LEADING ARTICLE

Clinical utility of thiopurine metabolite monitoring in inflammatory bowel disease and its impact on healthcare utilization in Singapore

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Abstract

Background and Aim: Thiopurines are recommended for maintenance of steroid-free remission (SFR) in inflammatory bowel disease (IBD). Thiopurine metabolite monitoring (MM) is increasingly used in the West but remains novel in Singapore, with limited information on its therapeutic and economic benefits. Hence, this study aims to investigate MM’s clinical utility and its impact on healthcare resource utilization in Singaporean IBD patients.

Methods: A retrospective observational study was conducted at Singapore General Hospital outpatient IBD Centre. Patients with IBD, baseline MM during 2014–2017, and weight-based thiopurine doses for ≥24 weeks were followed up for 1 year. Actions were taken to optimize therapy, and metabolite levels before and after the first action were documented. Outcomes assessed included SFR, no therapy escalation or surgery, healthcare resource utilization, and direct healthcare costs.

Results: Ninety IBD patients (50 Crohn’s disease, 40 ulcerative colitis) were included. Among them, 40% had baseline metabolite levels within therapeutic range, 31.1% sub-therapeutic, 21.1% supra-therapeutic, and 7.8% shunters. Repeated MM with subsequent dose optimization helped 67.2% of patients achieve therapeutic levels after 1 year. Overall, 87.8% of patients achieved SFR and 90% had no therapy escalation or surgery. Despite greater outpatient visits and laboratory investigations with MM, the median total healthcare costs at 1 year only increased marginally ($6407.66 [shunters] vs $5215.20 [supra-therapeutic] vs $4970.80 [sub-therapeutic] vs $4370.48 [control (within therapeutic range)], P = 0.592).

Conclusion: MM guided timely therapy escalation for non-responders, identification of non-adherence, and reversal of shunting. Therefore, it is a useful clinical tool to optimize thiopurines without significantly increasing healthcare costs.

Introduction

Inflammatory bowel disease (IBD), broadly classified into Crohn’s disease (CD) and ulcerative colitis (UC), is a relapsing, idiopathic inflammatory disorder of the gastrointestinal tract. Primary therapy focuses on the dysregulated immune system to control the active inflammation and prevent disease progression. Thiopurines, azathioprine (AZA) and 6-mercaptopurine (6-MP), are used as steroid-sparing agents with a 55–70% response rate. However, up to 40% of IBD patients discontinue thiopurines from toxicity or non-response, which reflects the heterogeneity in metabolism. Measures to individualize thiopurine dosing to optimize therapeutic outcomes while avoiding toxicity are thus desirable.

After oral absorption, the prodrug AZA is converted non-enzymatically to 6-MP, then further metabolized through several competing pathways to the active 6-thioguanine nucleotide (6-TGN) and inactive 6-methylmercaptopurine (6-MMP) metabolites. Assays for measuring 6-TGN and 6-MMP are now widely available. The 6-TGN levels between 235 and 450 pmol/8×10^8 red blood cells (RBC) are found to correlate with therapeutic benefits, while 6-MMP levels >5700 pmol/8×10^8 RBC correlate with hepatotoxicity. “Shunters” preferentially metabolize thiopurines.
to 6-MMP, causing low 6-TGN or non-response. Identifying shunters using MM is crucial as co-treatment with allopurinol corrects the unfavorable 6-MMP/6-TGN ratio by reducing 6-MMP while increasing 6-TGN levels, allowing the continued use of thiopurines. Given the limited treatment armamentarium for IBD, metabolite monitoring (MM) may be useful to optimize thiopurine therapy.

Studies in Western adult IBD patients have suggested that MM-guided dosing strategies improved therapeutic outcomes. A retrospective study involving 189 patients found MM identified patients who were non-adherent, nonresponders, shunters, under- and over-dosed, thus facilitating timely treatment change. In nonresponders, where actions taken were 6-TGN directed, 90% had significantly better outcomes compared with 33% where treatment decisions were not 6-TGN directed (P < 0.001). Furthermore, more patients achieved 6-month steroid-free remission (SFR) when thiopurines were optimized using MM compared with those who ignored 6-TGN results (70 vs 30%, P = 0.037).

