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ORIGINAL ARTICLE

Long-term safety and effectiveness of azathioprine in the management of inflammatory bowel disease: A real-world experience

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Key words
adverse events, azathioprine, inflammatory bowel disease, long-term effectiveness, tolerance.

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Abstract

Background and Aim: Azathioprine (AZA) forms the cornerstone for maintenance of sustained remission in inflammatory bowel disease (IBD). There is apprehension regarding the long-term effectiveness and safety of AZA in IBD. We present our experience with AZA use and outcomes in a cohort of IBD patients followed up over a long period of time.

Methods: Records of 507 IBD patients under treatment at a single, tertiary care center in south India between 2013 and 2022 were evaluated retrospectively. Long-term compliance, tolerance, clinical outcome at the point of last follow-up, type and duration to the onset of adverse events, and subsequent amendment to treatment with regard to AZA were analyzed.

Results: Of 507 patients with IBD, 320 patients (207 Crohn's disease [CD], 113 ulcerative colitis [UC]) who received AZA were included. The median follow-up was 41 months (interquartile range 15.5–77.5). Total duration of exposure was 1359 patient-years with median usage of 33 months. Of the patients, 26.9% received AZA for >5 years. Mean initiation and maximum doses of AZA were 0.97 and 1.72 mg/kg/day. Among the participants, 20.6% experienced side effects, including myelotoxicity (7.2%) and gastrointestinal intolerance (5.6%). Six patients developed malignancy. Among the side effects, 39.4% of side effects were dose-dependent. Among the patients, 38.1% had relapses requiring pulse corticosteroid therapy, and 16.2% had more than one relapse after commencement of AZA. AZA was continued till the last follow-up in 76.5%. Among the patients, 49.7% (UC 51.3, CD 48.8) attained durable remission without biologics, and 5.3% continued to have active disease.

Conclusion: AZA is safe and effective in the long-term in IBD. Effectiveness, tolerance, and compliance with AZA are well sustained beyond 5 years of usage and comparable between UC and CD.

Introduction

Inflammatory bowel disease (IBD) is an immune-mediated, chronic, life-long condition characterized by inflammation of the intestinal wall in the presence of various environmental factors in a genetically predisposed individual. It has a wide phenotypic spectrum ranging from limited colonic disease to disease involving both small and large intestine, and a clinical course ranging from prolonged quiescence to a relapsing, remitting form with continuous, active, steroid-dependent disease and related complications on the other end of the spectrum. Presence of a dysregulated, intestinal immune response warrants "immune modulation" as the primary mode of therapy in IBD. Thiopurine analogs such as 6-mercaptopurine (6-MP) and its prodrug azathioprine (AZA) are steroid-sparing, immunomodulator agents.[1,2] 6-thioguanine nucleotides (6-TGNs) are the predominant active metabolites responsible for their therapeutic efficacy, whereas 6-methyl-mercaptopurine (6-MMP) levels correlate with their side effects.[3-5] 6-TGNs exert their immunosuppressive effect by targeting leukocytes and inhibiting their DNA synthesis and downstream T-cell proliferation.[2,6-9] They also down-regulate the expression of multiple pro-inflammatory and gut-homing factors.[9]

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Thiopurine analogs form the mainstay of treatment for "maintenance" of durable remission and prevention of clinical relapses in both Crohn's disease (CD) and ulcerative colitis (UC), based on the course and severity of the disease. Specific evidence-based indications for AZA in UC include co-therapy during induction of remission in steroid-dependent active disease; subsequent therapy following response to cyclosporine (CSA) or tacrolimus in steroid-refractory acute severe UC; as adjunct to biologics such as infliximab (IFX); and intolerance or early/frequent relapse with mesalamine during maintenance of remission.[10-12] Similarly, evidence-based indications for AZA in CD include concomitant therapy with IFX in inducing remission in moderate-to-severe CD with an inadequate response to conventional therapy and induction and maintenance of remission in steroid-dependent CD.[13,14] At present, there is insufficient evidence to suggest their role as monotherapy or as adjuncts in inducing remission in peri-anal, fistulizing CD. The rationale behind the combination of anti-tumor necrosis factor (anti-TNF) agents, especially infliximab (IFX) with thiopurines, is to reduce immunogenicity or antibody formation against these biologics and/or increase trough levels of IFX and thereby efficacy of treatment.[15-17]

AZA has a slow onset of action, which peaks at around 17 weeks.[18,19] Sustained AZA usage is often plagued by dose-dependent as well as dose-independent adverse effects such as myelotoxicity, gastrointestinal disturbance, hepatotoxicity, pancreatitis, fever, and rash.[20] There are also reports of malignancies such as non-Hodgkin's lymphoma and nonmelanoma skin cancer (NMSC) associated with long-term AZA usage.[21,22] The onset of AZA-related adverse events in the initial 3–6 months of treatment precludes its usage at an optimal dose and duration essential to induce an immunomodulator effect in affected patients. A retrospective analysis of two 8-year intercept cohorts had previously revealed that thiopurines were discontinued in 57% of IBD patients at the end of 5 years due to reasons such as adverse effects (39%), refractoriness (16%), and ongoing remission/patient's request (4%).[23] Levels of the AZA metabolite, 6-MMP, typically determine the incidence of most adverse effects associated with AZA.[3,4,9] Individual variations in drug metabolism often account for differences in therapeutic efficacy and development of adverse reactions in IBD patients. Aberration in AZA metabolism is largely governed by polymorphisms and variants in genes that determine the activity of key enzymes such as thiopurine methyl-transferase (TPMT) and Nudix Hydrolase 15 (NUDT-15). Certain TPMT gene polymorphisms divert 6-MP catabolism toward excess 6-MMP formation and away from the active metabolite 6-TGNs.[2,3,24,25] NUDT-15 hydrolyses thiopurine effector metabolites and its mutations lead to accumulation of these metabolites and resultant cytotoxicity. The incidence of these polymorphisms varies significantly across different ethnicities, with NUDT-15 mutation being more prevalent in IBD patients with an Asian ancestry.[26-30]

