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Limited added value of laboratory monitoring in thiopurine maintenance monotherapy in inflammatory bowel disease patients

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Summary

Background: To timely detect myelotoxicity and hepatotoxicity, laboratory monitoring at 3-month intervals is advised throughout thiopurine maintenance treatment for IBD. However, reported incidence rates of myelotoxicity and hepatotoxicity in maintenance treatment are low.

Aim: To assess incidence rates and clinical consequences of myelotoxicity and hepatotoxicity in thiopurine maintenance therapy after at least 1 year of thiopurine treatment.

Methods: Retrospective analysis of therapy adjustment for laboratory toxicity in adult IBD patients after 12 consecutive months of azathioprine (AZA) or mercaptopurine monotherapy (ie baseline) between 2000 and 2016. Incidence rates of laboratory toxicity (ie myelotoxicity [leucocyte count <4.0 × 10e9/L, and/or platelet count <150 × 10e9/L] and/or hepatotoxicity (gamma-glutamyltransferase [GGT], alkaline phosphatase [AP], ALT and/or AST above ULN, excluding isolated increased AST/AP]) and associated diagnostic procedures and complications were assessed.

Results: In total, 12.391 laboratory assessments were performed on 1132 patients (56% female, AZA 74%) during 3.3 years of median follow-up. Median monitoring frequency was 3.1 assessments/treatment year. Only 83/12.391 (0.7%) assessments resulted in therapy adjustment, dose reduction in 46 patients, cessation in 28 and allopurinol initiation in nine; risk of therapy adjustment was 1.9% per treatment year. Incidence rates of myelotoxicity were 7.1% (5.1% mild/1.8% moderate/0.1% severe) and hepatotoxicity 5.1% (3.8% mild/1.1% moderate/0.2% severe) per treatment year. Treatment-related complications with concurrent laboratory toxicity occurred in 12 patients (1.1%) and would not have been prevented by monitoring.

Conclusion: Severe laboratory toxicity is uncommon after 1 year of thiopurine monotherapy at 4-month monitoring intervals. Therapy adjustments are rare after detection of laboratory toxicity. After 1 year of thiopurine monotherapy, laboratory monitoring may be lowered to less than a 4-month interval.

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1 | INTRODUCTION

Thiopurines, azathioprine (AZA) and mercaptopurine (MP), are an effective maintenance therapy for patients with IBD. Advantages of thiopurine therapy include a steroid-sparing effect, and its association with a reduced risk of colorectal carcinoma.[1-3] A recent study on the effect of thiopurines on the natural history of ulcerative colitis showed that thiopurine continuation was associated with a lower rate of hospital admission and a reduced risk of progression of disease extent and a colectomy.[1] Adverse events (AEs) are the most important downside of thiopurine therapy and result in therapy withdrawal in up to 40% of patients, primarily within the initial months of treatment.[4-6] These AEs can be divided into dose-independent events, such as pancreatitis and arthralgia and dose-dependent events. The most alarming dose-dependent AEs, hepatotoxicity and myelotoxicity, warrant laboratory monitoring, including a full blood count (FBC) and serum liver enzyme tests (LTs).[7] The risk of laboratory toxicity is high in the first year of treatment, which is reflected by high incidence rates of 11% for myelotoxicity and 13% for hepatotoxicity.[8-10] Myelotoxicity and hepatotoxicity rates may be reduced after the introduction of thiopurine S-methyltransferase (*TPMT*) genotype testing before and/or assessment of drug metabolites in thiopurine therapy.[7,11]

Safety concerns associated with thiopurines can be attenuated by the early identification of toxicity through routine laboratory monitoring and subsequent modification of therapy.[8,10-13] This potential benefit of laboratory monitoring should be balanced against the burden for patients and associated direct and indirect healthcare costs. Currently, international guidelines advise an intensive laboratory monitoring schedule in the first 3 months of treatment.[14] During subsequent maintenance therapy, routine laboratory monitoring at 2 to 3-month intervals is recommended. Laboratory toxicity is not always clinically relevant as it often reverses spontaneously.[9,10,15,16] Also, laboratory toxicity usually develops within the first few months of treatment and the reported incidence rate maintenance treatment is low.[9,10] In addition, leukopenia can develop at any time during treatment without preceding signs of myelotoxicity.[9,15] Therefore, frequent routine assessment of laboratory parameters in long-term maintenance thiopurine therapy may have a limited clinical impact. Data on therapy adjustments or diagnostic procedures based on toxicity found with laboratory monitoring are lacking. This study aims to assess the incidence rate and clinical consequences of myelotoxicity and hepatotoxicity detected with the current laboratory monitoring regimen in IBD patients who have been on thiopurine maintenance therapy for more than 1 year.

2 | MATERIALS AND METHODS

2.1 | Study design and patient selection

A retrospective cohort study was conducted in four tertiary referral centres and two teaching hospitals in the Netherlands. Adult IBD patients with confirmed diagnosis of Crohn's disease (CD), ulcerative colitis (UC), or IBD-unclassified (IBDU), treated with AZA or MP between 1 January 2000 and 31 December 2016 were included after 1 year of thiopurine treatment. Inclusion criteria were maintenance thiopurine monotherapy, defined as 12 consecutive months of treatment, and quiescent disease, defined as clinical, systemic steroid-free remission without the need for step-up treatment. Exclusion criteria were unavailability of laboratory assessments, a known history of chronic liver disease (ie viral hepatitis, auto-immune hepatitis, steatosis, primary sclerosing cholangitis, primary biliary cholangitis or liver cirrhosis), treatment with concomitant immunosuppressive medication (systemic corticosteroids, methotrexate, ciclosporin, tacrolimus, mycophenolate mofetil and/or biological agents) and thiopurine therapy for a non-IBD indication. In addition, patients with short bowel syndrome (<200 cm small bowel) were excluded from analysis, because of possible interference with thiopurine absorption. This study conformed to the principles of the Declaration of Helsinki and was approved by the institutional ethics review committee of the corresponding centre and all participating centres as per local regulations.