However, the cost of MM should be weighed against its clinical benefits. Currently, there is only one cost-effectiveness study on MM. Using economic modeling over 1 year from the third-party payer perspective for mild to moderately active, steroid-treated CD patients, MM was cost-effective with lower cost (US$6441 vs US$7142) and improved outcomes, defined by a faster time to sustained treatment response (39.83 vs 45.36 weeks), compared with the base case of standard community care. While MM may achieve faster clinical response, patients may incur higher healthcare costs from additional outpatient follow-up with MM-guided optimization strategies. To date, the healthcare resource utilization and costs associated with MM in clinical practice have not been investigated.

Although MM has been well established in the United Kingdom and Australia, it remains a new strategy for thiopurine optimization in Singapore. This study therefore aims to investigate the clinical utility of MM and its impact on healthcare resource utilization in Singaporean IBD patients. Knowledge of the therapeutic and economic benefits of MM is pivotal to inform healthcare policy-makers on its relevance in clinical practice and provide evidence for incorporation as a standard of care in IBD management.

Methods

Study design and participants. In this retrospective observational study, we reviewed IBD patients followed up at the Singapore General Hospital outpatient IBD center over 1 year from their baseline MM. Patients with a confirmed diagnosis of CD or UC, baseline MM during 2014–2017, and receiving weight-based thiopurine doses (2.0–3.0 mg/kg AZA, 1.0–1.5 mg/kg 6-MP) rounded to the nearest 50 mg tablet, for at least 4 weeks before the baseline MM (steady state) were included. Patients concomitantly treated with antitumor necrosis factor (anti-TNF) at baseline or with less than 1-year follow-up were excluded. This study was approved by the SingHealth Centralized Institutional Review Board (CIRB no. 2012/193/E) and all patients provided informed consent.

Patient characteristics. Patient demographics, disease characteristics (Montreal classification), thiopurine therapy (dose, duration, and metabolite levels), and concomitant medications were extracted from the electronic medical and prescription records. We scaled the 6-MP doses by 2.07 for direct comparison with AZA. Endoscopy results and laboratory measurements (C-reactive protein [CRP] and fecal calprotectin [FC]) were used as objective inflammatory markers to assess disease activity.

Follow-up evaluation. For patients newly initiated on thiopurines, they are required to visit the outpatient clinic 2 weeks after each thiopurine dose adjustment until the target dose is achieved. Once the target dose has been reached and maintained for at least 4 weeks, the baseline MM is performed. Following that, patient will be monitored at weeks 12, 26, and 52 (Fig. 1). However, patient may return earlier to the clinic if the physician’s assessment of the individual’s disease control is deemed to be suboptimal. For any subsequent therapy changes based on the repeated MM results, patients are to return to the clinic 2 weeks later. Laboratory tests were conducted to monitor disease activity and adverse effects at each visit. Routine blood investigations include complete blood count, transaminase, creatinine, and CRP.

Metabolite levels and actions taken. Steady-state levels of 6-TGN and 6-MMP metabolites were measured using the liquid chromatography–tandem mass spectrometry method adapted from Dervieux et al. Patients were classified into four groups using their baseline metabolite levels (Table S1, Supporting information). Within the subtherapeutic group, we identified non-adherent patients from self-reported adherence or undetectable metabolite levels.

1. Sub-therapeutic: 6-TGN < 235 pmol/8 × 10⁸ RBC, 6-MMP < 5700 pmol/8 × 10⁸ RBC
2. Shunters: 6-TGN < 235 pmol/8 × 10⁸ RBC, 6-MMP > 5700 pmol/8 × 10⁸ RBC (6-MMP/6-TGN ≥ 11)

Figure 1 Timeline of follow-up evaluation. AZA, azathioprine.
3. **Therapeutic range**: 6-TGN 235–450 pmol/8 × 10^8 RBC, 6-MMP < 5700 pmol/8 × 10^8 RBC
4. **Supra-therapeutic**: 6-TGN > 450 pmol/8 × 10^8 RBC, 6-MMP > 5700 pmol/8 × 10^8 RBC

Actions taken to optimize therapy in response to the baseline MM were recorded. Recommended strategies include thiopurine dose adjustment, co-administration with allopurinol, and escalation to methotrexate or anti-TNF (Table S1). For patients with repeated MM at steady state, metabolite levels after the first action and the last available levels at the end of 1 year were documented.

