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ORIGINAL ARTICLE

Proactive Metabolite Testing in Patients on Thiopurine May Yield Long-Term Clinical Benefits in Inflammatory Bowel Disease

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Abstract

Background The thiopurine medications are well established in the treatment of inflammatory bowel disease (IBD). There is significant variation in levels of toxic and therapeutic metabolites. Current data from small or short-term studies support therapeutic drug monitoring (TDM) in assessing azathioprine (AZA) and 6-mercaptopurine (6MP). TDM of thiopurines involves measurement and interpretation of metabolites 6-TGN and 6-MMPR.

Aims This study aimed to assess long-cterm outcomes of patients on thiopurines following therapeutic drug monitoring.

Methods A multicenter retrospective observational study of outcomes post thiopurine TDM was conducted. Demographics, disease characteristics, physician global assessment, IBD therapy at baseline TDM and again at 12 months were collected. Clinical outcomes were analyzed according to TDM result, and indication for TDM including proactive and other indications.

Results The study included 541 patients. Only 39% of patients had appropriate dosing of thiopurines. AZA/6MP TDM informed a management change in 61.9%, and enabled 88.8% of the cohort to continue AZA/6MP following TDM. At 12 months following TDM the majority (74.1%) of the cohort remained on AZA/6MP. Clinical remission was higher at 12-months following thiopurines TDM (68%) compared to baseline (37%), including proactive TDM. Post TDM, 13.0% of patients were identified as shunters and commenced on thiopurine-allopurinol co-therapy.

Conclusion Thiopurine TDM resulted in a change in management for the majority of patients. Post TDM significantly more patients were in remission. TDM allowed the identification of non-adherence and shunters who, without intervention, would not reach therapeutic drug levels. Proactive TDM allowed identification and management of inappropriate dosing, and was associated with increased levels of clinical remission.

Keywords Thiopurines · Therapeutic drug monitoring · Thiopurine metabolite measurement · Inflammatory bowel disease · Adverse drug reactions · Clinical pharmacology

Abbreviations

6MP	6-Mercaptopurine
6-MMPR	6-Methyl-mercaptopurine ribonucleotides
6-TGN	6-Thioguanine nucleotide
ADR	Adverse drug reaction
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AZA	Azathioprine

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RBC	Red blood cell
CD	Crohn's disease
IBD	Inflammatory bowel disease
IBD-U	IBD-unspecified
IQR	Interquartile range
PGA	Physician global assessment
TDM	Therapeutic drug monitoring
TPMT	Thiopurine methyltransferase
UC	Ulcerative colitis

Background

The thiopurine immunomodulators, azathioprine (AZA) and 6-mercaptopurine (6MP) are effective agents for the maintenance of remission in inflammatory bowel disease (IBD) [1–5]. AZA achieves a reported overall maintenance of remission rate of 71% (CI 95% 0.64–0.77) in Crohn's disease (CD) and 54% (CI 95% 0.54–0.86) in ulcerative colitis (UC) [6, 7]. Thiopurine maintenance therapy has been shown to reduce the requirement for corticosteroid usage, and is associated with reduced rates of surgery in Crohn's Disease [8, 9].

The metabolism of AZA and 6MP is complex. AZA is a prodrug converted to 6MP and methyl-nitroimidazole in the liver [10]. 6MP in turn is metabolized via three competing pathways (*see* Supplementary Figure 1):

1. Xanthine oxidase converts 6MP to 6-thiouric acid, an inactive metabolite;
2. Thiopurine methyltransferase (TPMT) converts 6MP to 6-methyl-mercaptopurine ribonucleotides (6-MMPR), a potentially hepatotoxic metabolite;
3. A series of enzymatic steps exist wherein 6MP is converted to 6-thioguanine nucleotide (6-TGN), which is recognized as the therapeutic and potentially myelotoxic metabolite [9, 11].

