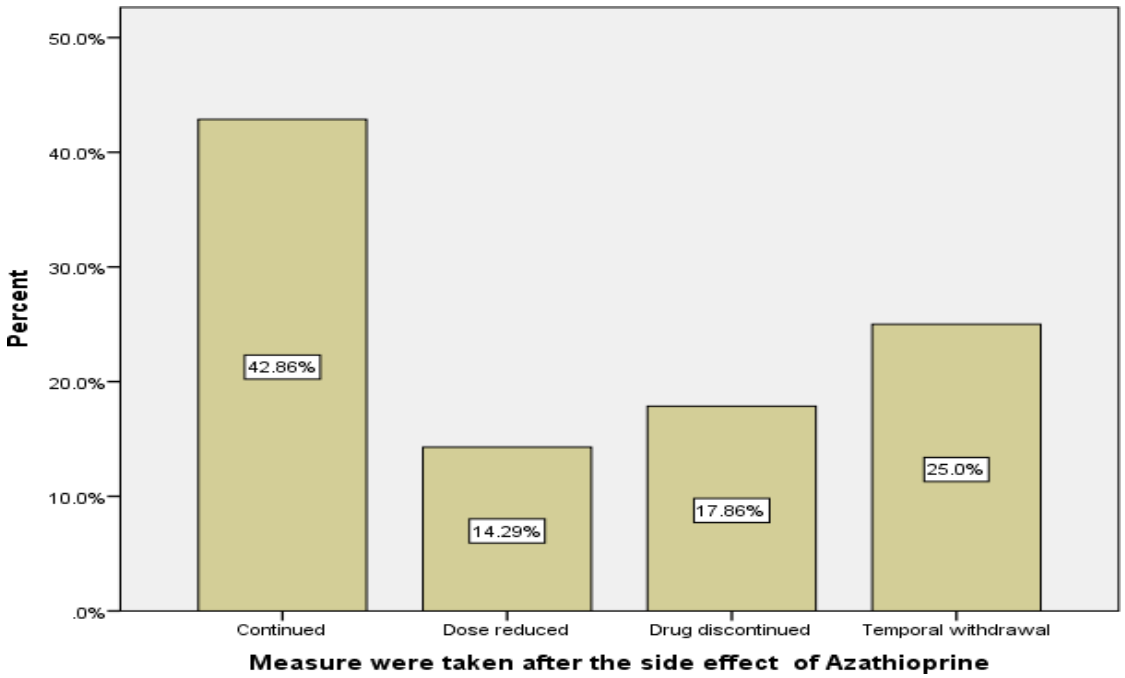

Figure 4 Measures taken after the side effect of Azathioprine has occurred in IBD patients who was on azathioprine from 2022 to 2024GC at TASH Addis Ababa, Ethiopia, (n=123)

Table 3 Side effects of Azathioprine and time gap betewen side effect occurance and Azathioprine intiation in weeks of participants who was on azathioprine in the treatment IBD from 2022 to 2024GC at TASH Addis Ababa, Ethiopia, (n=123)

		Time gap in weeks		Total	Percentage %
		5-24 week	>24 weeks		
Side effects of Azathioprine	GI Intolerance	9	4	13	10.6
	Heavey/irregular mensus	2	1	3	2.4
	Leucopinea	0	8	8	6.5
	Lymphoniea	0	6	6	4.8
	Pancytopenia	0	2	2	1.6
	Thrombocytopnea	0	5	5	4.0
	Bicitopnea	0	2	2	1.6
	Anemia	2	7	9	7.3
	Secondary amenorhea	0	1	1	0.8
	Abnormal liver enzymes	6	0	6	4..8
	Azathioprine induced liver injury	1	0	1	0.8
	LOSS OF SCALP HAIR	0	1	1	0.8
Total Episoides of the Azathioprine side effect		20	37	57	46.%

5.3 Laboratory parameters of IBD patients before and after the Azathioprine intitation

Table 4 Difference in the laboratory finding before and after initiation of Azathioprine patients who was on Azathioprine for more than 6 months at TASH from 2022-2014 GC Ethiopia (N=123)