**Therapeutic outcomes.** Therapeutic outcomes were assessed in two ways: (i) SFR, defined as no steroid use (steroid-naïve patients) or no re-introduction (patients tapering their steroid course) during the last 3 months of the 1-year follow-up, and (ii) no escalation to anti-TNF or surgery throughout the 1 year. We adapted these outcomes from similar studies on MM as insufficient information was available to calculate disease activity scores.

For thiopurine safety, leucopenia was defined as WBC <3.0 × 10^9 cells/L and hepatotoxicity as alanine aminotransferase or aspartate aminotransferase >2 times the upper limit of normal.

**Healthcare resource utilization and cost.** All IBD-related resource utilization of each patient, throughout the 1-year follow-up from baseline MM, was categorized according to outpatient services, medication collection, emergency department (ED) visits, and inpatient services and medications.

Patients within the therapeutic range at baseline had the least repeated MM and actions taken to optimize therapy that best reflected clinical practice when MM was unavailable. They were thus used as the control group (proxy for patients without MM) for evaluating healthcare resource utilization and cost.

Healthcare resource utilization data were combined with relevant unit prices (price year 2017) to estimate total costs. We calculated direct healthcare costs from the patient perspective before subsidies. The hospital acquisition costs and indirect costs were unavailable to adopt a hospital or societal perspective respectively.

**Statistical analysis.** Descriptive statistics were used to summarize patient demographics, clinical characteristics, healthcare resource utilization, and cost. Continuous variables were presented as median and interquartile range (IQR), while categorical variables were presented as frequency and percentages. Categorical variables were compared using Fisher’s exact test while skewed continuous variables with Kruskal–Wallis or Mann–Whitney U-test. Thiopurine dose change and metabolite levels pre- and post-action were analyzed using paired t-test or Wilcoxon signed-rank test. All statistical analyses were performed using IBM SPSS Statistics version 24 (IBM SPSS Statistics, Chicago, IL, USA). A P-value of <0.05 was considered statistically significant.

**Results**

**Patient sample and baseline characteristics.** A total of 191 IBD patients with MM were identified within the study period (Fig. 2). Ninety patients were included for analysis. The baseline demographics and clinical characteristics are summarized in Table 1. The median age was 44 years old (31.8–57.0). The majority were male (74.4%), Chinese (64.4%), non-smoker (74.4%), and receiving thiopurines for CD (55.6%). Following the Montreal classification, 60–70% of CD patients had ileocolonic involvement and inflammatory disease, whereas a similar proportion of UC patients had left-sided colitis and pancolitis.

Most patients received AZA (95.6%) with a median thiopurine dose of 2.03 mg/kg (1.83–2.22) and median therapy duration of 2.1 years (0.4–6.7). The majority were on concurrent 5-aminosalicylates (84.4%) and approximately one-third on steroids at baseline MM.

Only two patients (2.2%) had leucopenia, while none had hepatotoxicity at baseline. Since these numbers remained small throughout the 1-year follow-up (three leucopenia [3.3%] and five hepatotoxicity [5.5%]), thiopurine-induced toxicity was not investigated further in this study.

**Baseline metabolite levels.** Among the 90 patients, only 36 (40%) achieved metabolite levels within therapeutic range, 28 (31.1%) had sub-therapeutic, and 19 (21.1%) had supra-therapeutic levels (Table 2). Within the sub-therapeutic group, seven patients were identified to be non-adherent to thiopurines. Another 7 (7.8%) patients were detected as shunters (preferential metabolism toward 6-MMP) with elevated median 6-MMP level and 6-MMP/6-TGN ratio.

