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AGA SECTION

American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease

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This article has an accompanying continuing medical education activity, also eligible for MOC credit, on page e20. Learning Objective: Upon completion of this CME activity, successful learners will able to explain the appropriate use of therapeutic drug monitoring in patients with inflammatory bowel disease, treated with anti-tumor neurosis factor medications or thiopurine medications.

This document presents the official recommendations of the American Gastroenterological Association (AGA) on therapeutic drug monitoring (TDM) in inflammatory bowel disease (IBD). The guideline was developed by the AGA's Clinical Guidelines Committee and approved by the AGA Governing Board. It is accompanied by a Technical Review, which is a compilation of clinical evidence from which these recommendations were formulated.[1]

IBD is often treated with immunomodulators and/or biologics. The trough concentrations of these drugs can vary due to disease severity, phenotype, degree of inflammation, use of immunomodulator, patient sex, and body mass index, as well as variability in drug clearance through immune- and non–immune-mediated mechanisms. In order to better optimize the drug concentration and clinical improvement, TDM is used to check the drug trough concentration and assess for the presence of anti-drug antibodies.[2] TDM can be performed at any point of therapy in induction or maintenance therapy.[2] It can be performed in a routine proactive fashion when a patient is in remission, or as reactive testing in response to suboptimal disease control. For the purposes of this guideline, reactive testing refers to TDM performed in patients who have active IBD, defined as having active symptoms related to IBD that are confirmed with objective findings from biochemical markers, endoscopic, or radiologic findings of active inflammation or in patients who are asymptomatic clinically but have findings of objective inflammation on endoscopy or radiology.

In the event of drug failure, there are 3 possible causes: mechanistic failure, non–immune-mediated pharmacokinetic failure, and immune-mediated pharmacokinetic failure.[1] Mechanistic failure occurs when the patient is not responding despite optimal drug trough concentrations. This type of failure is likely related to the disease process being driven by inflammatory mediators that are not blocked by the particular drug. Therefore, these patients are unlikely to respond to other drugs within the same class. Non–immune-mediated pharmacokinetic failure occurs when patients do not adequately respond to therapy in the setting of subtherapeutic trough concentrations and absence of anti-drug antibodies. This phenomenon results from rapid drug clearance, often in the setting of a high inflammatory burden. Immune-mediated pharmacokinetic failure occurs in patients who have low or undetectable trough concentrations and high titers of anti-drug antibodies. This type of drug failure results from the immune-mediated formation of neutralizing anti-drug antibodies.[1] Currently, there are many commercial assays available to test trough concentrations and antibodies. In general, measurement of trough concentrations, but not of anti-drug antibodies, is relatively comparable with acceptable specificity, accuracy, and reproducibility between assays. In a comparative study, quantitative drug concentrations of infliximab with different assays was −7% to +20% of each other.[3,4] However, in another study comparing enzyme-linked immunosorbent assay and homogeneous mobility shift assay for measuring adalimumab trough levels, considerable inter-assay variability was observed.[5] Due to paucity of convincing comparative data, in case of repeated trough concentration and anti-drug antibody measurements for a patient, we suggest using the same assay. In contrast to trough concentration, the reporting of anti-drug antibodies is variable between commercial assays and there is no standardized reporting of these values. In addition, uniform thresholds for clinically relevant anti-drug antibody titers are lacking. Therefore, it may be beneficial to utilize the same assay when checking for trough concentration and anti-drug antibodies.[1]

This guideline was developed to inform appropriate utilization of TDM with anti-tumor necrosis factor (TNF)-α agents and thiopurines. Additionally, the guideline also

Abbreviations used in this paper: **AGA, American Gastroenterological Association; CBC, complete blood count; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IBD, inflammatory bowel disease; RCT, randomized controlled trial; RR, relative risk; TDM, therapeutic drug monitoring; 6-TGN, 6-thioguanine; TNF, tumor necrosis factor; TPMT, thiopurine methyltransferase.**

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sought to determine the role of testing the genetic or enzymatic activity of thiopurine methyltransferase (TPMT) before starting a thiopurine. Due to a paucity of data at the time of publication, this guideline does not address the role of TDM in patients treated with vedolizumab or ustekinumab.