There is a dearth of real-world data regarding durable effectiveness, safety, and clinical outcomes associated with long-term AZA usage. The recent European Crohn's and Colitis Organization (ECCO) guidelines on management of UC and CD highlight the lack of evidence to form recommendations regarding long-term safety, dose reduction, or withdrawal of thiopurines in IBD patients with stable long-term remission.[13] From an IBD patient's perspective, prolonged clinical remission often generates a false sense of disease cure, leading to medication noncompliance in the remission phase and resultant breakthrough symptoms or disease flares. These factors jointly account for reasonable apprehension among physicians as well as patients regarding long-term effectiveness, safety profile, and need for prolonged usage of AZA in IBD. The objective of the present study was to evaluate the real-world outcomes of AZA exposure in a mixed cohort of IBD patients followed up over a prolonged course of time.

Methods

Data collection. This was a retrospective analysis of a prospectively followed-up cohort of IBD patients under treatment at the Institute of Gastroenterology, Hepatobiliary Sciences and Transplantation, SRM Institutes for Medical Science, a multidisciplinary, tertiary care referral center in Chennai in south India, between the years 2013 and 2022. Apart from catering to the local urban population, the institute frequently receives regular as well as complicated IBD referrals from different states on the eastern coast of India and neighboring countries. The study protocol was approved by the Institutional Ethics Committee prior to commencement of data collection. Clinical notes from a prospectively maintained electronic database of all IBD patients referred/diagnosed and treated at the Institute over the previous decade were reviewed. These patients had been under regular follow-up till the time of data retrieval and analysis in March–April 2022.

Baseline characteristics such as age, gender, type of IBD, duration of disease, disease profile (extent, clinical severity, Mayo endoscopic score at diagnosis of UC, Montreal classification of disease of CD), treatment regime, complications, and duration of follow-up were noted for all study participants. For patients who received AZA, both historic as well as initiated at our clinic, we collected additional data such as time to initiation of AZA after diagnosis of IBD, "starting" and "maximum attained dose" of AZA (mg/kg), compliance, breakthrough flares, number of clinical relapses necessitating steroid use/escalation to biologics while on AZA, need for surgical management while on AZA, adverse events associated with AZA, duration to onset of adverse events, response to adverse events (dose reduction, temporary withdrawal, discontinuation), duration of AZA exposure, whether patient remained on AZA at the point of last follow-up and clinical outcome at the point of last follow-up. In patients who attained durable, clinical remission at the point of last follow-up, usage of concomitant medication such as 5-aminosalicylates (5-ASA) and biologics was noted. For patients who had not followed up as outpatients in the 12 months prior to analysis, a telephonic follow-up was conducted to determine their present clinical status and AZA-related events. Patients who were lost to follow-up after index consultation were excluded from the analysis. Effectiveness outcomes were assessed only in patients who received AZA ± 5-ASA for a minimum of 3 months.

Outcomes. Our primary objective was to evaluate the long-term effectiveness and safety profile of AZA. "*Effectiveness*" of AZA in real-world settings was determined based on the attainment of durable, clinical remission at the point of last follow-up.

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"*Clinical remission*" was assessed by a combined evaluation of factors such as symptomatic improvement along with various hematologic, biochemical, and inflammatory parameters as deemed necessary by the treating team of gastroenterologists. "*Durability*" of remission was determined by the absence of need for corticosteroid medication and/or not more than one clinical relapse after induction of remission. "*Clinical relapse*" was defined as the recurrence of symptoms with or without derangement in hematologic, biochemical, and inflammatory parameters after induction of clinical remission. A "*breakthrough*" episode was defined by recurrence of symptoms or a clinical flare-up, in a "noncompliant" patient after induction of remission. Patients who had ongoing disease activity or those who continued to require corticosteroids (steroid-dependent) or had more than one clinical relapse after commencement of AZA were identified as "*nonresponders*." We also examined "*AZA-tolerance*" by assessing the incidence, type, time to onset of adverse events, and the subsequent amendment in treatment regime. Adverse events, which abated after dose reduction or temporary withdrawal of AZA, were classified as "*dose-dependent*" and those precluding further use of AZA were identified as "*dose-independent*."

Statistical analysis. Descriptive statistics of the clinical characteristics were calculated, with continuous variables expressed as medians with the inter-quartile range (25th–75th percentile) and categorical variables as frequencies and percentages. Duration, tolerance, and compliance to AZA therapy were calculated from initiation to point of last follow-up and summarized using Kaplan–Meier estimates. Statistical analyses were performed using IBM SPSS v20.0 (IBM North America, 590 Madison Avenue, NY, USA).

Results

Baseline characteristics. Five hundred and seven patients with IBD, were seen at our institute between March 2013 and 2022, amongst whom complete follow up details were available in 472 (316 CD, 156 UC). Three hundred and twenty patients (207 CD, 113 UC) were prescribed AZA at some point of time after the diagnosis of IBD and formed the study cohort. One hundred and seventy-six patients (55%) were commenced on AZA right from the diagnosis of IBD. Our results are based on the assessment of a total of 1359 patient-years (16 308 months) of AZA exposure. Median time to initiation of AZA was 13 months (interquartile range [IQR] 5.8–48). Mean "initiation dose" of AZA was 0.97 mg/kg (range 0.5–1.25). Mean "maximum attained dose" of AZA was 1.72 mg/kg (range 1–3.75). Concomitant therapy in patients with AZA included oral/topical 5-ASA agents, oral/iv/topical corticosteroids, biologics (infliximab, adalimumab, vedolizumab, biosimilars), oral small molecules and surgical management for disease-related complications such as stricture, fistula, intra-abdominal abscess, bowel obstruction/perforation, and malignancy. Table 1 summarizes the baseline characteristics and outcomes of patients who received AZA stratified according to the IBD subtype.