**Actions taken to optimize therapy**

**Sub-therapeutic.** Following the baseline MM, dose increments were observed for 60.7% (17/28) of patients (Table 3). This included two non-adherent patients due to endoscopy evidence of active disease. The median thiopurine dose increased from 2.13 to 2.56 mg/kg (P < 0.05) with improved median 6-TGN levels from 175.10 (146.80–198.65) to 247 (177.00–255.05) pmol/8 × 10^8 RBC (P = 0.099). Therapeutic 6-TGN levels were achieved in only 5 of 17 patients. Five patients were revealed as delayed shunters after the dose increment, with significantly elevated median 6-MMP levels from 2292.6 to 5907.20 pmol/8 × 10^8 RBC (P = 0.021) and median 6-MMP/6-TGN ratio from 12 to...
Table 1  Patient demographics and clinical characteristics at baseline metabolite monitoring (MM)

| Socio-demographics                        | Total (n = 90) |
|-------------------------------------------|----------------|
| Age (years), median (IQR)                 | 44.0 (31.8–67.0) |
| Gender: Male, n (%)                       | 67 (74.4)      |
| Race, n (%)                               |                |
| Chinese                                   | 58 (64.4)      |
| Malay                                     | 10 (11.1)      |
| Indian                                    | 16 (17.8)      |
| Others (including Asians and others)      | 6 (6.7)        |
| Smoking status, n (%)                     |                |
| Non-smoker                                | 67 (74.4)      |
| Smoker                                    | 5 (6.6)        |
| Former smoker                             | 18 (20.0)      |
| Disease type, n (%)                       |                |
| Crohn’s disease                           | 50 (55.6)      |
| Ulcerative colitis                        | 40 (44.4)      |
| Disease duration (years)‡, median (IQR)   | 7 (2–16)       |
| CD: Disease location, n (%)               |                |
| L1 Terminal ileum                         | 9 (18.0)       |
| L2 Colon                                  | 6 (12.0)       |
| L3 Ileoceolic                             | 35 (70.0)      |
| CD: Disease behavior, n (%)               |                |
| B1 Inflammatory                           | 31 (62.0)      |
| B2 Strictures                             | 10 (20.0)      |
| B3 Fistulisation                          | 9 (18.0)       |
| CD: Perianal disease, n (%)               | 8 (16.0)       |
| UC: Type§, n (%)                          |                |
| E1 Proctitis                              | 3 (7.5)        |
| E2 Left-sided colitis                     | 19 (47.5)      |
| E3 Pancolitis                             | 17 (42.5)      |
| Thiopurine therapy                        |                |
| Azathioprine, n (%)                       | 86 (95.6)      |
| 6-Mercaptopurine, n (%)                   | 4 (4.4)        |
| Dose (mg/kg), median (IQR)                | 2.03 (1.83–2.22) |
| Duration of therapy (years), median (IQR) | 2.1 (0.4–6.7)  |
| Concomitant pharmacological therapy        |                |
| Oral or rectal 5-aminosalicylates, n (%)  | 76 (84.4)      |
| Oral corticosteroids§, n (%)              | 26 (28.9)      |

†Difference taken between the year of baseline MM and the year of inflammatory bowel disease diagnosis, assuming 1 January for each year as the exact date of diagnosis was unknown.
§One patient (2.5%) had pouchitis (not under the Montreal classification).
¶Exposure to oral prednisolone or budesonide, up to 3 months before the baseline MM.

28 (P = 0.004). Four patients with dose increments did not repeat MM.

One patient had further dose reduction due to borderline leucopenia at baseline and remained sub-therapeutic. The remaining 35.7% (10/28) of patients did not change thiopurine therapy, including five non-adherent patients. In the latter, non-adherence was discussed and patient education was provided, where two subsequently achieved therapeutic levels and one had supra-therapeutic levels.