2.2 | Data collection

Baseline was set at the first laboratory assessment after 1 year of thiopurine treatment. Data collection was completed on 31 December 2016. The following patient characteristics were collected from the patient's electronic medical records: gender, weight, smoking status and IBD type and Montreal classification. Treatment characteristics included type of thiopurine, date of initiation, dosage, concomitant IBD medication and *TPMT* genotype. Laboratory results performed throughout maintenance thiopurine treatment (ie after 1 year of treatment) were recorded and screened for toxicity. Myelotoxicity was defined as leukopenia and/or thrombocytopenia. Leukopenia was classified as mild (3.0-4.0 × 10e9/L), moderate (2.0-3.0 × 10e9/L) and severe (<2.0 × 10e9/L). Thrombocytopenia was also classified as mild (100-150 × 10e9/L), moderate (50-100 × 10e9/L) and severe (<50 × 10e9/L). When both leukopenia and thrombocytopenia were detected within a laboratory assessment, myelotoxicity was graded based on the most severe detected value. Hepatotoxicity was defined as abnormal liver tests (LTs), ie an increase of alkaline phosphatase (AP), gamma-glutamyltransferase (GGT), alanine aminotransferase (ALT) and/or alanine aminotransferase (AST) above the upper limit of normal (ULN). Hepatotoxicity was classified into three grades according to the Common Terminology Criteria for Adverse Events (CTCAE) v. 4.0.[17] Grade 1 is defined as LTs between upper limit of normal (ULN) and 2.5xULN, grade 2 is between 2.5 and 5.0xULN and grade 3 is between 5.0 and 20.0xULN. In line with previous literature, an isolated increase in AP or AST <2.5xULN was not considered as hepatotoxicity as it is not necessarily a sign of liver injury.[10,18] When more than one aberrant LT was detected within a laboratory assessment, the grade of hepatotoxicity was based on the most severe detected value. When myelotoxicity and hepatotoxicity were detected in one assessment, the severity of "combined" toxicity was based on the most severe detected grade. Treatment changes and/or additional diagnostic procedures were recorded for patients with laboratory

toxicity. Patients were followed until treatment cessation or end of follow-up on 31 December 2016. Reasons for cessation of treatment included disease flare warranting step-up treatment or initiation of therapy with systemic (glucocortico)steroids, long-term remission, AEs, on patient initiative, family planning or loss to follow-up.

2.3 | Outcomes

The primary outcome was therapy adjustment based on laboratory toxicity, defined as therapy cessation, dose reduction or additional therapy with allopurinol alongside a reduced thiopurine dose (LDTA). Secondary outcomes were additional diagnostic procedures triggered by laboratory toxicity, incidence rates of myelotoxicity and hepatotoxicity and laboratory toxicity-related complications. Additional diagnostic procedures comprised extra laboratory assessments, abdominal ultrasonography, magnetic resonance imaging, bone marrow examination and liver biopsy. Complications associated with concurrent laboratory toxicity (including hospitalisation, surgery or infections) were classified according to the CTCAE (version 4.0) and categorised according to system organ class and severity. Severity was subdivided in grade 1 (asymptomatic or mild symptoms without indication for treatment or intervention), grade 2 (moderate symptoms; local or non-invasive intervention indicated), grade 3 (severe medically significant symptoms, invasive treatment and/or hospitalisation indicated), grade 4 (life-threatening consequences) or grade 5 (death related to AE). Only therapy-related clinical complications were included in the analysis.

2.4 | Statistics

The primary outcome of this study was defined as therapy adjustments based on laboratory toxicity. For Kaplan-Meier survival analyses, patients without therapy adjustments were censored at time of last follow-up or treatment cessation for other reasons than laboratory toxicity. Characteristics between patients with and without AEs were compared using the chi-square test for dichotomous variables, and student's *t* tests or Mann–Whitney U tests were used for continuous variables. Univariate and multivariable Cox proportional hazards models and logistic regression models were performed to assess risk factors of patient characteristics and laboratory covariates associated with therapy adjustments, and the time of development of laboratory toxicity. Variables with a $P < 0.20$ were included in a multivariate Cox proportional hazard model. Incidence rates of myelotoxicity and hepatotoxicity were expressed as the percentage of patients with detected laboratory toxicity per patient per treatment year (abbreviated as treatment year). Cumulative incidence of myelotoxicity and hepatotoxicity was calculated using Kaplan-Meier estimates, and stratified according to the most severe value (mild, moderate or severe toxicity), with time to event set at the first event in the corresponding category of severity. Detection rates of myelotoxicity and hepatotoxicity were expressed as the percentage of laboratory assessments showing signs of toxicity. The AZA drug dose was calculated into an equivalent pharmaceutical MP dose with a conversion factor of 2.08 based on molecular weight and bioavailability, the so-called AZA-adjusted dose.[19] Data are presented as median and its interquartile range for continuous variables when applicable. A value of $P < 0.05$ was considered to be statistically significant. All analyses were conducted using IBM SPSS Statistics V.22.0 (IBM).

3 | RESULTS

3.1 | Cohort characteristics

A total of 1132 IBD patients on long-term thiopurine treatment were included (56% female, median age 37 years (IQR 26-49). In total, 843 patients (74%) were treated with AZA (adjusted median dose 0.9 mg/kg [IQR 0.8-1.0]) and 289 patients (26%) were treated with MP (median dose 0.8 mg/kg [IQR 0.6-1.1]). Median follow-up until cessation of therapy or censoring was 3.3 years (IQR 1.7-5.6) (Table 1). Treatment was discontinued in 641 patients (57%) after median follow-up of 4.4 years (IQR 28-6.7). Main reasons for discontinuation were IBD flare in 265 patients (23%), sustained remission in 167 patients (15%), patient initiative in 70 patients (6%) and AEs in 70 patients (6%). These AEs comprised clinical AEs in 29 patients (2.6%) (general malaise n = 11, skin reactions n = 11, arthralgia n = 4, other n = 3) and laboratory toxicity in 41 patients (3.5%).