Variables	**Before initiation of the drug**	**After initiation of the drug**
WBC	8.014 ± 3.08	6.18 ± 3.20
Hgb	18.17 ± 53.95	13.32 ± 2.17
Lymphocyte count	25.05 ± 6.45	22.97 ± 9.78
Platelet count	379.15 ± 137.08	323.41 ± 109.65
ALT	14.51 ± 11.39	16.16 ± 23.62
AST	21.49 ± 18.32	21.61 ± 10.56

5.4 Prevalence of Azathioprine side effect

The prevalence of azathioprine side effect among IBD patient attending at TASH during the study period was 27.64% with 95%CI, (19.63%, 35.66%)and 57 episodes of side effect had occurred .This mean among the 100 patient who took azathioprine in IBD patients, 28 of them developed at least one side effect. Of these total side effect, 13(10.5%) of them had GI intolerance, 10 (8.1) had mylosupression and 6(4.8 %) had isolated lymphopenia and 4(had heavy irregular mensus (Table 3, Fig.5)

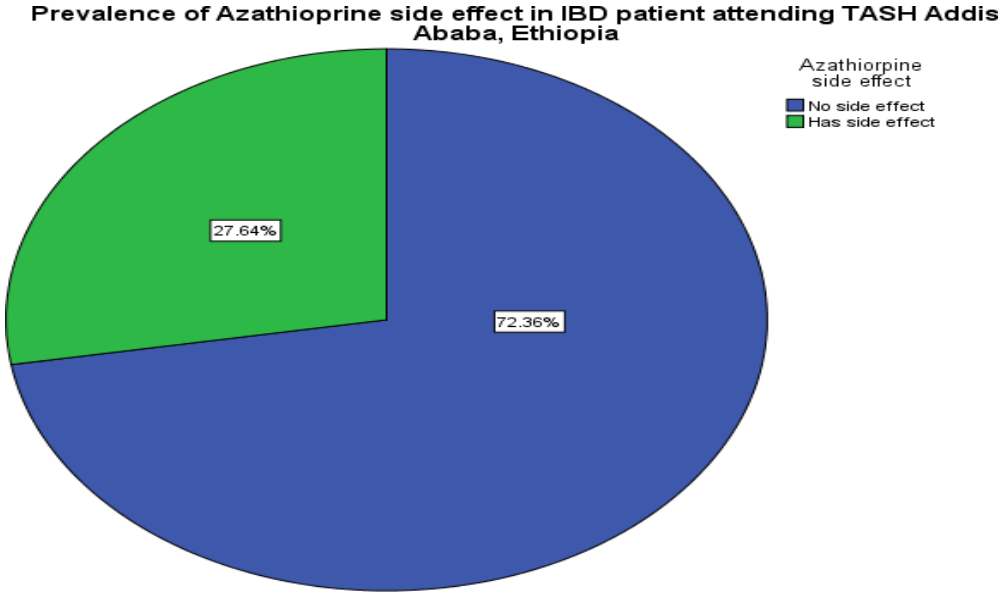

Figure 5 prevalence of Azathioprine side effect of participants who were on azathioprine in the treatment IBD from september 2022 to september 2024 at TASH Addis Ababa, Ethiopia, (n=123)

5.5 Correlation between azathioprine side effect and other variables

According to the correlation outcome of occurance azathioprine side effect and patient hemoglobin level

before initiation of the azathioprine side effect had statistically significant correlation with azathioprine drug with a p value of less than 0.05. This correlation showed a moderate positive correlation between azathioprine side effect and low hemoglobin level before the initiation of the azathioprine drug with the correlation coefficient of 0.336 (Table 3).

Table 5 Correlation between azathioprine side effects with other variables of participants who was on azathioprine in the treatment IBD from september 2022 to september 2024 at TASH Addis Ababa, Ethiopia, (n=123)

	Azathioprine side effect	Correlation Coefficient	P value
Hemoglobin result before initiation of the azathioprine drug	Occurance of one 0r more side effects of Azathioprine	0.336**	0.001