**Shunters.** All seven shunters were switched to the MM-guided thiopurine/allopurinol combination. The median thiopurine dose decreased from 2.06 to 0.65 mg/kg (P < 0.0001). Adding allopurinol successfully reversed shunting by significantly reducing the median 6-MMP/6-TGN ratio from 52.2 to 0.6 (P = 0.018) and median 6-MMP levels from 7578.10 to 126.90 pmol/8 × 10^8 RBC (P = 0.018). After the change, three patients achieved therapeutic levels, one had supra-therapeutic, and three had sub-therapeutic levels. None developed hepatotoxicity despite elevated 6-MMP levels.

**Therapeutic range.** No dose adjustments were made for 70% (28 of 36) of patients. The majority (19 of 28) had achieved biochemical remission with a median CRP level of 0.7 mg/L and FC 69 µg/g. The remaining nine had mildly elevated median CRP of 5.5 mg/L and FC 247 µg/g, which may not have warranted therapy change. Only 10 patients had repeated MM (four achieved therapeutic levels, three had supra-therapeutic, and three had sub-therapeutic levels).

Five thiopurine-refractory patients with active disease, indicated by ulceration seen endoscopically and elevated median FC of .383 µg/g, had MM-guided therapy escalation (two switched to methotrexate and three started anti-TNF).

Despite achieving therapeutic levels, three patients had dose reduction due to baseline thiopurine-induced toxicity (two had leucopenia and one had hepatotoxicity).

**Supra-therapeutic.** Thiopurine doses were reduced in 84.2% (16 of 19) of patients. Four had borderline leucopenia at baseline, while five had achieved biochemical remission with a median CRP level of 0.7 mg/L and FC 69 µg/g. The remaining seven had dose reductions due to high median 6-TGN levels of 776.80 (581.60–1009.70) pmol/8 × 10^8 RBC despite elevated FC levels >300 µg/g. The median thiopurine dose decreased from 2.13 to 1.52 mg/kg (P < 0.0001), with significant reduction in median 6-TGN levels from 606.60 (524.25–812.45) to 387.80 (276.93–458.40) pmol/8 × 10^8 RBC (P = 0.003). Ten patients achieved therapeutic levels, four remained supra-therapeutic, while two patients did not repeat MM.

Three patients had no dose adjustments due to biochemical or endoscopy evidence of active disease. They also had lower median baseline 6-TGN levels compared with patients with dose reductions (547.50 vs 606.60, P = 0.171).

**Therapeutic outcomes.** Thirty-nine patients (67.2%) with repeated MM achieved metabolite levels within the therapeutic range at the end of 1 year. Overall, 87.8% (79/90) achieved SFR, although no significant difference was observed among the four groups (Table 3). Of note, 90.5% (19 of 21) of adherent patients achieved SFR compared with only 57.1% (4 of 7) of non-adherent patients within the sub-therapeutic group.

For the second outcome, 90% (81 of 90) had no therapy escalation and none required surgery throughout the 1-year follow-up. All shunters remained on thiopurine/allopurinol combination.

**Healthcare resource utilization.** Table 4 summarizes the healthcare resource utilization. The median outpatient visits were higher across the three groups not within therapeutic range...
compared with the control (patients within therapeutic range at baseline) (9 [shunters] vs 6.5 [sub-therapeutic] vs 6 [supra-therapeutic] vs 5 [control], \( P = 0.074 \)).

Similarly, the median outpatient laboratory investigations were higher (28 [shunters] vs 22.5 [sub-therapeutic] vs 20 [supra-therapeutic] vs 17 [control], \( P = 0.027 \)), especially increased

| Table 2 | Baseline grouping of patients by metabolite levels |
|---|---|---|---|---|
| Baseline grouping† | \( n (%) \) | 6-TGN level (pmol/8 \times 10^8 RBC), median (IQR) | 6-MMP level (pmol/8 \times 10^8 RBC), median (IQR) |
| Sub-therapeutic | 28 (31.1) | 161.45 (134.95–203.68) | 1077.45 (185.78–2343.29) |
| Adherent | 21 (75.0) | 175.10 (135.45–205.30) | 1470.00 (304.20–2693.23) |
| Non-adherent‡ | 7 (25.0) | 144.30 (106.30–173.40) | 146.10 (78.50–1090.90) |
| Shunters§ | 7 (7.8) | 190.70 (159.10–193.40) | 7578.10 (6693.10–18 998.60) |
| Therapeutic range | 36 (40.0) | 343.30 (293.83–392.25) | 1305.35 (514.55–2506.58) |
| Supra-therapeutic | 19 (21.1) | 581.60 (531.50–776.80) | 2216.90 (744.50–3670.60) |