Adverse events associated with AZA. A total of 72 episodes of adverse events were noted in 66 patients (20.6%) after commencement of AZA (Table 2). Median time to onset of side effects was 6 months (IQR 3–25.5). Myelotoxicity (AZA-induced cytopenia) was the most commonly observed adverse event (7.2%) with a median time to onset of 6 months (IQR 3–24.5). Various myelotoxic side effects seen included pancytopenia, bi-cytopenia, leukopenia, selective neutropenia, severe anemia, and pure-red cell aplasia. Five patients developed severe neutropenia requiring granulocyte-colony-stimulating-factor injections. One of the patients who had AZA-induced pancytopenia developed acute myeloid leukemia 6 months after the episode. However, AZA had been withheld in this case soon after the onset of pancytopenia. AZA could be restarted and continued, albeit at a lower dose, in 52.1% (12 of 23) patients who experienced myelotoxic side effects. Gastrointestinal intolerance was the second most frequently reported side effect (5.6%). Symptoms varied from nausea, vomiting, to severe abdominal pain. Three patients of CD developed self-limited episodes of acute, mild interstitial pancreatitis within few days of initiation of AZA and the drug was discontinued in all of them. Six patients (1.8%) developed AZA-induced hepatotoxicity. Biochemical derangement varied from transaminitis (<10 times ULN) in four patients, elevated alkaline phosphatase in one patient, and mixed features in one patient. None of these patients were symptomatic and these derangements were identified during routine liver biochemistry monitoring after initiation of AZA. Six patients developed infectious complications, which included herpes zoster, cellulitis, sepsis, urinary tract infections, emphysematous pyelonephritis, and intra-abdominal abscess. In addition, three UC patients on AZA had disease flares attributable to cytomegalovirus (CMV) super-infection, which was diagnosed on the basis of typical histopathological changes and detection of high quantities of CMV on tissue quantitative polymerase chain reaction (PCR). Six patients on long-term AZA developed a malignancy, which may or may not be directly attributed to AZA alone (CD—one case of acute myeloid leukemia, two cases of small bowel adenocarcinoma; UC—one case of colonic adenocarcinoma, one case of squamous cell carcinoma of the skin, and one case of squamous cell carcinoma of the eyelid). Other sporadic side effects noted were skin rash, arthralgia, fatigue, flu-like illness, ageusia, anosmia, hair loss, etc. The cumulative incidence of adverse events in our study were 2.2, 6.3, 10.3, 11.6, 14.7, and 19.4% at 1, 3, 6, 12, 24, and 60 months, respectively. The incidence of adverse events was comparable between UC and CD ($P = 0.779$).

In summary, 26 of 66 (39.4%) patients were considered to have dose-dependent side effects, which abated after dose modification/temporary withdrawal of AZA, and 40 of 66 (60.6%) were considered to have dose-independent side effects precluding further use of AZA. Figure 1 highlights various types of treatment interventions executed in the study cohort, on encountering an AZA-related adverse event. Figure 2 depicts reasons for discontinuation of AZA in the study cohort stratified according to the IBD subtype.

Follow-up clinical outcomes on AZA. Median duration of follow-up after initiation of AZA was 37.5 months (IQR 18–72). CD patients had a relatively longer duration of follow-up (median 40.5 months [IQR 21.75–73.5]). Median duration of AZA use was 33 months (IQR 11.75–60). Eighty-six patients

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Table 1 Baseline characteristics and outcomes of patients who received azathioprine (AZA)