6. Discussion

Our study assessed the treatment side effect related with azathioprine intake among IBD patient those attending TASH during the study period. It also assessed the correlation between the azathioprine side effect and other clinical factors. To the best of my knowledge this is the first study done at the study areas. According to our study the prevalence of azathioprine side effect among IBD patient was 27.64 86% with 95%CI, (19.63%, 35.66%).This finding was similar with previous studies done in france and India (15%-28%)[32]. Study done in France-showed prevalence of Azathioprine was (15.8%)[33] and 20.6% in India [34] but our finding is a bit higher than a study done at Germany(7.3%)[35], UK(14%)[36], and Netherlands (4.9%)[36]. The possible reason for this might be due to difference in sample size and study areas. The study done in Germany included 324 samples which is more than two times higher than our study sample and also they did a multicenter study centers[35]. But our finding was lower than a systematic review study result (43.6%)[38], United Kindom(47%)[39], and Italy(32.4%)[40]. The possible reason for this might be due to difference in study types and study participant, which was systematic review and focused on Crohn's disease only [38] [40].

In our study the commonest side effect of azathioprine was GI intolerance. This finding was similar with previous studies[34] [38][41] Azathioprine affect the rapidly dividing cells of the intestinal epithelium, and its metabolites can be cytotoxic, particularly to the rapidly dividing cells in the gastrointestinal tract which leads to GI symptoms such as nausea, vomiting, and diarrhea[38][41].From our study out of 13 patients those developed GI intolerance, 9(69.2%) of them took steroid which might be a confinding factor for Azathioprine GI side effect .

In our study mylosupression was found in 10 patients (8.1) which was as compared to studies done in Italy and china including 98 and 267 IBD patients with myelosupression prevalene of 16.6 % and 14.6% respectively [42][41]. The posssible explanation could be genetic difference .on the other hand in our study our finding was similar with a study done in india , Myelotoxicity was 7.2% Among 320 patients with a median time to onset of 6 months [43].

In our study lymphopenia has occurred in 6(4.8%) of patients .Similar study done in switherland the prevalence of Lymphopenia was 9.3%.[44] Lymphopenia is usally due to exceeding 6-TGN levels [44]. These metabolites accumulate in the tissue and can be measured in erythrocytes, this is gnna be the future means of drug monitoring [45].

In our study there were 4(3.25 %) patients of menstural Abnormality (3 heavy mensus and 1secondary ammenoria) after the intiation of AZA which were not seen in other study it could be because of the underlying disease and this may needs further study with large sample size.

In our study drug induced liver enzyme abnormality occurs in 5(4%) patients and AZA induced liver injury occurred in one(0.8%) patient with in 6 months of intation of the Azathioprine . Similarly study done in china [41] abnormal liver function tests were seen in 2 patients (0.75%) within a median time of 22.8 months (IQR, 20.9–24.8), another 2 patients (0.75%) developed hepatitis within 6.9 months (IQR, 4.5– 9.2).In same study done in chaina [41], hair loss occurred among 4 (1.4%) of patients and in study done in india [43] hair loss was seen in 2 patients (0.6%) similarly in our study 1(0.8%) had hair loss .The reason for low number of patients having the side effect could be under-reporting.

Asystemic review done in Greece Showed azathioprine was discontinued in 58 patients due to side effects like : hepatotoxicity (11.7%), gastrointestinal intolerance (11.4%), myelotoxicity (7%), pyrexia (6.2%), and acute pancreatitis (4.8%)[46] As compared to the above study the number of patients who discontinue d the drug were low ,5 (17.5%) in our study and the reason for discontinuation were 1(20%)(patient was having Drug induced liver injury the rest 4 (80%)were due to severe mylosupression .the possible explanation for low number of drug discontinuation could be due to the difference in study design and sample size .

In our study dose of azathioprine did not have any correlation with the occurrence of azathioprine side effect But in study done in India including 507 patients, there were 26 of 66 (39.4%) patients were considered to have dose-dependent side effects[43].The possible explanation could be due to dose titration practice of azathioprine in our setting and low sample size .

In our multivariate loggestic regression low hemoglobin level < 12gm/dl was found to be statistically significant with a p value 0.336 in predicting occurance of side effect of Azathioprine .Similarly study in chaina on multivariate logistic regression identified a lower baseline hemoglobin (< 108 g/L) when initiate thiopurines treatment (HR, 0.34; 95%CI 0.18–0.67) was statistically significant [41].

7. Conclusion

The prevalence of azathioprine side effect among IBD patients seen at TASH was 27.64% The commonest azathioprine side effect was GI intolerance followed by myelosupression . There is a positive correlation between azathioprine side effects with patients' with base line low hemoglobin level .