† Grouping criteria of 6-TGN and 6-MMP levels are explained in Section 2.4 and Table S1.
‡ One patient had undetectable metabolite levels indicating non-adherence.
§ One patient had an exceptionally high 6-MMP level of 37 676.40 pmol/8 \times 10^8 RBC, thus skewing the median 6-MMP level and median 6-MMP/6-TGN ratio of 52.2.
6-MMP, 6-methylmercaptopurine; 6-TGN, 6-thioguanine nucleotide; IQR, interquartile range; RBC, red blood cells.

| Table 3 | Clinical actions taken in response to baseline metabolite monitoring (MM), metabolite levels after the first action, and therapeutic outcomes at the end of the 1-year follow-up |
|---|---|---|---|---|
| Baseline grouping | First action taken | Metabolite levels after the first action† | 1-year outcomes |
| | | | Steroid-free remission, \( n (%) \) | No escalation to anti-TNF or surgery, \( n (%) \) |
| Sub-therapeutic (\( n = 28 \)) | 17 Increase thiopurine dose§ | 5 Therapeutic |
| | | 5 Decrease thiopurine dose |
| | | 10 No change (includes 5 non-adherent†) |
| | | 1 Decrease thiopurine dose |
| Shunters (\( n = 7 \)) | 7 Add 100 mg allopurinol and decrease to \( 1/4 \) of initial thiopurine dose‡ | 3 Therapeutic |
| Therapeutic range (\( n = 36 \)) | 28 No change‡ | 4 Therapeutic |
| | | 3 Decrease thiopurine dose |
| | | 3 Sub-therapeutic |
| | | 18 did not repeat MM |
| | | 5 did not repeat MM |
| | | 5 did not repeat MM |
| Supra-therapeutic (\( n = 19 \)) | 16 Decrease thiopurine dose¶ | 10 Therapeutic |
| | | 4 Supra-therapeutic |
| | | 2 without repeat MM |
| | | 1 Therapeutic |
| | | 2 did not repeat MM |

† Out of 90 patients, 58 patients repeated MM after the baseline MM.
‡ Recommended actions guided by the MM algorithm in the literature (Table S1).
§ anti-TNF, antitumor necrosis factor.
¶ Recommended actions guided by the MM algorithm in the literature (Table S1).
monitoring for full blood count and inflammatory markers (Table S2). All three groups also had significantly higher median MM tests compared with the control (3 [shunters] vs 2 [supra-therapeutic]) vs 2 [supra-therapeutic] vs 1 [control], \( P < 0.001 \)). The proportion with repeated MM was highest in shunters (100%), followed by the sub-therapeutic (82.1%), supra-therapeutic (78.9%), and control (36.1%) groups. No significant difference was noted for the rates of radiological procedures and colonoscopies.

Overall, 10 patients had ED visits and 13 had inpatient admissions (4 elective, 11 non-elective). No significant difference was found across the four groups.

**Healthcare cost.** All three groups not within therapeutic range incurred similar total healthcare costs at 1 year compared with the control (\( P = 0.592 \)) (Table 5). The median cost was highest in shunters (S$6407.66), followed by the supra-therapeutic (S$5215.20), sub-therapeutic (S$4970.80), and control (S$4370.48) groups. Outpatient services contributed the most to total costs for shunters (52.2%) and the supra-therapeutic group (45.6%), whereas outpatient medications were the main cost component for the sub-therapeutic (44.8%) and control (37%) groups.

The costs of outpatient services were also similar across the four groups (\( P = 0.463 \)). The supra-therapeutic group incurred higher median costs than the control (S$3872.4 vs S$2686.45). The contribution of radiological procedures and colonoscopies to outpatient services costs was approximately half for all patients (47.7%) and greatest in the supra-therapeutic group (52%).