Early efficacy studies concluded the therapeutic effect of thiopurines was dose-dependent, and dosing was generally targeted according to body weight. However, the availability of metabolite measurement has subsequently demonstrated inconsistent correlation between weight-based drug dosing and metabolite levels [12]. Gardiner et al. described this further by identifying the variation in AZA/6MP dosing required to achieve therapeutic 6-TGN between intermediate and normal TPMT metabolizers [13]. TPMT metabolism is inversely related to 6-TGN levels, and consequently intermediate metabolisers of TPMT are associated with higher 6-TGN levels for an equivalent dose and associated risk of adverse effects. Leukopenia is common and is associated with, although not exclusive to, higher 6-TGN levels (> 450 pmol/8 × 10^8 red blood cells (RBC)) [9], and similarly, hepatotoxicity is more likely to be associated with higher levels of 6-MMPR (> 5700 pmol/8 × 10^8 RBC) [10].

Prior to the introduction of metabolite measurement, ongoing active disease was commonly attributed to resistance and resulted in escalation of therapy to other agents. Thiopurine metabolite measurement has since been demonstrated to facilitate clinical management by identifying other explanations for an apparent failure of thiopurines. Reasons for therapeutic "failure" have included non-adherence, under-dosing determined by sub-therapeutic metabolite 6-TGN level, and preferential production of 6-MMPR—commonly referred to as "shunting" [9, 14]. Shunting is considered to be significant when 6-MMPR:6-TGN ratio > 11. In addition to this, adverse drug reactions (ADR) account for discontinuation of thiopurines in 10–25% of patients and are mainly attributed to idiosyncratic drug reactions, myelotoxicity or hepatotoxicity [9].

Although several studies have supported the use of metabolite measurement in guiding clinician management for patients with active disease, suspected non-adherence or ADRs [14–17], some observational studies suggest this role is overstated and fails to predict treatment outcomes [16, 18]. Moreover, the studies on which this proposition is based have been limited by small numbers, short-term follow-up and design issues which do not allow the role of proactive AZA/6MP therapeutic drug monitoring (TDM) in achieving clinical outcomes to be evaluated [14–17]. The British Society of Gastroenterology [19] and the American Gastroenterological Association [20] guidelines currently recommend thiopurine TDM if there is an inadequate response to thiopurine therapy or suspected toxicity and do not recommend proactive thiopurine TDM. Australian guidelines [21] discuss the various clinical scenarios and interpretation of thiopurine TDM but do not explicitly recommend proactive thiopurine TDM.

The aim of this study was therefore to evaluate the impact of thiopurine TDM-led management on long-term outcomes in a large multi-center cohort.

Methods

A multi-center, cross-sectional retrospective study was undertaken at four large IBD services across three different states of Australia (see supplementary Table 1). Patients were identified from local, prospectively maintained IBD service databases and cross-referenced with pathology databases to find those in whom thiopurine metabolite testing had been undertaken over the time period of 2009 to 2014. Inclusion criteria were: an established diagnosis of IBD (CD, UC or IBD-unspecified (IBD-U)); a minimum of 4 weeks of AZA/6MP therapy prior to baseline metabolite measurement; and documented clinical assessment at

the time of baseline metabolite measurement and again at 12 months.

Data Extraction

All data were collected at the time of baseline metabolite measurement and again after 12 months and included: demographics, disease characteristics, previous and current treatment modalities, clinical status according to physician global assessment (PGA), indication for metabolite measurement, and blood tests results. Indications for metabolite measurement were classified as: proactive TDM (thiopurine TDM following dose adjustment or to correlate metabolite measurement to current dose, irrespective of disease activity as per PGA); persistent IBD activity (based upon PGA); new IBD flare; suspected non-adherence; suspected adverse drug reaction; and other. The classification decision was made at the time of review of the case notes and was based on the reviewer's impression. Clinician interpretation of metabolite measurements and subsequent TDM-based management decisions were also documented based on contemporaneous case-note entries. Thiopurine metabolites and interpretation can be seen in Table 1 along with interpretation in setting of active disease.

The disease activity at 12 months post TDM was categorized as: active no clinical response, clinical response (active disease that has improved compared to baseline assessment) and clinical remission (no active disease based upon PGA). Pre-specified outcomes were defined as: potentially toxic 6-MMPR level > 5700 pmol/8 × 10^8 RBC [20]; leukopenia—white cell count < 3.5 × 10^9/L; lymphopenia < 1.0 × 10^9/L, and hepatotoxicity as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > two times the upper limit of normal (i.e., > 90 U/L). Target 6-TGN range was considered to be 235–450 pmol/8 × 10^8 RBC. Target dosing was considered to be the thiopurine dose required to achieve target 6-TGN and 6-MMPR levels as defined above.