Parameter	Total	Ulcerative colitis	Crohn's disease
AZA exposure (*n*, %)	320/472 (67.8%)	113 (72.4%)	207 (65.5%)
Age in years (median, IQR)	34 (26–48)	36.5 (28–48)	32 (24–47.5)
Gender (*n*)			
Male	216	74	142
Female	104	39	65
Disease profile		*Extent*	*Age*
		Proctitis (E1)—21	A1-41
		Left-sided colitis (E2)—36	A2-108
		Extensive colitis (E3)—56	A3-58
		Endoscopic severity	*Location*
		Mayo I—2	L1-47
		Mayo II—67	L2-24
		Mayo III—44	L3-136
		Clinical severity index (Truelove–Witt's criteria)	L4-10
		Mild—18	*Behavior*
		Moderate—86	B1-116
		Severe—9	B2-70
			B3-21
			Peri-anal modifier
			p-47
Treatment profile (*n*) (Drugs which the patients received at some point of time/for some duration of time during the course of their illness)			
Oral 5-ASA	308	102	206
Topical 5-ASA	38	36	2
Prednisolone	264	90	174
Budesonide	63	23	40
IV steroids	18	15	3
Mycophenolate mofetil	5	1	4
Infliximab	22	3	19
Adalimumab	23	2	21
Methotrexate	14	1	13
ATT	28	0	28
Topical steroid	15	15	0
Surgery	42	5	37
Oral small molecules	4	4	0
AZA initiated at the time of diagnosis of IBD (*n*, %)	176/320 (55%)	57/113 (50.4%)	119/207 (57.5%)
Time to initiation of AZA after diagnosis of IBD (months) (median, IQR)	13 (5.8–48)	23 (7.8–49.5)	11 (5–48)
AZA starting dose (mean, median, IQR)	0.97 mg/kg, 1 mg/kg (1)	0.97 mg/kg, 1 mg/kg (1)	0.97 mg/kg, 1 mg/kg (1)
AZA maximum dose (mean, median, IQR)	1.72 mg/kg, 1.8 mg/kg (1.5–2)	1.77 mg/kg, 2 mg/kg (1.5–2)	1.7 mg/kg, 1.7 mg/kg (1.5–2)
Duration of follow-up after initiation of AZA (months) (median, IQR)	37.5 (18–72)	36 (13.5–55)	40.5 (21.75–73.5)
Duration of AZA use (months) (median, IQR)	33 (11.75–60)	32.5 (11–52.75)	33.5 (12–63.25)
AZA compliance (*n*, %)	265/320 (82.8%)	90/113 (79.6%)	175/207 (84.5%)
Breakthrough flares among noncompliant (*n*, %)	40/55 (72.7%)	16/23 (69.6%)	24/32 (75%)
Voluntary/self-discontinuation of AZA (*n*, %)	21/320 (6.5%)	8/113 (7.1%)	13/207 (6.3%)
Clinical relapse after initiation of AZA (*n*, %)	122/320 (38.1%)	49/113 (43.3%)	73/207 (35.3%)
Requirement of surgical management while on AZA (*n*, %)	35/320 (10.9%)	2/113 (1.8%)	33/207 (15.9%)
AZA continued till last review (*n, %*)	245/320 (76.5%)	91/113 (80.5%)	154/207 (74.4%)
AZA exposure > 5 years (*n, %*)	86 (26.9%)	26 (23%)	60 (28.9%)
AZA exposure > 7 years (*n, %*)	46 (14.4%)	11 (9.7%)	35 (16.9%)
AZA exposure > 10 years (*n, %*)	19 (5.9%)	6 (5.3%)	13 (6.2%)
Total patient-years of AZA exposure (*n*)	1359	396	963

ASA, aminosalicylates; ATT, antituberculous treatment; IBD, inflammatory bowel disease; IQR, interquartile range; IV, intravenous.

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Table 2 Azathioprine (AZA) related adverse-event profile

AZA related adverse events	Total (*n*, %)	Ulcerative colitis (*n*)	Crohn's disease (*n*)	*P* value	Time to onset in months (median, range)
Myelotoxicity/cytopenia	23 (7.2%)	6	17	0.375	6 months (1–71)
GI intolerance	18 (5.6%)	5	13	0.615	6 months (1–85)
Infections	9 (2.8%)	6	3	0.072	6 months (1–71)
Hepatotoxicity	6 (1.8%)	1	5	0.429	6 months (2–41)
Flu-like illness/arthralgia	4 (1.25%)	2	2	0.616	6 months (1–48)
Malignancy	6 (1.8%)	3	3	0.669	56 months (49–81)
Acute pancreatitis	3 (0.9%)	0	3	0.554	6.25 months (2–11)
Skin rash	1 (0.3%)	0	1	1.000	36 months
Others (anosmia, dysgeusia, hair loss)	2 (0.6%)	1	1	1.000	1, 3 months
Total	72	24	48	0.779	6 months (3–25.5)

GI, gastrointestinal.

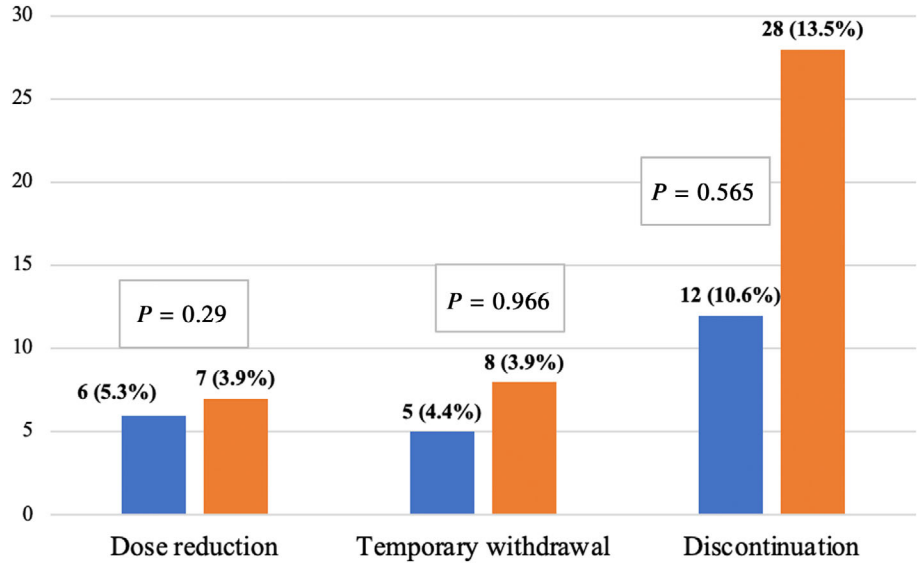

Figure 1 Type of intervention on encountering azathioprine-related adverse event. (■), Ulcerative colitis; (■), Crohn's disease.