The AGA process for developing clinical practice guidelines follows the standards set by the Institute of Medicine.[6] This process is described in more detail elsewhere and was used in developing the Technical Review and the guideline.[7] The GRADE (Grading of Recommendations Assessment, Development and Evaluation) framework was used to evaluate the certainty of the evidence and grade the strength of the recommendations.[7] Understanding of this guideline and the evidence supporting the recommendations will be enhanced by reading the Technical Review.[1] The guideline panel and the authors of the Technical Review met face-to-face on February 26, 2017 to discuss the findings from the Technical Review. The guideline authors subsequently formulated the recommendations. Although quality of evidence (Table 1) was a key factor in determining the strength of the recommendation (Table 2), the panel also assessed the balance between benefit and harm of interventions, patients' values and preferences, and resource utilization. While cost is usually factored into the recommendation, in this situation it was not feasible to accurately assess cost-effectiveness, given the variable costs of the commercial trough concentration and antibody testing assays throughout the United States and internationally. The recommendations, quality of evidence, and strength of the recommendations are summarized in Table 3.

Recommendation: In adults with active IBD treated with anti-TNF agents, the AGA suggests reactive therapeutic drug monitoring to guide treatment changes. Conditional recommendation, very low quality of evidence.
Comment: Table 4 summarizes suggested trough concentration for anti-TNF therapy, for patients with active IBD on maintenance therapy. Of note, there may be a small subset of patients who may still respond by targeting higher target concentrations. Optimal trough concentrations for induction therapy are uncertain.

Table 1. Grading of Recommendations Assessment, Development, and Evaluation Definitions of Quality/Certainty of the Evidence

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

The guideline panel conditionally recommends in favor of using reactive TDM in patients with active IBD to help guide treatment changes. To answer this question, there was 1 randomized control trial (RCT) and 3 observational studies of patients with IBD who were receiving maintenance therapy with anti-TNF.[8–11] The RCT included 69 patients on maintenance therapy with infliximab who developed active Crohn's disease symptoms and were randomized to TDM-guided treatment changes vs empiric dose escalation.[8] A significant limitation of this study was an infliximab trough $\geq$0.5 μg/mL was considered optimal. Patients with a trough $\geq$0.5 μg/mL were deemed to have mechanistic drug failure and switched to an alternative non−TNF-based therapy (76% of patients). However, this trough concentration is considerably lower than the trough level of $\geq$5 μg/mL that is supported by the current evidence (Table 4).[1,8] On intention-to-treat analysis at 12 weeks, there was no significant difference in achieving remission between the 2 strategies (relative risk [RR], 0.78; 95% confidence interval [CI], 0.40−1.51).[8] When pooling the 3 observational studies together, only 30% (139 of 464) were considered mechanistic failures (adequate trough), likely related to the higher target trough concentrations of 2.0−3.8 μg/mL for infliximab and an adalimumab trough of 4.5−4.9 μg/mL.[9–11] Similar to the RCT, 19% (90 of 464) were deemed to have immune-mediated pharmacokinetic failure with subtherapeutic trough concentration and presence of anti-drug antibodies. However, in contrast to the 4% of patients in the RCT, 51% (235 of 464) were deemed to have non−immune-mediated pharmacokinetic failure with subtherapeutic trough levels but no anti-drug antibodies.[9–11] In pooling 2 of the studies retroactively, 45% of patients responded to empiric dose escalation.[9,10] On retrospectively applying TDM, 82% of patients with a subtherapeutic trough and no anti-drug antibodies would have responded to dose escalation (RR, 1.71; 95% CI, 1.39−2.11), while only 8% of patients with low or undetectable trough in the presence of anti-drug antibodies would have responded (RR, 0.26; 95% CI, 0.08−0.86).[9,10]

The quality of evidence of the RCT was downgraded to very low due to a high risk of bias from a high degree of nonadherence to the protocol, indirectness resulting from the low therapeutic trough level utilized ($\geq$0.5 μg/mL), and imprecision. Similarly, the observational studies were considered very low quality from the risk of bias related to study design and imprecision.[1]

There are several issues that remain unresolved even after assessing the evidence. The best-available evidence did not address the optimal timing for measuring trough concentrations. In most cases, the panel recommends that a trough level for infliximab or adalimumab be drawn as close to the next dose as possible (ie, within 24 hours). Additionally, while the drug trough concentration is consistent across different commercial assays, assays for anti-drug antibodies are not readily comparable with each other.[1]

When anti-drug antibodies are detected, it is unclear what antibody level is clinically meaningful. Low-titer antibodies may be transient and non-neutralizing, such that shortening the drug-dosing interval and/or escalating the dose may optimize the trough concentration in this setting of low-titer antibodies. In contrast, high-titer anti-drug

Table 2. Grading of Recommendations Assessment, Development, and Evaluation Definitions on Strength of Recommendation

Grade	Wording in the Guideline	For the patient	For the clinician
Strong	"The AGA recommends . . ."	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	"The AGA suggests . . ."	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.
No recommendation	"No recommendation"		The confidence in the effect estimate is so low that any recommendation is speculative at this time

antibodies, especially with undetectable trough concentrations, are generally persistent and neutralizing. In this setting, especially with undetectable drug, there may be very limited benefit to attempting dose escalation of the index agent, and switching to a different drug within the same class may be more effective. Unfortunately, current data do not allow us to identify optimal anti-drug antibody cutoffs for high- vs low-titer antibodies, in the current commercially available assays.[1]