3.2 | Detection rate of myelotoxicity and hepatotoxicity

Overall, toxicity was detected in 2.030 (16%) of 12.391 laboratory assessments. During follow-up, 546 patients (48%) had signs of toxicity in one or more laboratory assessments. No difference was observed in monitoring rates between patients with or without laboratory toxicity ($P = 0.259$). Myelotoxicity was observed in 370 patients (33%) in 1066 assessments. Overall detection rate of myelotoxicity was 8.6% ie 7.6% for mild myelotoxicity, 0.9% for moderate myelotoxicity and 0.04% for severe myelotoxicity (Table 2). Hepatotoxicity was present in 275 patients (24%) in 950 assessments with an overall detection rate of 7.7% ie 6.7% for mild hepatotoxicity, 0.8% for moderate hepatotoxicity and 0.1% for severe hepatotoxicity (Table 2).

3.3 | Incidence rate of myelotoxicity and hepatotoxicity

3.3.1 | Myelotoxicity

The overall incidence rate of myelotoxicity was 7.1% per treatment year, specifically 5.2% for mild myelotoxicity, 1.8% for moderate myelotoxicity and 0.1% for severe myelotoxicity (Figure 1A). In addition to 9% of

TABLE 1 Baseline Characteristics

	N = 1132
Male sex, n (%)	500 (44)
Age (y), median [IQR]	37 [26-49]
Age at IBD diagnosis (y), median [IQR]	26 [20-36]
Weight (kg), median [IQR][a]	73 [64-85]
Diagnosis, n (%)	
Ulcerative colitis	363 (32)
Crohn's disease	736 (65)
IBD unclassified	33 (3)
CD—montreal age at diagnosis, n (%)	
A1 <17 y	93 (13)
A2 17-40 y	508 (69)
A3 >40 y	135 (18)
CD—montreal localisation, n (%)	
L1 ileal	239 (32)
L2 colonic	162 (22)
L3 ileocolonic	335 (46)
L4 upper GI disease	47 (6)
Perianal involvement	192 (26)
CD—montreal disease behaviour	
B1 nonstricturing, nonpenetrating	383 (52)
B2 stricturing	212 (29)
B3 penetrating	141 (19)
UC—Montreal disease extent[a,b]	
E1 proctitis	27 (7)
E2 left-sided	123 (33)
E3 extensive colitis	228 (60)
History of IBD related surgery, n (%)	334 (30)
Current smokers, n (%)[a]	241 (21)
Thiopurine therapy	
AZA	843 (74)
MP	289 (26)
Thiopurine dose (mg/kg), median [IQR][a,c]	
AZA, adjusted[d]	0.9 [0.8-1.0]
MP	0.8 [0.6-1.0]
Concomitant IBD medication, n (%)	481 (42)
5-ASA	382 (34)
Allopurinol + AZA/Allopurinol + MP	57 (5)/42 (4)
TPMT genotype, n (%)	
Normal	163 (14.4)
Heterozygote mutation	29 (2.6)
Homozygote mutation	1 (0.1)
Unknown	939 (82.9)

Note: Abbreviations: 5-ASA, 5-Aminosalicylic acid;AZA, azathioprine; IBD, inflammatory bowel disease; IQR, interquartile range; kg, kilogram; mg, milligram; MP, mercaptopurine; TPMT, thiopurine S-methyltransferase.

[a]Limited data for weight, n = 1124; for Montreal disease extent, n = 369; for smoking status n = 1020; for thiopurine dose, n = 1124; for TPMT genotype, n = 193.

[b]Combined for UC/IBDU.

[c]Excluding patients with concomitant use of allopurinol (n = 99).

[d]Adjusted AZA drug dose represents the equivalent pharmaceutical MP dose with a conversion factor of 2.08.

patients (n = 129) who showed myelotoxicity at baseline, cumulative incidence rates of myelotoxicity on maintenance thiopurine therapy were 12% at 1 year, 24% at 3 years and 29% at 5 years of follow-up. Median time to the development of myelotoxicity was 6 months from baseline (IQR 0-20). The majority of detected myelotoxicity in laboratory assessments was classified as mild toxicity (945/1066 assessments, 89%) and comprised leukopenia in 97% (1032/1066 assessments). Concomitant allopurinol treatment was a risk factor for myelotoxicity when compared to patients without laboratory toxicity (HR 1.59, 95% CI 1.04-2.43, $P < 0.034$) (Table 3). A borderline significant interaction was observed between MP and allopurinol ($P = 0.08$).

3.3.2 | Hepatotoxicity

The overall incidence rate of hepatotoxicity was 5.1% per treatment year ie 3.8% for mild hepatotoxicity, 1.1% for moderate hepatotoxicity and 0.2% for severe hepatotoxicity (Figure 1B). In addition to the 8% of patients (n = 91) who showed hepatotoxicity at baseline, cumulative incidence rates of patients who showed signs of hepatotoxicity were 6% at 1 year, 14% at 3 years and 21% at 5 years of follow-up. Median onset of hepatotoxicity was 9 months from baseline (IQR 0-26). In univariate and multivariate Cox regression analyses treatment with MP (HR 1.40 95% CI 1.10-1.78, $P < 0.006$) and concomitant use of allopurinol (HR 2.73 95% CI 1.56-4.79, $P < 0.0001$) were associated with an increased risk of hepatotoxicity in long-term thiopurine treatment (Table 3). No interaction was observed between MP and allopurinol.