Statistical Analysis

Ethics approval was granted by each site's relevant Research Ethics Committee. Statistical analysis was performed using Stata version 15 (StataCorp LLC, Texas, USA) and SAS 9.3 (SAS, North Carolina, USA). For normally distributed variables, mean and standard deviation were reported with comparisons made using the student t-test. For non-normally distributed variables, median and interquartile range (IQR) were reported, with comparisons made using the Mann–Whitney *U* test. For categorical data, Pearson's χ^2 test was used, or Fisher's exact test where appropriate. A *p* value was considered statistically significant if $p < 0.05$.

Results

A total of 541 patients were eligible for analysis, with a median age of 40 years (IQR 30–53), 50.1% female, and 70.2% Crohn's disease, with 28.3% having ulcerative colitis, with median IBD disease duration of 10.2 years (IQR 5.8–16.8) (see Table 2). The majority of patients (61.2%) had active disease at baseline. 314 patients (58.0%) were on an IBD medication in addition to their thiopurine at baseline.

Thiopurine Metabolites

Baseline population median 6-TGN and 6MMPR concentrations were within the therapeutic reference range for all indications except for suspected non-adherence (*see* Table 3). However, only 215 patients (39.7%) had thiopurine metabolite levels consistent with appropriate dosing, with 27.2% felt to be underdosed, and a further 16.3% identified as shunters. Overall, 335 patients (61.9%) had a change in medication management based on their thiopurine TDM.

Repeat thiopurine TDM was available for 259 patients. 6-TGN was significantly higher at repeat TDM than at baseline (306 (235–417) vs. 255 (168–368), respectively, $p < 0.001$). 6-MMPR was not significantly different (1107 (482–3165) vs. 1151 (456–3554) $p = 0.64$) (median, interquartile range). The proportion of patients with therapeutic 6-TGN level (Target 6-TGN range 235–450 pmol/8 × 10^8

Table 1 Dosing and clinical interpretation of thiopurine metabolite levels

6-TGN	6-MMPR	Dosing interpretation	Clinical interpretation
Therapeutic[†]	Low, normal or high	Appropriately dosed	Thiopurine refractory (*if active disease*)
Low	Low or normal	Underdosed	Requires increased dose or increased medication compliance
High	Low, normal or high	Overdosed	Thiopurine refractory (*if active disease*)
Low	High	6-MMPR shunter[‡]	Requires dose augmentation with allopurinol if shunter

[†]Target 6-TGN range 235-450 pmol/8 × 10^8 RBC, target 6-MMPR range < 5700 pmol/8 × 10^8 RBC

[‡]6-MMPR shunter considered when 6-MMPR:6-TGN ratio > 11

Table 2 Inflammatory bowel disease population on thiopurine characteristics including disease activity and IBD medications ($n=541$)

Age (years), median (IQR)	40 (30–53)
Female gender	271 (50.1)
Smoker (current or reformed), *n* (%)	172 (31.8)
Previous surgical resection(s), *n* (%)	144 (26.6)
Diagnosis, *n* (%)	
Crohn's disease	367 (70.2)
Ulcerative colitis	147 (28.3)
IBD unspecified	8 (1.5)
Disease duration (years), median (IQR)	10.2 (5.8–16.8)
Disease activity (PGA), *n* (%)	
Active	331 (61.8)
Clinical remission	201 (37.1)
Unknown	9 (1.6)
Concomittant IBD medications *n* (%)	
Thiopurine monotherapy	227 (41.9)
Allopurinol†	16 (2.9)
5-ASA	214 (39.6)
@anti-TNFα	80 (14.8)
Methotrexate	4 (0.7)

†Allopurinol used in addition to thiopurine due to shunting of 6-MP

RBC) at 12 months was significantly higher than those at baseline (55.9% v 39.0%, $p<0.001$).