(26.9%) received AZA for >5 years, 46 (14.4%) for >7 years, and 19 (5.9%) for >10 years. Overall, 82.8% patients exhibited compliance to AZA. Among them, 17.2% patients were irregular with AZA use and 72.7% of these experienced "breakthrough symptoms/clinical flares" after induction of remission. Among the patients, 6.5% of patients self-discontinued AZA in the remission phase due to clinical improvement and/or fear of side effects of prolonged AZA use; 38.1% experienced at least one clinical relapse during the follow-up period requiring pulse corticosteroid use; and 15.9% of patients with CD required some form of surgical treatment while on AZA. Two UC patients required colectomy while still on AZA, due to development of colonic adenocarcinoma and refractory pancolitis, respectively. AZA was continued till point of last follow-up in 245 of 320 patients (76.5%). At the point of last follow-up, 178 of 320 patients (55.6%) were in durable clinical remission. From the effectiveness analysis, 5.9% (19 of 320) of patients on combination therapy with biologics were excluded. Of the remaining, 9.1% (29/320) were on AZA monotherapy and 40.6% (130/320) were on combination therapy with 5-ASA. Among them, 5.3% (17 of 320) patients continued to have active disease and 16.2% (50 of 320) had more than one relapse after commencement of AZA (Fig. 3). Need for surgical intervention was significantly lower in UC in comparison with CD (1.8 *vs* 15.5%, $P = 0.0002$, respectively). On the other hand, a substantially higher proportion of patients with UC experienced more than one clinical relapse requiring steroid therapy while on AZA (27.4 *vs* 10.1%, $P = 0.0001$, respectively). No other significant differences were observed with regard to the outcome of durable clinical remission between patients with UC and CD. Figure 4 depicts the survival curve of patients who withdrew from AZA due to various reasons during the follow-up period. The key results of our study are summarized in Figure 5.

Discussion

The Indian subcontinent has witnessed a remarkable rise in the incidence and prevalence of IBD over the past few decades.[31]

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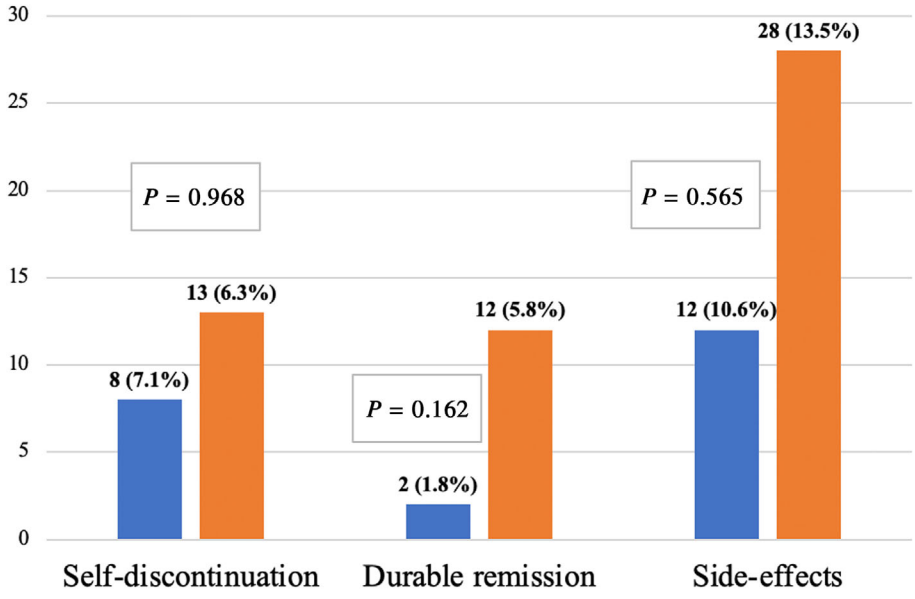

Figure 2 Reasons for discontinuation of azathioprine. (■), Ulcerative colitis; (■), Crohn's disease.

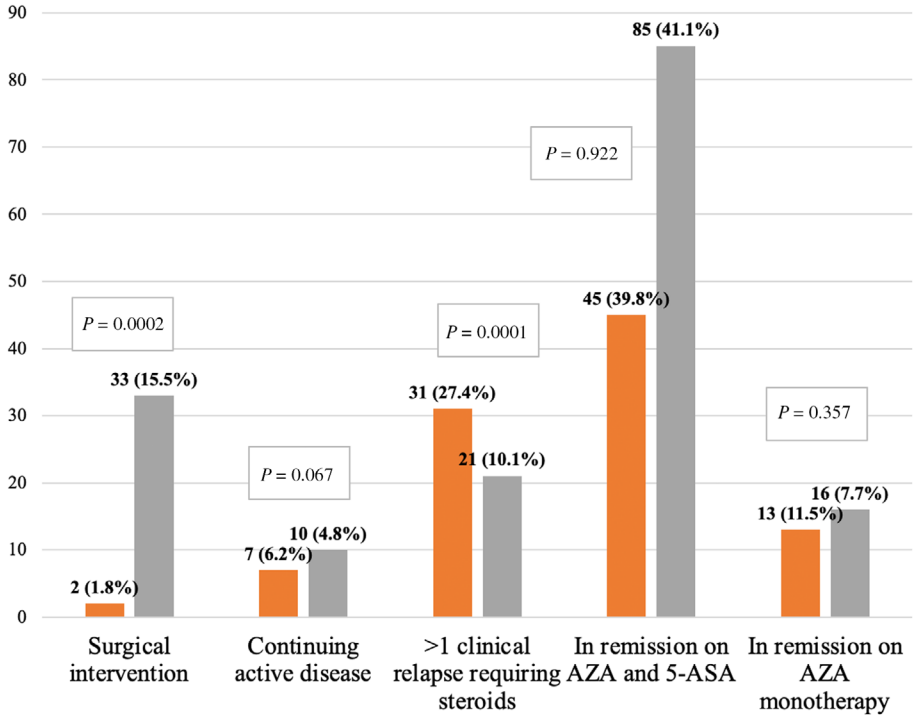

Figure 3 Outcome of azathioprine (AZA)-exposed patients at the point of last follow-up. (■), Ulcerative colitis; (■), Crohn's disease. ASA, aminosalicylates.