In univariate and multivariate Cox regression analyses, male gender (hazard ratio [HR] 1.302; 95% confidence interval [CI] 1.10-1.54, $P < 0.009$), treatment with MP (HR 1.56 95% CI 1.30-1.87, $P < 0.0001$) and diagnosis of UC/IBDU (HR 1.27 95% CI 1.09-1.54, $P < 0.003$) were associated with an increased risk of laboratory toxicity of any type in long-term thiopurine treatment (Table 3). No differences in overall toxicity, myelotoxicity and hepatotoxicity were observed in patients with TPMT abnormalities. Notably, thiopurine dose in patients with intermediate TPMT activity (0.78 mg/kg ± 0.27) was significantly lower than in patients with normal TPMT activity (0.90 mg/kg ± 0.26) ($P = 0.027$).

3.4 | Clinical consequences of laboratory toxicity

3.4.1 | Therapy adjustments for toxicity

After detection of laboratory toxicity, therapy adjustments were performed in 83 patients (7.3%) after a median follow-up time of 1.8 years (IQR 0.5-3.5). Overall, 0.7% (83/12.391) of laboratory assessments in this cohort resulted in a therapy adjustment. These therapy adjustments comprised therapy cessation (n = 28, 34%), dose reductions (n = 46, 55%) and switch to LDTA therapy (n = 9, 11%) (Table 4). Reasons for therapy cessation in these 28 patients were myelotoxicity (n = 14), hepatotoxicity (n = 9) and combined toxicity

TABLE 2 Detection rate of laboratory toxicity

	Patients n = 1132	Overall assessments n = 12 874
Median monitoring frequency/treatment year, n (IQR)	3.1 [2.2-3.9]	—
Detection of laboratory toxicity, n (%)	546 (48.2)	2030 (16.4)
Myelotoxicity, n (%)	370 (32.7)	1066 (8.6)
Mild	284 (25.1)	945 (7.6)
Moderate	82 (7.2)	116 (0.9)
Severe	4 (0.4)	5 (0.04)
Hepatotoxicity, n (%)	275 (24.3)	950 (7.7)
Mild	229 (20.2)	836 (6.7)
Moderate	38 (3.4)	101 (0.8)
Severe	8 (0.7)	13 (0.1)

Abbreviation: IQR, interquartile range.

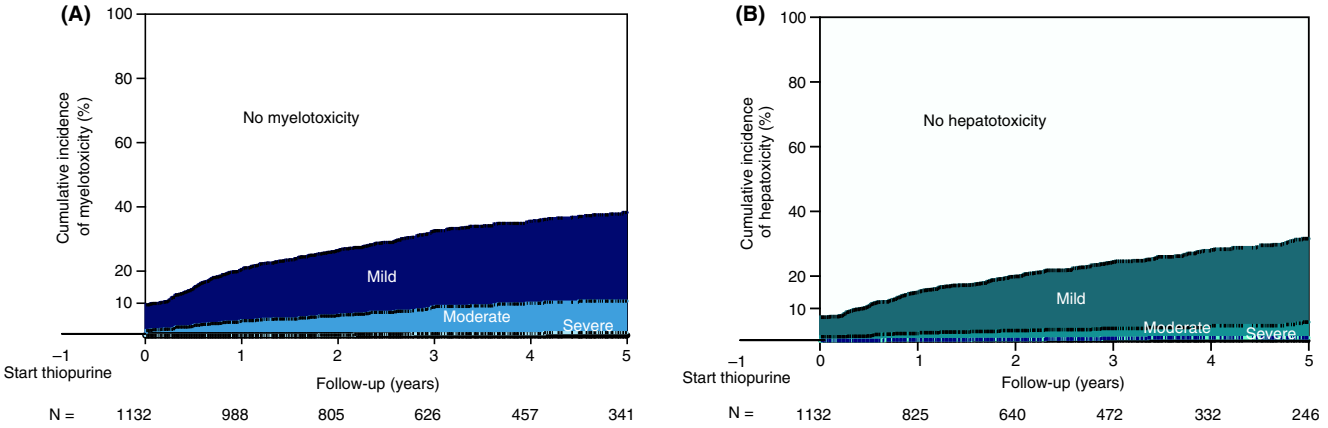

FIGURE 1 incidence rate of laboratory toxicity. Cumulative incidence of laboratory toxicity, stratified according to severity of myelotoxicity (A) or hepatotoxicity (B). A, Patients were categorised based on the most severe value of myelotoxicity detected during follow-up, with time to event set at first event in the corresponding category of severity. The black area represents severe myelotoxicity (n = 6); the dark grey area represents moderate myelotoxicity (n = 83); the grey area represents mild myelotoxicity (n = 282); the light grey area represents patients without myelotoxicity (n = 761). B, Patients were categorised based on the most severe value of hepatotoxicity detected during follow-up, with time to event set at first event in the corresponding category of severity. The black area represents severe hepatotoxicity (n = 8); the dark grey area represents moderate hepatotoxicity (n = 38); the grey area represents mild hepatotoxicity (n = 253); the light grey area represents patients without hepatotoxicity (n = 833)

(n = 5). Dose reductions were performed for myelotoxicity in 38/46 patients (83%), hepatotoxicity in 7/46 (15%) patients and combined toxicity in 1/46 patients (2%). Treatment with LDTA was initiated for hepatotoxicity in 6/9 (67%) patients and for myelotoxicity in 3/9 patients (33%). The overall incidence rate for treatment adjustment in patients on maintenance thiopurine treatment after detected laboratory toxicity was 1.9% per treatment year. Cumulative incidence rate of therapy adjustments were 2.5% at 1 year, 6.2% at 3 years, 8.9% at 5 years and 15.4% at 10 years of follow-up (Figure 2). A higher thiopurine dose (HR 3.1 95% CI 1.5-6.4, $P < 0.004$), higher annual monitoring frequency (HR 1.01 95% CI 1.00-1.01, $P < 0.0001$) and higher number of aberrant assessments (HR 1.04 95% CI 1.04-1.05, $P < 0.0001$) were independently associated with therapy adjustments. No correlation was observed between annual monitoring rate and the number of aberrant assessments (Spearman correlation $R = 0.09$, $P = 0.762$).