The thiopurine TDM result for those with active disease as the indication for TDM was: 39.7% (98) appropriately dosed, 29.9% (74) under-dosed or non-compliant, 13.8% (34) overdosed, 16.6% (41) were consistent with MMP-6 shunting (see Table 3). Median 6-TGN level was only slightly lower in those with active disease, as defined by physician global assessment, compared to inactive disease (248 (IQR156-348) vs 265 (199–402), respectively, $p=0.012$).

Thiopurine TDM and Medication Outcomes

Overall, the majority of patients (88.8%) were able to continue thiopurine based therapy following the baseline metabolite measurement without the need for escalation to biologics agents, trial of a different medical therapy or surgery. Medications at baseline and at 12 months post TDM are shown in Fig. 1. The proportion of patients on allopurinol and thiopurine therapy for management of 6-MMP shunting increased from study entrance to 12 months post TDM (3.1% vs. 13.0% $p=0.001$). At 12 months 4.1% (22) of patients required a non-thiopurine containing regime, and 4 patients required surgical treatment.

Thiopurine TDM was performed proactively in 233 patients (43.1%), resulting in a change in medication management in over half of patients (52.3%). In those with TDM performed for proactive indication, thiopurines were continued at twelve months in 93.9%. Escalation to biologic medication occurred in 7.3% (17 patients). Addition of allopurinol due to shunting metabolism occurred in 9.0% (21 patients). For those with proactive TDM indication there were 30.0% with active disease at baseline which reduced to 15.0% at twelve months post TDM ($p<0.001$).

Table 3 Medication management changes in patients with IBD on thiopurine according to thiopurine metabolites and thiopurine dosing interpretation

Indication	Number of patients *n* (%)	6-TGN, Median (IQR)	6-MMPR, Median (IQR)	Appropriately dosed† *n* (%)	Underdosed *n* (%)	Overdosed *n* (%)	6-MMPR shunter‡ *n* (%)	Change in medication management, *n* (%)
Proactive ($n=233$)	233 (43.1)	262 (192–389)	1164 (499–3140)	95 (40.7)	56 (24.0)	45 (19.3)	37 (15.9)	122 (52.3)
Persistent IBD activity ($n=164$)	164 (30.3)	249 (157–357)	1004 (461–3127)	68 (41.4)	49 (29.8)	23 (14.0)	24 (14.6)	109 (66.4)
New IBD flare ($n=83$)	83 (15.3)	232 (149–350)	1119 (495–3680)	30 (36.1)	25 (30.1)	11 (13.2)	17 (20.5)	61 (73.4)
Suspected non-adherence ($n=7$)	7 (1.3)	145 (103–455)	508 (482–1168)	1 (14.2)	2 (28.6)	2 (28.6)	2 (28.6)	4 (57.1)
Suspected adverse drug reaction ($n=47$)	47 (8.7)	258 (163–409)	1162 (391–3938)	18 (38.2)	12 (25.5)	9 (19.1)	8 (17.0)	36 (76.5)
Other ($n=7$)	7 (1.3)	235 (109–275)	1372 (582–4750)	3 (42.8)	3 (42.8)	1 (14.2)	0 (0.0)	3 (42.8)

†Target 6-TGN range 235-450 pmol/8 × 10^8 RBC, target 6-MMPR range < 5700 pmol/8 × 10^8 RBC