Logistic and financial constraints often confine biologic usage to a limited cohort of patients. AZA is frequently used as first-line therapy for maintenance of remission in CD and as second-line after mesalamine for maintenance of remission in UC. Despite widespread use, real-world data demonstrating durable effectiveness and safety of AZA are sparse and mostly derived from small cohorts with limited follow-up.[32–34] Long-term tolerance and durability form the key elements in planning therapy for IBD

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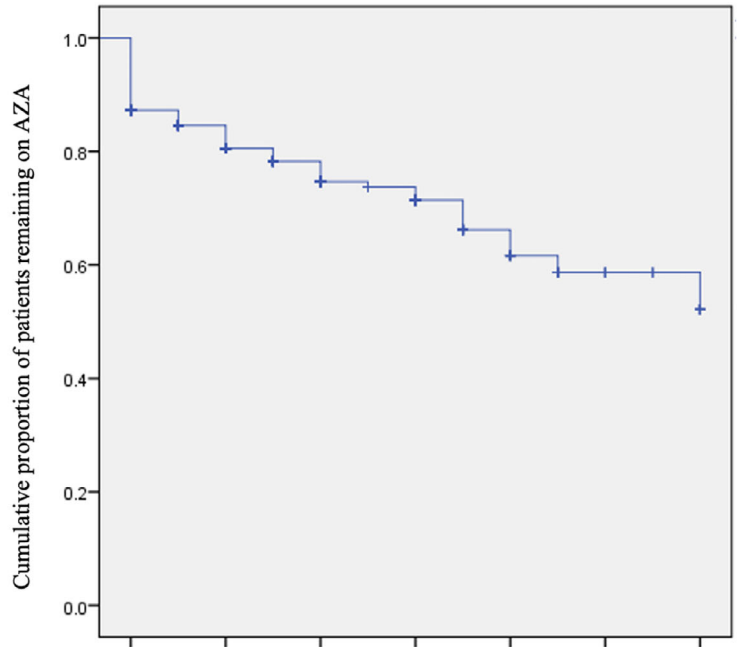

Patients (%)	87.1	82.1	79.6	78.7	77.1	76.8	76.5
Patients (*n*)	241	154	86	46	23	12	9

Figure 4 Survival curve of patients who withdrew azathioprine (AZA) due to "various reasons" such as adverse events, self-discontinuation, durable remission, pregnancy, ongoing treatment for infertility, surgery, and switch-over to biologics. Patients (*n*, %): Number/percentage of patients who remained on AZA at different time periods of follow-up.

given its chronic nature. Our study reports the adverse events and long-term clinical outcomes observed in a large, prospectively followed-up cohort of IBD patients on AZA.

Around one-fifth of the study cohort experienced some form of adverse event after commencement of AZA. However, AZA was eventually tolerated, albeit after temporary withdrawal and dose reduction in more than one-third of patients. A decade ago, the Spanish Working Group in Crohn's and Colitis had reported the long-term safety profile of thiopurines in a large cohort of 3931 IBD patients from a prospectively maintained Spanish database (ENEIDA) with a median follow-up of 44 months (range, 0–420). The study highlighted that the median time to onset of thiopurine-related adverse events was 1 month after starting treatment. Their cumulative incidence of adverse effects (26%) was higher than what was seen in our study (20.6%) and 17% of these patients had to discontinue thiopurine treatment. However, contrary to our report, more than half of the patients in this study tolerated thiopurine treatment upon re-initiation after dose adjustment. In addition, the study identified mercaptopurine treatment and female gender as risk factors for thiopurine-induced myelotoxicity.[35]

In our study, myelotoxicity led to discontinuation of AZA in a significant proportion of patients. This was probably because TPMT/NUDT-15 gene variant and quantitative red cell thiopurine metabolite testing were not easily accessible in our setting for a major duration of the study period. TPMT polymorphisms are known to have an impact on thiopurine toxic metabolite (6-MMP) as well as 6-TGN levels and are therefore routinely tested for, prior to commencement of AZA, especially in Western countries.[2,6,8,36,37] Recently, quite a few studies have reported that detection of NUDT-15 gene variant predicts thiopurine-induced leukopenia better than TPMT gene variants in Asian IBD patients.[26-30] Genetic and thiopurine metabolite testing may reduce apprehension in dose-escalation in tolerant patients and dose-adjustment or re-initiation of AZA in patients who have experienced a dose-dependent adverse effect of AZA in the near future. Thiopurine metabolite testing may also assist in identifying "hyper-methylators or metabolic shunters" who may benefit from the addition of allopurinol to low-dose AZA for long-term usage and prolongation of remission. Previously, a few observational studies have demonstrated favorable long-term safety and high efficacy of low-dose AZA and allopurinol co-therapy (LDAA) in thiopurine-naïve IBD patients as well as patients with active disease while on thiopurine monotherapy or those who experienced side-effects.[38-40] Other evidence-based strategies described in the literature to optimize thiopurine metabolite levels and reduce the incidence of side effects include substitution of AZA with 6-MP, desensitization, split-dosing, and usage of 6-thioguanine.[41-44]

Gastrointestinal intolerance was the second most common form of adverse event (5.6%) reported in our cohort. Although non-life-threatening, nausea, vomiting, and abdominal pain