In addition, the costs of outpatient medications across the four groups were not significantly different (\( P = 0.722 \)). Oral 5-aminosalicylates were the main cost component (58.5%) for patients without therapy escalation. In contrast, anti-TNF accounted for 90.1% of medication costs for the nine patients who escalated therapy. The sample size for ED visits and inpatient costs was small, thus no statistical analysis was done.

**Discussion**

Thiopurines are commonly used for maintaining SFR in IBD. Given the variable thiopurine metabolism and response,
monitoring metabolite levels is increasingly used in the Western population to improve therapeutic outcomes and reduce toxicity.\textsuperscript{2,9,10,24} However, it remains a new strategy in Singapore. This is the first study investigating the clinical utility of MM in Singaporean IBD patients and its impact on healthcare resource utilization over a 1-year follow-up.

Despite optimal weight-based dosing at baseline, 60% of our cohort were not within the therapeutic range. The majority had either sub-therapeutic (31.1%) or supra-therapeutic (21.1%) 6-TGN levels, which are consistent with published literature.\textsuperscript{2,9,25} These findings suggest that conventional weight-based dosing has limitations, as evidenced by the poor correlation with 6-TGN levels.\textsuperscript{3,10,26} With MM-guided dose optimization, 82.4% of the sub-therapeutic group and 93.8% of the supra-therapeutic group achieved clinical benefit without escalation to anti-TNF or surgery. Our findings are comparable with that of published studies on MM, where 70% (14 of 20) achieved 6-month SFR and 94.3% (82 of 87) avoided therapy escalation.\textsuperscript{2,27} Therefore, MM may be useful in current clinical practice to optimize IBD therapy.

The American Gastroenterology Association (AGA) suggests that MM may guide treatment changes in nonresponders, with either therapy escalation if 6-TGN levels were already within therapeutic range, or thiopurine dose optimization.\textsuperscript{12} In our cohort, MM resulted in timely escalation for five patients with active disease despite achieving therapeutic 6-TGN levels. This prevents delay of effective therapy, compared with gradual titration in conventional weight-based dosing where thiopurines may take up to 6 months for therapeutic efficacy.\textsuperscript{28,30} On the other hand, identifying sub-therapeutic 6-TGN levels may guide more aggressive dose adjustments to achieve therapeutic levels and SFR. Likewise, without MM to detect sub-therapeutic 6-TGN levels from preferential metabolism toward 6-MMP, shunters may have unnecessary escalation or blind dose increments with potential toxicity.\textsuperscript{20} Our results show that the addition of allopurinol favorably reduced 6-MMP levels and reversed 6-MMP/6-TGN ratios, enabling all shunters to maintain thiopurines at the end of 1 year. Similarly, Goldberg \textit{et al.} demonstrated that 93% of shunters successfully reversed shunting by reducing 6-MMP using allopurinol.\textsuperscript{10}

Furthermore, MM detects thiopurine non-adherence by identifying patients with undetectable metabolite levels.\textsuperscript{2,9,31} This timely intervention provides opportunities for patient education and discussion on the importance of continuing thiopurines to achieve disease remission.\textsuperscript{2,20} Our study found that adherent patients had better therapeutic outcomes, where 90.5% achieved SFR compared with 57.1% of non-adherent patients. Adherence also varied over time as some patients initially with therapeutic levels had undetectable or sub-therapeutic TGN levels, or thiopurine dose optimization.