‡6-MMPR shunter considered when 6-MMPR:6-TGN ratio > 11

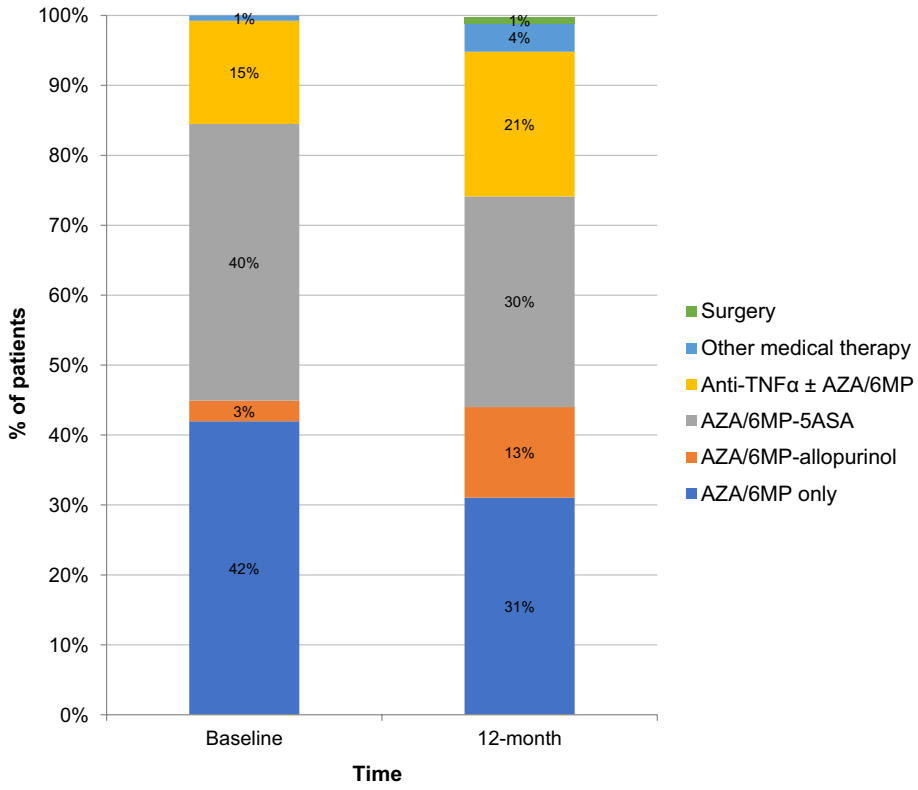

Fig. 1 Medications at baseline, time of TDM, and 12 months post TDM. AZA, azathioprine; 6MP, 6-mercaptourine; 5ASA, 5-aminosalcylic acid; anti-TNFa, anti-TNF. Monoclonal antibody such as infliximab, adalimumab, golimumab

Metabolite Measurement for Adverse Drug Reactions

Metabolite measurement was performed for suspected ADR in 47 patients (8.6%). Of these, 24 patients (51%) were judged to have unexplained symptoms/reactions not due to AZA/6MP. Fourteen patients (30%) were judged to have idiosyncratic ADR and 9 patients (19%) to have dose-dependent ADR. Lymphopenia was common, present in 23.1% of the cohort, with hepatoxicity and leukopenia uncommon (*see* Table 4). 6-TGN was significantly higher in those with leukopenia and trended to significance in those with lymphopenia ($p=0.0003$, $p=0.06$, respectively). The proportion with elevated 6-MMPR was not significantly different in those with hepatotoxicity ($p=0.10$). The majority of patients with lymphopenia, leukopenia or hepatoxicity continued on thiopurine therapy at 12 months post study entrance (*see* Table 4).

Longitudinal Clinical Outcomes

At baseline, a majority (61.2%) of patients had active disease and 37.1% of patients were in clinical remission. In comparison, 12 months following TDM, 22.9% had active disease, while 73.7% of patients ($n=399$) had achieved clinical response, and significantly more patients 68.0% ($n=368$)

Table 4 Adverse drug reactions in patients on thiopurine medication and thiopurine metabolite levels and continuation on thiopurine

Adverse drug reaction	Number of patients *n* (%)	Elevated 6-TGN level[†] *n* (%)	Elevated 6-MMPR level[‡] *n* (%)	Number patients remaining on thiopurine at 12 months *n* (%)
Lymphopenia[§]	125 (23.1)	30 (24.0)	16 (12.8)	114 (91.2)
Leukopenia[¥]	15 (2.7)	8 (53.3)	3 (20.0)	12 (80.0)
Hepatotoxicity[¶]	19 (3.5)	2 (105)	3 (15.8)	15 (78.9)

[‡]6-MMPR level > 5700 pmol/8 × 10^8 RBC[22]

[†]6-TGN > 450 pmol/8 × 10^8 RBC

[§]Leukopenia as white cell count < 3.5 × 10^9/L

[¥]Lymphopenia as lymphocyte count < 1.0 × 10^9/L

[¶]Hepatotoxicity as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 90U/L

were in clinical remission ($p < 0.001$). Of the 399 patients who achieved clinical response at 12 months, 291 (72.9%) were able to do so while remaining on azathioprine without the need to escalate to other therapies. Clinical response and clinical remission in patients with ulcerative colitis were 76.2% and 70.7%, and similarly, respectively, in Crohn's disease were 76.8% and 71.1%.