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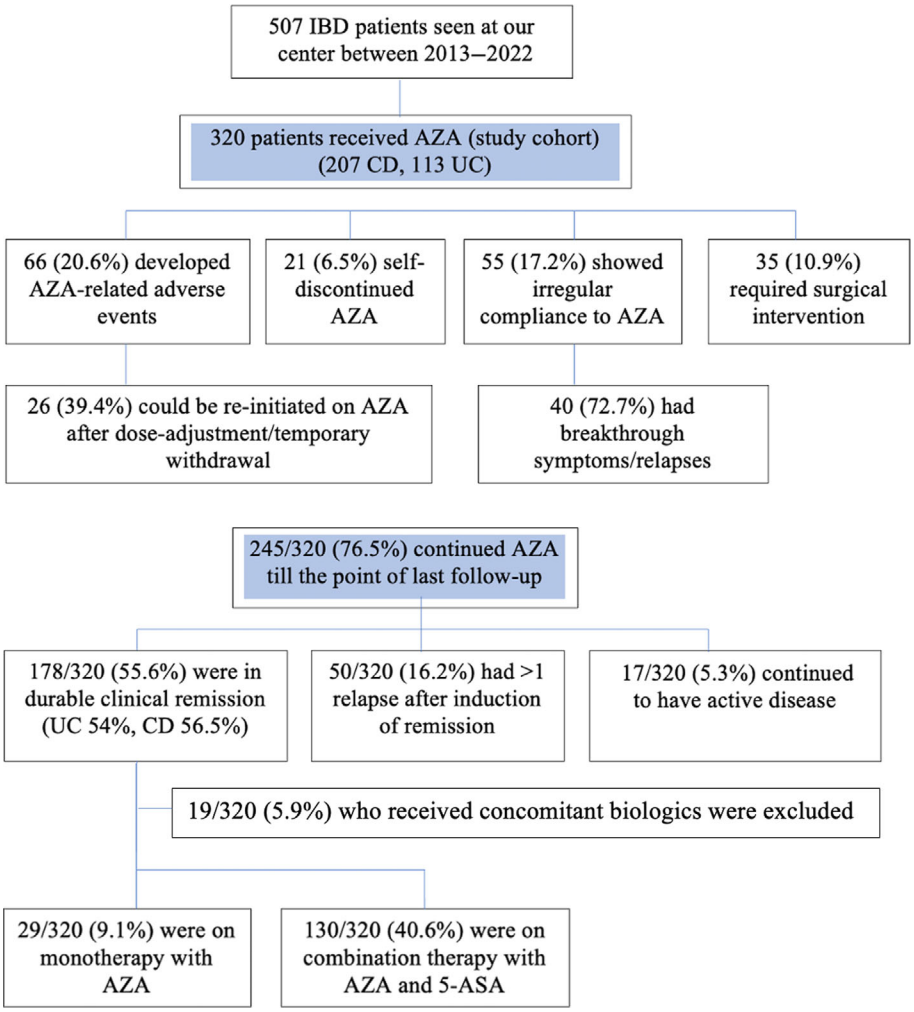

Figure 5 Flowchart of key results of the study. ASA, aminosalicylates; AZA, azathioprine; CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.

severely limit long-term compliance with thiopurines. It has been suggested that gastrointestinal intolerance might be caused by imidazole derivatives cleaved from the prodrug AZA, when its metabolite mercaptopurine is released.[41-45] Although a few patients (all CD) in our IBD database developed acute pancreatitis during the course of their natural history, only three of these patients were on AZA. The exact reason for this association seems unclear at present and is thus considered as an idiosyncratic side effect.

The prevalence of hepatotoxicity varies widely among different studies due to lack of a standardized definition. Exactly 1.8% of our cohort showed some form of asymptomatic liver biochemical derangement. This figure is somewhat lower than the cumulative incidence of thiopurine-induced hepatotoxicity reported in a systematic review, which was 3.4% with an incidence rate of 1.4% per patient-year of treatment.[46] In the Spanish study, 42% of patients with abnormal liver function tests were continued on thiopurine treatment after temporary withdrawal and resolution of derangement in liver enzymes, probably suggestive of hepatic adaptation rather than hepatotoxicity.[35] There are currently no established cutoff values for elevated liver enzymes to suggest discontinuation of thiopurine treatment.

Susceptibility to infections causes significant angst among IBD patients on immune-suppressive agents. This was one of the major causes of self-discontinuation of AZA seen in our patients in long-term clinical remission. The reported prevalence of infections in patients on thiopurines ranges from 0.3 to 7.4%.[47] A recent study concluded that the incidence of systemic serious viral infections in IBD tripled compared with the general population with clinically active IBD, and exposure to thiopurines was identified as the main driver of the risk.[48] In our cohort, 2.8% of patients on AZA developed infections such as herpes zoster, cellulitis, urinary tract infections, CMV, and neutropenic sepsis at varied time intervals after the commencement of AZA.

There have been concerns raised regarding safety issues associated with long-term usage of AZA. We observed that majority of the AZA-related side effects occurred within the first 6 months of starting AZA with only 1.2% of patients developing

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a new onset of side effects beyond 5 years of AZA usage. This pattern is in congruence with results from multiple other studies in the past and suggests that most patients who tolerate AZA in the initial few months of treatment may continue to do so in the longer run.[33–35] It also reiterates the need for strict adverse-event surveillance in the first few months after commencement of AZA. Regular clinical examination coupled with complete blood count and liver function test weekly during the first 2 months and once every 3 months thereafter are recommended by most guidelines on thiopurine surveillance.