3.4.2 | Monitoring rate

The median monitoring frequency was 3.1 laboratory assessments per treatment year (IQR 2.2-3.9) with a slight decreasing trend in monitoring rate over time, ranging from 3.1 assessments in the first year of follow-up (monitoring interval 3.9 months) to 2.0 assessments per year (monitoring interval 6.0 months) after 6 years of follow-up. The mean monitoring interval in patients receiving a therapy adjustment (3.3 months, SD 1.8) was shorter (ie more stringent) than in patients without an adjustment (4.1 months, SD

TABLE 3 Univariate and multivariate Cox proportional hazards regression analysis to explore factors associated with development of laboratory toxicity (A) myelotoxicity (B) or hepatotoxicity (C) in patients on long-term maintenance thiopurine therapy

	Laboratory toxicity				Myelotoxicity		Hepatotoxicity			
	Univariate analysis		Multivariate analysis		Univariate analysis		Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Male gender	1.30 (1.10-1.54)	0.002*	1.29 (1.09-1.52)	0.009	1.13 (0.92-1.40)	0.240	1.13 (0.90-1.42)	0.309		
Mercaptopurine[a]	1.56 (1.30-1.87)	<0.0001*	1.56 (1.30-1.87)	<0.0001	1.02 (0.81-1.29)	0.869	1.46 (1.15-1.85)	0.002*	1.40 (1.10-1.78)	0.006
Ulcerative colitis/ IBDU[b]	1.30 (1.09-1.54)	0.003*	1.25 (1.06-1.49)	0.003	1.10 (0.89-1.35)	0.399	1.07 (0.84-1.35)	0.601		
Previous surgery	0.90 (0.75-1.09)	0.821			0.96 (0.75-1.19)	0.626	0.89 (0.70-1.15)	0.377		
Current smoking	0.80 (0.64-1.01)	0.055			0.80 (0.60-1.07)	0.795	1.12 (0.83-1.51)	0.460		
Concomitant allopurinol	1.45 (0.93-2.27)	0.317			1.59 (1.04-2.43)	0.034	1.75 (1.16-2.66)	0.008*	2.73 (1.56-4.79)	<0.0001
Concomitant 5-ASA	1.12 (0.90-1.39)	0.102			1.04 (0.82-1.33)	0.751	0.83 (0.62-1.10)	0.186		

Note: Laboratory toxicity was defined as any type of myelotoxicity and/or hepatotoxicity.

Abbreviations: 5-ASA, 5-aminosalicylic acid; CI, confidence interval; HR, hazard ratio; IBDU, inflammatory bowel disease unclassified.

[a]Drug type, mercaptopurine vs azathioprine.

[b]IBD diagnosis, UC/IBDU vs. Crohn's disease.

*Covariates with a *P* value < 0.2 were included in the multivariable regression analysis.

TABLE 4 Clinical consequences of laboratory toxicity

	Patients n = 1.132	Laboratory assessments n = 12.391
Therapy adjustments, n (%)	83 (7.3)	83 (0.7)
Cessation	28 (2.5)	28 (0.2)
Dose reduction[b]	46 (4.1)	46 (0.4)
LDTA therapy	9 (0.8)	9 (0.1)
Median time to adjustment, IQR	1.8 [0.5-3.5]	—
Indication therapy adjustment, n (%)		
Myelotoxicity	55 (3.0)	55 (0.4)
Mild/moderate/severe	17/36/2	
Hepatotoxicity	22 (3.9)	22 (0.2)
Mild/moderate/severe	14/6/2	
Myelotoxicity and hepatotoxicity	6 (0.4)	6 (0.05)
Mild/moderate/severe	2/3/1	
Diagnostic procedures, n (%)	111 (9.8)	154 (1.2)
Laboratory assessment[a]	86 (7.6)	121 (1.0)
Ultrasound[a]	19 (1.8)	22 (0.2)
MRI/MRCP	6 (0.5)	6 (0.05)
Ultrasound and liver biopsy[b]	5 (0.4)	5 (0.04)
Indication diagnostic procedure, n (%)		
Myelotoxicity	56 (4.9)	67 (0.5)
Hepatotoxicity	47 (4.2)	77 (0.6)
Myelotoxicity and hepatotoxicity	8 (0.7)	10 (0.1)
Complications, n (%)	12 (1.1)	12 (0.1)
Infections	7 (0.6)	7 (0.06)
Blood and lymphatic system	4 (0.4)	4 (0.03)
Gastro-intestinal disorders	1 (0.1)	1 (0.01)

Note: Complications included 6 grade 1 complications, 9 grade 2 complications and 11 grade 3 complications.

Abbreviations: IQR, interquartile range; MRCP, Magnetic Resonance Cholangio-Pancreatography; MRI, magnetic resonance imaging.

[a]13 patients received extra laboratory assessments and ultrasound.

[b]Performed within a trial.