Discussion

This is the largest reported cohort of patients with IBD undergoing thiopurine TDM and it provides support for the role of thiopurine TDM in optimizing patient management. It informed a change in management in the majority of cases (61.9%) and the vast majority of patients were able to continue thiopurine therapy over the twelve month observation period (88.8%) with an increase in the number of patients in clinical remission. This is important from a cost-efficacy point of view, as although newer biologic therapies are highly effective, they are also significantly more expensive than thiopurines.

Our findings expand upon previous smaller studies reporting thiopurine TDM resulting in change in management in the majority of cases. Goldberg et al. reported on a cohort of 169 patients on thiopurine with metabolite testing resulting in change of management in 68% of patients [17]. Kennedy et al. reported on a cohort of 151 patients with thiopurine TDM resulting in change in management in 42% of patients [15]. Haines et al. examined a population of 63 patients with IBD on thiopurine with patient reported active disease and subsequent thiopurine TDM with clinical improvement noted in the 87% that followed a TDM based algorithm [17].

Our study population is widely representative of tertiary IBD services with a predominance of Crohn's disease and relatively equal gender distribution. The heterogeneity of baseline treatments reflects the various agents used in conjunction with AZA/6MP by clinicians worldwide. It is important to recognize that AZA/6MP are relatively inexpensive agents in comparison to current biologic agents and surgical intervention. The potential for metabolite measurement to optimize and prolong the use of AZA/6MP has significant cost implications for health care systems worldwide.

Only 38.6% of patients with active disease, as determined by the treating physician, were on an appropriate dose of thiopurine according to TDM, with 46.2% felt to be underdosed or undergoing shunting. In the absence of thiopurine TDM, a significant proportion of these patients may have been labeled thiopurine refractory. Rather than appropriately adjusting/augmenting the thiopurine dose, they may then have been subjected to escalation of therapy, such as blind AZA/6MP dose escalation, long-term corticosteroids, switching treatment to methotrexate, escalation to biologic agents or surgery. In our cohort only 8.2% of those with active disease on thiopurines were truly thiopurine refractory, according to our definition, and following medication changes including thiopurine dose optimisation there was a significant decrease in the proportion with active disease at 12 months post TDM (61.2% vs 22.9% $p < 0.001$). A significant proportion of our cohort (13.0%) was identified as 6-MMPR shunters as a result of TDM and would be unlikely to reach therapeutic TDM levels without identification and initiation of allopurinol.

Thiopurine TDM may also assist with the interpretation of adverse drug reactions. The size and importance of this problem is well exemplified by a previous report that 25.9% of a moderately sized patient cohort ($n = 216$) discontinued AZA/6MP due to apparent ADRs [22]. In our cohort TDM was performed for suspected adverse drug reaction in 8.7% of indications, and in this setting led to the conclusion that thiopurine was not the culprit in half of these cases. Data from two Cochrane reviews [6, 7] suggested an overall adverse event rate of 8.6% in patients with ulcerative colitis on thiopurine and 6.0% in patients with Crohn's disease on thiopurine, which is similar to the event rate prior to thiopurine TDM.

The role of proactive metabolite measurement has previously been less well-defined and difficult to study prospectively [9, 23]. In our cohort, 233 patients had proactive metabolite measurement performed and therapeutic 6-TGN levels were documented in less than half (43.3%). Proactive TDM resulted in just over half (52.3%) warranting a change in thiopurine management. Previous studies have only advocated metabolite measurement in patients with active disease, suspected non-adherence and adverse drug reactions [14–17]. In our cohort, the proportion of proactive TDM patients with active disease reduced from 30.0% at baseline to 15.0% at 12 months ($p < 0.001$), which, by no means may we assign causality of TDM-induced medication changes, however we may postulate an association of proactive thiopurine TDM-induced thiopurine augmentation with improved clinical outcomes. The authors feel these findings provide additional support to existing data for the previously proposed indications for thiopurine TDM and suggest proactive TDM should also be performed. Analogous to the increasingly accepted paradigm of "treating to target" in IBD [24] it follows that proactive thiopurines TDM should therefore play a more important role in the routine management of IBD.