The association between long-term thiopurine exposure and malignancies is complex. There may be an overlap of contributing factors such as concomitant medication, genetic and environmental factors, sporadic onset of malignancy, or the disease activity itself. Previously, it has been reported that the risk for developing lymphoma was fourfold higher among IBD patients exposed to thiopurines.[21] The CESAME study provided further evidence to this hypothesis and suggested a fivefold risk of lymphoproliferative disorders in IBD patients on long-term thiopurines.[49] Another UK population-based case–control study investigated the risk of cancer in IBD patients on AZA and concluded that diagnosis of lymphoma was associated with exposure to AZA with an odds ratio of 3.22 (confidence interval 1.01–10.18).[50] Fortunately, none of our patients developed lymphoma although we observed few other types of malignancies on long-term follow-up, two cases of small bowel adenocarcinoma, one acute myeloid leukemia (AML) in CD, one colonic adenocarcinoma, and two cases of squamous cell carcinoma of the skin and eyelid in UC. The patient who developed AML had discontinued AZA due to development of pancytopenia within a few months of AZA use. The three cases of intestinal adenocarcinoma may be due to the disease activity per se and AZA exposure may just be an incidental association. The association between long-term AZA exposure and NMSC has been previously reported too.[22] However, most recently, a longitudinal cohort analysis from north India, which evaluated 1093 IBD patients on AZA with a median follow-up of 7 years, reported that not a single patient on AZA developed lymphoma or NMSC.[51] Thus, at present, it may be safe to conclude that the benefits of long-term immune modulation with AZA significantly outweigh the minor risk of malignancy in patients with IBD.

Our study also assessed various clinical outcomes in patients on long-term AZA. Long-term tolerance and compliance to AZA were noted in more than 75% of the patients. A little less than a third of our study cohort was exposed to AZA for >5 years and nearly one-sixth of the cohort was on AZA for >7 years at the point of last follow-up. The mean "maximum attained dose" of AZA in our study (1.72 mg/kg) was lower than what is recommended and followed in Western countries, that is, 2–2.5 mg/kg body weight. Despite this, the end-point of durable, clinical remission was achieved in more than half of our patients (55.6%) who continued AZA till the point of last follow-up and 159 of 320 (49.7%) did not require the additional use of biologics. The cumulative effectiveness of AZA in patients who received "AZA monotherapy (9.1%)" and those who received "AZA in combination with 5-ASA (40.6%)" may be considered for assessment of "exclusive effectiveness of AZA" without biologics (49.7%). Some studies have demonstrated that Japanese IBD patients might reach sufficient 6-TGN values with substantially lower AZA dosages in comparison with Western population.[52] The role of ethnicity in determining AZA dosage recommendations needs further exploration. While 16% of CD patients on AZA in our study required some form of surgical intervention, only two patients with UC on AZA required colectomy. However, more than a third of the cohort had at least one clinical relapse requiring a short course of pulse corticosteroids while on AZA. At the point of last follow-up, less than one-fifth of our patients were identified to have a relapsing, remitting course having experienced more than one relapse after commencement of AZA. Previously, a 30-year review of patients attending the Oxford IBD clinic had established that efficacy of AZA in IBD was reasonably well sustained over 5 years.[53] Later, Chebli *et al.* in their long-term prospective study on 69 adults with steroid-dependent CD reported that clinical remission was more often maintained during the first 2 years of AZA therapy and the rate of failure increased significantly from 6.7 to 17.6% after this period.[32] In another study by Sood *et al.*, which assessed for sustained clinical remission at different time intervals of follow-up in 156 Indian patients with UC, it was observed that the therapeutic benefits of AZA lasted as long as 4 years.[33] In contradiction, a retrospective analysis of 255 patients with UC in England revealed that there was no significant difference in sustained, clinical benefit between patients receiving AZA for less than or more than 5 years.[34] Recently, a large, multicenter, retrospective study analyzing the long-term outcomes of AZA in 11 928 patients with IBD in the United Kingdom IBD bioresource concluded that thiopurine monotherapy was an effective long-term treatment, which prevented the need for escalation to biologics or surgical management in UC but significantly less in CD.[54] Thus, there is no definite consensus yet regarding the duration of thiopurine treatment in IBD. Relapses following cessation of treatment are common and response cannot always be recaptured.

Limitations associated with the study design need to be acknowledged while interpreting our results, especially regarding the long-term effectiveness of AZA. Due to nonuniformity in recorded data and variation in patient follow-up, we could not assess for more comprehensive, objective, and unbiased parameters of remission such as improvement in Harvey–Bradshaw index (HBI) for CD and Mayo score for UC. Clinical assessments were pragmatically performed as part of routine clinical practice rather than in the context of a predefined clinical trial protocol. In addition, heterogenicity in cohort disease behavior and severity may also have exerted an influence on AZA-related outcomes. Lastly, due to logistic reasons, AZA-related side effects seen in our cohort were classified as dose-dependent or independent based on ability to re-initiate the affected patients on AZA after dose adjustment rather than being directed by TPMT/NUDT-15 activity and red cell thiopurine metabolite levels. Nevertheless, this is one of the largest, single-center, long-term follow-up series reporting the challenges and outcomes associated with exposure to AZA in a real-world context. Since less than 10% of our cohort received biologics, we could investigate the outcomes of exclusive AZA ± 5-ASA therapy in most of our patients. Long-term follow-up and low attrition in cohort size in a real-world setting are the other highlights of our study.

In summary, long-term AZA therapy undirected by thiopurine metabolite levels and metabolic enzyme activity

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testing appears to be reasonably safe and clinically effective for maintaining durable clinical remission in IBD. Long-term data from real-world milieu and different treatment landscapes are vital for clinical decision-making and can seldom be retrieved from prospective clinical trials.[55,56] Our study results are reassuring and provide corroborative evidence to existing literature on the safety and effectiveness of AZA in the management of IBD in the long term. Large, multicenter studies on heterogenous IBD cohorts from different ancestries are perhaps the need of the future in order to provide more concrete evidence that translates into standard recommendations on duration of thiopurine use in IBD.

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