2.1, $P < 0.0001$). Also, the mean monitoring interval in patients receiving a therapy adjustment was shorter than in patients with laboratory toxicity but without an adjustment (4.2 months, SD 2.0, $P < 0.0001$). No difference was observed in the mean monitoring interval in patients with laboratory toxicity (4.0, SD 2.0) and patients without toxicity (4.1, SD 2.2) ($P = 0.757$). In patients receiving a therapy adjustment, the antecedent-monitoring interval was not significantly different from the mean monitoring interval (3.8 months [SD 3.7] vs. 3.3 months [SD 1.8], $P = 0.154$). When comparing the incidence rate of toxicity in patients on the most stringent monitoring regime (upper quartile [mean monitoring interval 2.3 months]) with patients on the most liberal monitoring regime (in the lower quartile [mean monitoring interval 6.3 months]) no differences were observed in *overall* laboratory toxicity. However, the incidence rates of moderate leukopenia and severe hepatotoxicity were higher in patients on a stringent monitoring regimen than in patients on a liberal monitoring regimen (12% vs 4.2%, $P = 0.001$) (5% vs 0%, $P = 0.025$). Details are depicted in Table 5. Cumulative incidence rate of therapy adjustments throughout follow-up was higher in patients on a stringent monitoring regimen than on a liberal monitoring regimen (Figure S1).

3.4.3 | Diagnostic procedures

Additional diagnostic procedures following established laboratory toxicity were performed in 154 aberrant laboratory assessments (7.6%) in 111 patients (9.8%). Overall, 1.2% of all assessments resulted in additional diagnostic procedures (Table 4). Most physicians followed-up on detected toxicity through extra laboratory assessments (121 assessments in 86 patients), and 55% of these additional assessments were triggered by myelotoxicity. Ultrasound was performed after established hepatotoxicity in 27 patients (2.4%). No cases of nodular regenerative hyperplasia were reported.

3.4.4 | Complications

Clinical treatment-related complications with concurrent laboratory toxicity were detected in 12 patients (1.1%) in this cohort. The incidence rate of treatment-related complications with concurrent laboratory toxicity was 0.27% per treatment year (Table 4). Details on treatment-related complications are depicted in Table 6. Complications were more often observed in patients treated with MP than in AZA-treated patients (n = 6, 2.1% versus n = 6, 0.7%, $P = 0.015$). Complication rate was higher in patients on a stringent monitoring regimen than in patients on a liberal monitoring regimen (2.8% vs 0.4%, $P = 0.019$) (Table 5). Stringent monitoring remained associated with a higher complication rate when excluding all laboratory assessments after the onset of complications. Strikingly, 3/12 patients (25%) developed mild myelotoxicity, 1/12 (13%) patients developed moderate myelotoxicity prior to complications and 8/12 patients (67%) presented with clinical symptoms and had no signs of toxicity in the preceding laboratory assessments. Five of these eight patients received stringent laboratory monitoring. No mortality was observed.

4 | DISCUSSION

Frequent laboratory monitoring is advised throughout thiopurine maintenance treatment to detect myelotoxicity and hepatotoxicity. However, laboratory toxicity usually develops within the first few months of treatment and the reported incidence rate in maintenance treatment is low. This large cohort study has demonstrated that current laboratory monitoring regimen has limited value in patients on

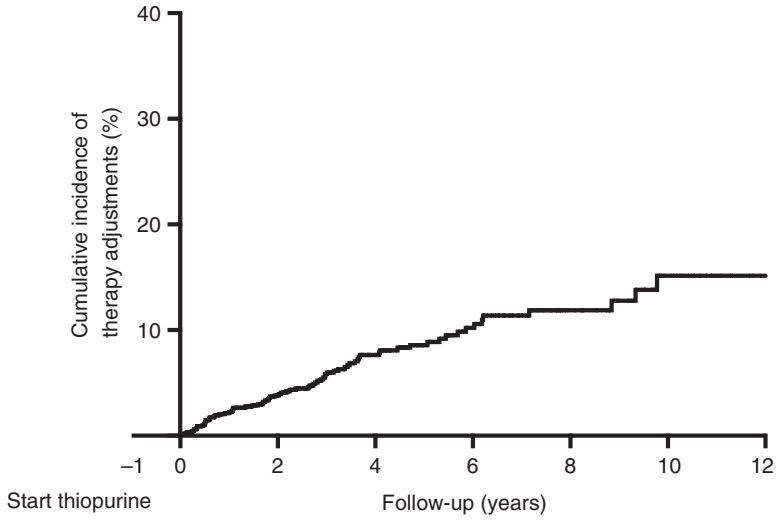

FIGURE 2 Cumulative incidence of therapy adjustments during thiopurine treatment for laboratory toxicity

Patients at risk	1132	779	428	243	123	58	30
All adjustments	0	43	67	76	81	83	83
Cessation	0	13	21	25	28	28	28
Dose reduction	0	27	38	43	44	46	46
LDTA	0	3	4	8	8	9	9

TABLE 5 Detection rate of laboratory toxicity stratified for monitoring rate

	Patients n = 1132	Liberal monitoring n = 283	Stringent monitoring n = 283	*P* value
Median monitoring rate/ treatment year, n (IQR)	3.1 [2.2-3.9]	1.8 [0.0-2.0]	4.8 [4.3-6.3]	
Mean monitoring interval (mo), (SD)	4.1 (2.1)	6.3 (2.5)	2.3 (1.3)	<0.0001
Detection of laboratory toxicity, n (%)	546 (48.2)	117 (41.3)	136 (48.0)	0.128
Myelotoxicity, n (%)	370 (32.7)	75 (26.5)	100 (35.3)	0.023
Mild	284 (25.1)	63 (22.3)	65 (23.0)	0.841
Moderate	82 (7.2)	12 (4.2)	34 (12.0)	0.001
Severe	4 (0.4)	0 (0.0)	1 (0.4)	0.317
Hepatotoxicity, n (%)	275 (24.3)	51 (18.0)	69 (24.4)	0.081
Mild	229 (20.2)	45 (15.9)	53 (18.7)	0.347
Moderate	38 (3.4)	7 (2,5)	11 (3.9)	0.338
Severe	8 (0.7)	0 (0.0)	5 (1.8)	0.025
Treatment-related complications	12 (1.1)	1 (0.4)	8 (2.8)	0.019

Note: Liberal monitoring group comprises the lower quartile (lowest monitoring rate/treatment year) of the study population. Stringent monitoring group comprises the upper quartile (highest monitoring rate/treatment year) of the study population. *P* values concern differences between liberal and stringent monitoring. Treatment-related complications comprised complications associated with concurrent laboratory toxicity.