8. Strength and limitation

9.

8.1 Strength of the study

Our study showed the prevalence of azathioprine side effects among IBD patienst. Up to researcher understanding this is the first study done in the study areas and it will be use a baseline finding for future research. The study also assessed the correlation between the azathioprine side effects with other clinical history of the patients which add more strength on the study findings.

8.2. Limitation of the Study

One of the limitations of our findings is due to ther etrospective cross-sectional study nature of the design which only showed the point in time and could not show the long term effect of the study effects. Also due to the study done at one institute, it might not be generalizable for Addis Ababa and Ethiopia at large.

9. Recommendation

- **For Clinicians** -p**re-treatment Screening**: Given the positive correlation between low baseline hemoglobin levels and azathioprine side effects, it is important to thoroughly screen patients for hemoglobin levels before starting azathioprine therapy. Patients with low hemoglobin should be closely monitored or alternative treatments considered to reduce the risk of adverse effects
- **For Researchers:**- Additional studies could be conducted to explore the mechanism linking low hemoglobin and azathioprine intolerance, as well as to investigate other potential risk factors for adverse reactions in IBD patients with large sample size .

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ANNEXS

QUESTIONARIE

Questionnaire for a proposal entitled with Safety profile of Azathioprine among IBD patients

Socio-demographic characteristics

1. Data collection site

   A .Tikur Anbessa hospital
   B. Tekelehaimanot hospital
   C. Adera medical and surgical center
   D. Others _____

2. Card no _____
3. Age in years ___
4. Place of residency

   A.Urban
   B.Rural

5. Sex

   A Female
   B Male

6. Level of education

   A. No formal education
   B. Only read and write
   C. Primary education
   D.Secondary education
   E. College and above
   F. Others _____

7. Marrital status

   A.Married
   B.Single
   C.Divorced
   D.Widowed

8. Occupation

   A.Civil servant
   B.Private workers
   C.Un employed
   D.Retired

E.Student
F.Farmer
G.Marchent
H.Other……

Clinical parameter

9. Age at the onset of IBD ----------
10 Type of IBD

A . Crhon's disease

B. Ulcerative colitis

C. Both

10. Sites of the lesion

A Ileum

B. Cecum

C. Ileocecal

D. Colon

E Rectum

F Others…….

11. Disease behavior

A .Penetrative

B. Stricturing

C. Stricturing and penetrating

D. Colitis

E. Proctitis

F. Proctocolitis

G. Others _____

Laboratory parameters before initiation of Azathioprine

12. Hemoglobin gm/dl_____
13. WBC _____
14. Lymphocye count _____

15. Platelet count _____

17. AST_____

18. ALT___
19. ALP___
20. Serum Albumin _____
21. Total biluribin
22. Direct biluribin _____

Laboratory parameters after initiation of Azathioprine

23. Hemoglobin gm/dl_____
24. WBC _____
25. Lymphocye count _____

26. Platelet count _____

27. AST_____

28. ALT_____

29. ALP_____

30. Serum Albumin _____

31. Total bilirubin _____

32. Direct bilirubin _____

33. Documented side effects of Azathioprine

A. GI intolerance

B. Clinical hepatitis

C. Asymptomatic transaminitis

D. Leukopenia

E. Lymphopenia

F. Anemia

G. Skin rash

H .Flu like symptoms

I. Acute pancreatitis

J. Pregnancy related complications

K. None
L. Others ___

34. What measure were taken After side effect of Azathioprine

A. Drug discontinued

B. Temporally hold

C. Withdrawal

D. Dose reduced

E .Continued

F. Others_____

35. Duration of Azathioprine treatment in months _____

36. Time gap between side effect occurrence of side effect and initiation of Azathioprine_____

37. Other drugs used with Azathioprine _____

38. Prior treatment for IBD before Azathioprine _____

39. Initial dose of Azathioprine in mg _____

40. Maximum dose of Azathioprine in mg _____

41. Comorbidity

A. DM

B. HTN

C. CKD

D. Hypercoagulability

E Others _____

42. History of Appendectomy

A. Yes

B. No

43. Substance use

A. Alcohol

B. Smoking

C. Chat

D. Others _____