The rate of clinical remission seen in ulcerative colitis patients in this study (70.7%) was superior to the previously published thiopurine maintenance data from a 2016 Cochrane review that quoted a remission rate of 56% in those on thiopurine and 35% in those on placebo [7]. In the case of Crohn's disease, the rate of clinical remission in this study (71.1%) was similar to published thiopurine maintenance

data from a Cochrane review that quoted a remission rate of 70.6% for those on thiopurine and was to superior to those on placebo with a remission rate of 55% [6]. The authors acknowledge the difficulties in making such a comparison and would suggest that the difference may in part be due to thiopurine TDM. It may also be due to selection bias, in that patients with theoretically more severe disease who had previously failed thiopurines and were on biological therapy alone were not included in the study.

There are several limitations to this study. Due to the observational nature of our study it was not feasible to have a control group of patients who did not undergo thiopurine TDM, and even if we had included patients not undergoing TDM in our services, this would have introduced significant bias. Hence, we can only postulate a beneficial role of thiopurine TDM for both proactive and other indications according to the reassuring and encouraging descriptive data we have presented. As a result of the multicenter nature of the study thiopurine metabolite measurement was undertaken at different laboratories and consequently there was no standardization of method of thiopurine measurement. However, thiopurine metabolite targets remained the same across all study sites. There may also be some effect from previous thiopurine related TDM prior to the initial TDM result and management change.

Another limitation was the use of the physician global assessment (PGA) to assess disease activity which is subjective and potentially open to bias, however given the retrospective nature of this study there were limitations as to the availability of clinical, laboratory and endoscopic data to provide correlating objective markers of disease activity. Future long-term studies should include validated biomarkers such as fecal calprotectin or endoscopic assessment.

Conclusion

This large observational cohort study evaluating long-term outcomes in patients with IBD on thiopurine TDM demonstrated that a large proportion of patients are not on an appropriate dose of thiopurine, and that TDM leads to over half of patients having augmentation of their therapy, with significant clinical management changes and a significant increase in the proportion of patients in remission. Thiopurine TDM allows continuation of thiopurine in the vast majority of cases and should be performed in the case of active disease and suspected adverse drug reaction. Thiopurine TDM has a role in identifying significant shunting of 6-MMPR, allowing addition of allopurinol to achieve therapeutic levels. Finally, we endorse that routine proactive TDM should be performed as it led to changes in management in the majority of cases.

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Author's contribution Soong-Yuan Ooi: Study concept and design, data acquisition, analysis and data interpretation, drafting of manuscript, critical revision of manuscript. Alex Barnes: Analysis and data interpretation, drafting and critical revision of manuscript. Kate Lynch: Data interpretation and critical revision of manuscript. Nina Parthasarathy: Data acquisition. Maria Bishara: Data acquisition. Michael Gounder: Data acquisition. Rachel Grafton: Data acquisition. Peta Leach: Data acquisition. Peter Bampton: Critical revision of manuscript. Alexandra Sechi: Ethics application for site, Data acquisition. Watson Ng: Critical revision of manuscript. Susan Connor: Critical revision of manuscript. Daniel van Langenberg: Critical revision of manuscript. Réme Mountifield: Critical revision of manuscript. Jane M Andrews: Study concept and design, data interpretation, critical revision of manuscript.

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Declarations

Conflict of interest Andrews JM has been on advisory boards, been a speaker and received research and/or educational support from AbbVie, Allergan, Anatara, Bayer, Celgene, Celltrion, Ferring, Gilead, Hospira, Immunic, Janssen, MSD, Nestle, Pfizer, Sandoz, Shire, Takeda, Vifor, Novartis. Connor S has been on advisory boards, been a speaker and received research and/or educational support from AbbVie, Janssen, Pfizer, Shire, Takeda, Ferring, MSD, Vifor, Celgene, Orphan, Gilead, Celltrion, Aspen. Other authors report no conflict of interest.

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