Abbreviations: IQR, interquartile range; SD, standard deviation.

thiopurine maintenance monotherapy for at least 1 year. Although the incidence of myelotoxicity was 7.1% and of hepatotoxicity 5.2% per treatment year, laboratory assessments had little impact on clinical decision making. Only 0.7% of laboratory assessments resulted in therapy adjustments, and only 1.4% to further diagnostic procedures. Furthermore, severe treatment-related complications, such as infection and hospitalisation, attributed to concurrent laboratory toxicity are rare and these complications were not prevented with

TABLE 6 Clinical treatment-related complications with concurrent laboratory toxicity

	Total n = 1132	Myelotoxicity	Hepatotoxicity	Myelotoxicity + Hepatotoxicity
Cytomegalovirus infection, n (%)	6 (0.5)	0 (0.0)	5 (0.4)	1 (0.1)
Blood transfusion[a], n (%)	2 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)
Hospital admission for gastroenteritis, n (%)	2 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)
Jaundice[b], n (%)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)

[a]Patients received a transfusion with packed red blood cells or iron for pancytopenia.

[b]Patient at stable thiopurine dose presented with jaundice and hepatotoxicity after weight loss due to gastric sleeve surgery.

current monitoring regimen as the majority of cases were not preceded by laboratory toxicity in previous assessments.

The incidence of myelotoxicity and hepatotoxicity is line with previous studies, although there is no universal standard definition of laboratory toxicity, and small sample size or short follow up in previou studies for comparison.[20-22] Myelotoxicity incidence in our study of 7.1% per treatment year of follow-up is based on stringent criteria and ranged from 5.1% for mild myelotoxicity, 1.8% for moderate myelotoxicity to 0.1% for severe myelotoxicity. Myelotoxicity incidence was evaluated in a review of studies, in which myelotoxicity definition varied from leucocyte count of <2.0 × 10e9/L to < 4.5 × 10e9/L. As expected, a higher incidence rate of 11% in the first year of treatment was reported than in our study. Nevertheless, the overall range of incidence rate of myelotoxicity incidence of 3%-8% per treatment year is compatible with our findings for maintenance treatment.[9]

In our study, hepatotoxicity incidence was 5.1% per treatment year. While incidence rates of 0%-17% have been reported in other studies, possibly attributable to the heterogeneity of definitions, our findings are in line with large cohort studies that have reported incidence rates of 4% and 7%.[8,20,23,24] Furthermore, the moderate to severe hepatotoxicity rate of 1.3% per treatment year in our cohort is in line with the rate of 1% per treatment year in other studies.[8,10]

In this study, the most stringent monitoring regimen was associated with increased incidence rates in moderate myelotoxicity and severe hepatotoxicity compared to the most liberal monitoring regimen. These results should be interpreted with caution, as the causal relation is unclear. The probability of detecting toxicity will increase with more frequent monitoring. Yet, abnormal laboratory values will urge physicians to increase the monitoring frequency to follow-up on toxicity. Thus, it cannot be concluded that more frequent monitoring is more likely to pick up toxicity, or that previously established toxicity increases the monitoring frequency without direct clinical consequences.

In our study, fewer therapy adjustments were made to thiopurine treatment as a result of laboratory toxicity than were reported in other studies.[25-28] Our study focused on the consequences of laboratory monitoring after 1 year of maintenance therapy in routine clinical practice and not on the consequences of laboratory findings shortly after initiation of thiopurines. In our study, laboratory toxicity resulted in therapy adjustment in 7% of patients during follow-up compared to reported rates of up to 15% in other studies. Furthermore, only 2.8% of patients in our cohort had to be withdrawn from therapy because of laboratory toxicity compared to 6%-13% of patients in other studies.[25-28] In line with the high risk of laboratory toxicity after the start of thiopurines compared to maintenance treatment, these results indicate that therapy withdrawal due to laboratory toxicity usually occurs within the first months of treatment rather than during maintenance treatment.[8,12,23]

Our study has shown that mild toxicity is often disregarded in clinical practice with respect to additional diagnostic procedures. Laboratory results may have been disregarded because of a presumed low association between mild myelotoxicity and increased risk of infections, and possibly favourable outcome of mild leukopenia on therapeutic effectiveness of thiopurines.[29]

A low risk of laboratory toxicity-associated complications was observed. Similarly, mild hepatotoxicity was often disregarded in our cohort probably because the association of transient hepatotoxicity with chronic liver disease is questionable. Laboratory toxicity-associated complications were detected in 1% of patients in our cohort. Only 33% of patients had signs of laboratory toxicity in previous assessments. We observed that 67% of these patients received stringent laboratory monitoring (upper quartile [highest] annual monitoring rate of the study population). Treatment-related complications were more often observed in patients who received stringent monitoring than in those who received more liberal monitoring (lower quartile annual monitoring rate). As such, stringent monitoring does not prevent myelotoxicity-related or hepatotoxicity-related complications. These observations are of considerable significance as the clinical impact of detecting laboratory toxicity in maintenance therapy is low, and thus routine monitoring is of limited benefit.