Regarding repeated MM, the AGA and North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guidelines do not have specific recommendations.\textsuperscript{12,24} Our study shows that repeated MM is useful after initial dose optimization because not all patients will achieve therapeutic levels after taking the first MM-guided action. The proportion achieving therapeutic levels increased modestly from

### Table 5: Direct healthcare costs incurred during the 1-year follow-up after baseline metabolite monitoring (MM)

| Cost category                      | Control (proxy without MM) | Not within therapeutic range (with MM) |
|------------------------------------|----------------------------|----------------------------------------|
| Total costs at 1 year, median (IGR) | 4370.48                   | 4970.80                                |
| Outpatient services\textsuperscript{1}, median (IGR) | (2119.95–7164.83)         | (2477.52–8037.85)                      |
| Outpatient medications, median (IGR) | 1075.60                   | 1101.54                                |
| Emergency department visits, median (IGR) | 70.940.00                 | 242.00\textsuperscript{1}             |
| Inpatient services\textsuperscript{1} and medications, median (IGR) | 25 383.06                 | 9261.64\textsuperscript{1}            |

Values are in SGD (S$). The breakdown within each cost category is illustrated in Table S3. Total costs at 1 year, costs of outpatient services, and medications were calculated for all 90 patients. Costs of emergency department visits and inpatient services and medications were weighted, excluding patients with zero relevant costs. The former was calculated for 10 patients (n = 3 [control], n = 5 [sub-therapeutic], n = 1 [shunter], n = 1 [supra-therapeutic]). The latter was calculated for 13 patients (n = 5 [control], n = 5 [sub-therapeutic], n = 1 [shunter], n = 2 [supra-therapeutic]).

\textsuperscript{1}Outpatient services: Outpatient visits, laboratory investigations, metabolite monitoring tests, radiological procedures, and colonoscopies.

\textsuperscript{2}Median cost presented without IQR as IQR cannot be calculated from SPSS.

\textsuperscript{3}Exact cost presented without IQR as median (IQR) = n = 7.

\textsuperscript{†}Inpatient services: Length of elective and non-elective admissions, inpatient laboratory investigations, inpatient radiological procedures, and colonoscopies.

IQR, interquartile range.
a baseline of 40% (36/90) to 54% (27/50) after taking the first MM-guided action. Possible reasons include inadequate titration, non-adherence with the new dose, or delayed development of shunting toward 6-MMP. More importantly, our study identified five delayed shunters through repeated MM after the initial dose increment. This supports a previous study reporting an association between increased doses and shifted metabolism toward 6-MMP rather than increased 6-TGN.10 Furthermore, Yarur et al.27 and Wright32 reported intra-patient variability between measurements at stable doses. We observed similar findings with patients showing fluctuating metabolite levels despite no therapy change. Overall, repeated MM with subsequent dose modification resulted in 67.2% of patients achieving therapeutic levels by the end of 1 year. Hence, our study provides supporting evidence on the need for repeated MM to guide thiopurine dose optimization.

Although MM is shown to be beneficial in clinical practice, the cost-versus-effectiveness of MM should be considered. Our results indicated that MM for patients not within therapeutic range at baseline incurred similar total costs at 1 year compared with the control (proxy without MM) from the patient perspective. MM was also associated with similar outpatient services costs despite higher costs of visits and laboratory investigations from increased outpatient monitoring after dose adjustments. Moreover, optimizing thiopurines using MM resulted in potential cost savings from avoiding escalation to anti-TNF for 90.7% of patients not within therapeutic range at baseline. Other potential cost savings cited in the literature include avoiding consequences from disease relapse or disease progression due to poorly controlled metabolite levels, especially in non-adherent patients.2,23

However, the cost-effectiveness study by Dubinsky et al. showed that MM reduced total costs with improved therapeutic outcomes (faster to sustained treatment response).11 The drug and procedure cost estimates in their model were derived from the 2004 American healthcare database and the literature. These may not reflect real-world costs in other countries and likely account for the disparity with our cost findings. For example, the costs for MM (US$14.77 vs US$100.00) and full blood count (FBC) tests (US$4.81 vs US$29.20) were lower in their model. Their steroid use was limited to prednisolone (US$0.11/dose), whereas our study included the more expensive budesonide formulation (S$1.84/dose). These likely explain why MM was not associated with significantly higher healthcare resource utilization and costs. Future cost-effectiveness studies are required to confirm the clinical benefits of MM, such as outcomes on mucosal healing, and the potential cost savings of MM, especially for thiopurine/anti-TNF combination therapy.

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Supporting information
Additional supporting information may be found in the online version of this article at the publisher’s website:

Appendix S1. Supporting information.