Mercaptopurine was found to be associated with a higher risk of myelotoxicity than AZA.[23,30] This finding may be attributed to higher dosing of MP than AZA in IBD patients, because of little variation in pharmaceutical dosages in MP tablets and relatively higher recommended dose in official clinical guidelines than for AZA when correcting for bioavailability.[30] This association was not confirmed in maintenance treatment in our cohort, presumably because of low dosing of thiopurines in general and MP in particular (lower dosing

than recommended in guidelines). In line with previous studies, MP was associated with hepatotoxicity (HR 1.40) in our cohort. This may well be influenced by the percentage of MP users (15%) receiving concomitant therapy with allopurinol. Patients treated with LDTA showed higher detection rates of hepatotoxicity in multivariate analysis but this interaction was not confirmed by statistical analysis. However, the likelihood of detecting hepatotoxicity in patients on LDTA is higher because some patients possibly started on allopurinol shortly before inclusion in the study and hepatotoxicity had not normalised in the course of combination therapy.

To our knowledge, our study is the first to describe the consequences of laboratory monitoring throughout thiopurine maintenance monotherapy in a large real-life cohort. Limitations relate mostly to the retrospective nature of this study. Firstly, we may have underestimated the incidence of laboratory toxicity because prospectively identified time points were not evaluated. True myelotoxicity can only be identified when a full blood count is completed. In addition, the absolute neutrophil count seems to be an important haematologic value in assessing susceptibility to infections.[31] As neutrophils were not routinely measured, transient episodes of myelotoxicity may not have been recorded. On the other hand, all detected laboratory toxicity was attributed to thiopurine therapy but other medication or viral infections are also associated with myelotoxicity.[32,33] Also, an increased risk of hepatotoxicity has been reported in IBD associated with other causal factors than thiopurine use, such as fatty liver disease.[24] Patients with a known history of liver disease were excluded in the analysis, but undiagnosed fatty liver disease in the patient population cannot be ruled out. High levels of the active thiopurine metabolite 6-thioguanine nucleotides are associated with myelotoxicity, and the byproducts 6-methyl mercaptopurine ribonucleotides are associated with both myelotoxicity and hepatotoxicity.[34,35] Considerations of thiopurine metabolite levels and adverse events are hampered because thiopurine metabolites were not routinely measured and thus not included in the analysis. Secondly, data from six hospitals were included and both cessation and dose reductions were left to the discretion of the treating physician. Thus, the monitoring regimen and the clinical consequences after toxicity detection reflect the daily practice of these physicians. A clinician's motivation to perform therapy adjustments or diagnostic procedures could be influenced by experience or patient-related factors. It is likely that repeated detection of laboratory abnormalities led the treating physician to adjust treatment. In addition, both patients and physicians influenced compliance to laboratory monitoring regimen. Thirdly, evaluation of clinical consequences of laboratory toxicity was hampered by the inability to discriminate between routine laboratory assessment for monitoring thiopurine therapy and laboratory assessments requested by other clinicians. This might also have led to overestimation of the monitoring frequency. Finally, almost 75% of patients were followed in a referral centre, and thus our population probably includes patients with a more complicated disease course or more comorbidity with a possible increased risk of laboratory toxicity. An important remark is that our results apply to patients on thiopurine monotherapy. The risk of laboratory toxicity in patients on combination therapy with biologic agents was not investigated, and the risk in this population may be higher.[36]

As thiopurine-induced laboratory toxicity occurs more frequently in the initial months of therapy, strict laboratory monitoring of the blood count and LTs in the first year of treatment as recommended in current guidelines seems justified.[9,10] Regular laboratory monitoring is recommended at 2-3 months intervals throughout maintenance thiopurine treatment.[16,22] These recommendations are largely based on concern about possible complications following late-onset toxicity, especially leukopenia. However, the (cost-) effectiveness of this schedule is not evidence-based.[15,16] Laboratory monitoring practices in this large real-life cohort were more liberal than recommended in the ECCO guideline; at 4-month intervals (our study) vs at 2-3 months intervals (ECCO guideline). The results of our study demonstrate that after 1 year of thiopurine treatment, monitoring at 4-month intervals rarely leads to therapy adjustments and more importantly is rarely associated with treatment-related complications. Also, (frequent) monitoring after 1 year of treatment does not seem to prevent laboratory toxicity-related complications, as preceding laboratory assessments were unremarkable in 67% of cases. Therefore, a firm conclusion can be drawn that the recommended monitoring frequency may be reduced to an interval of less than 4 months. We speculate that a monitoring regimen at 6-month intervals is sufficient in patients after 1 year of thiopurine treatment. This assumption is supported by the small number of complications in patients on the least frequent monitoring regimen (ie lower quartile based on annual in patients monitoring frequency). Also, we hypothesise that reducing laboratory monitoring to 6-month intervals decreases patient burden and healthcare costs (Supplementary Data 1). In order to confirm that laboratory monitoring at 6-month intervals is non-inferior to 4-month intervals, prospective evaluation in an impractically large study population with several years of follow-up would be required. Accurate risk stratification for complications, based on detected laboratory toxicity, is hampered by the heterogeneity of data in this study. It is unlikely that this will be avoided by a prospective design, as the detection of laboratory toxicity is expected to influence both treatment and monitoring. Therefore, a prospective cohort study will probably not provide the required data to test this hypothesis.

In conclusion, this study has demonstrated a limited yield of current laboratory monitoring practices in maintenance thiopurine monotherapy in IBD patients. Firstly, laboratory monitoring in clinical practice was less frequent than advised in current guidelines. Secondly, severe myelotoxicity and hepatotoxicity are uncommonly detected. Thirdly, this study showed that treating physicians tend to disregard aberrant laboratory findings, and were not inclined to adjust therapy or perform additional diagnostic evaluation. Finally, complications associated with laboratory toxicity occurred rarely, and most complications developed unpredictably and could not be avoided by frequent monitoring. Reducing laboratory monitoring in thiopurine maintenance therapy after 1 year of treatment to less than a 4-month interval seems sufficient and could result in reduced patient burden and healthcare costs.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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