The studies mentioned did not specifically address patients who were in clinical remission but had active disease on endoscopy or imaging. As treatment paradigms shift toward targeting mucosal healing, indirect evidence suggests that using reactive TDM in this situation would be reasonable.[12] However, optimal target trough concentrations for achieving mucosal healing are uncertain and may be higher than those suggested for achieving clinical remission.[1,12]

Importantly, none of the aforementioned studies evaluated the use of reactive TDM during induction therapy. In patients with suboptimal response to induction therapy, the benefit of applying TDM to direct treatment changes vs empiric dose escalation of index therapy is uncertain. Optimal target trough concentrations and timing of achieving maximal effectiveness of anti-TNF agents during induction therapy are unclear; if trough thresholds as suggested for maintenance therapy are applied to the induction phase, it may result in erroneous misclassification of

Table 3. Summary of Recommendations of the American Gastroenterological Association Clinical Guidelines for Therapeutic Drug Monitoring in Inflammatory Bowel Disease

Statement	Strength of recommendation	Quality of evidence
In adults with active IBD treated with anti-TNF agents, the AGA suggests reactive therapeutic drug monitoring to guide treatment changes. Conditional recommendation, very low quality of evidence.	Conditional recommendation	Very low quality
Comment: *Table 4 summarizes suggested trough concentration for anti-TNF therapy, for patients with active IBD on maintenance therapy. Of note, there may be a small subset of patients who may still respond by targeting higher target concentrations. Optimal trough concentrations for induction therapy are uncertain.*		
In adult patients with quiescent IBD treated with anti-TNF agents, the AGA makes no recommendation regarding the use of routine proactive therapeutic drug monitoring.	No recommendation	Knowledge gap
In adult patients with IBD being started on thiopurines, the AGA suggests routine TPMT testing (enzymatic activity or genotype) to guide thiopurine dosing.	Conditional recommendation	Low quality
Comment: *Routine laboratory monitoring, including CBC, should be performed, regardless of TPMT testing results.*		
In adult patients treated with thiopurines with active IBD or adverse effects thought to be due to thiopurine toxicity, the AGA suggests reactive thiopurine metabolite monitoring to guide treatment changes.	Conditional recommendation	Very low quality
Comment: *When measuring thiopurine metabolite monitoring in patients with active IBD-related symptoms, we suggest a target 6-thioguanine (6-TGN) cutoff between 230−450 pmol/8 × 10^8 RBCs when used as monotherapy; optimal 6-TGN cutoff when thiopurines are used in combination with anti-TNF agents is uncertain*		
In adult patients with quiescent IBD treated with thiopurines, the AGA suggests against routine thiopurine metabolite monitoring.	Conditional recommendation	Very low quality

Table 4. Suggested Target Trough Concentrations When Applying Reactive Therapeutic Drug Monitoring in Patients With Active Inflammatory Bowel Disease on Maintenance Therapy With Anti–Tumor Necrosis Factors[a]

Drug	Suggested trough concentration, μg/mL	Comments[b]
Infliximab	≥5	Six studies (929 patients) provided data on proportion of patients not in remission above predefined infliximab thresholds (1, 3, 5, 7, and 10 μg/mL). Based on these, proportion of patients not in remission decreased from 25% when using an infliximab threshold of ≥1 μg/mL, to 15% with an infliximab trough concentration of ≥3 μg/mL, to approximately 4% with an infliximab trough concentration of ≥7 μg/mL or ≥10 μg/mL
Adalimumab	≥7.5	Four studies provided data on proportion of patients not in remission above adalimumab trough concentration >5.0 ± 1 μg/mL or 7.5 ± 1 μg/mL. On analysis of different thresholds, proportion of patients not in remission progressively decreased from 17% when using an adalimumab threshold ≥5.0 ± 1 μg/mL, to 10% with an adalimumab trough concentration of ≥7.5 ± 1 μg/mL. Different studies used different assays, and there are limited data on comparability of trough concentrations identified in different assays for adalimumab It is unclear what proportion of patients on standard (40 mg every other wk) or escalated adalimumab dosing (40 mg every wk) would be able to achieve these thresholds
Certolizumab Pegol	≥20	One study provided data from an exposure response pooled analysis from 9 trials. On analysis of different thresholds, proportion of patients not in remission progressively decreased from 42% when using a certerolizumab threshold of ≥10 μg/mL to 26% with a certolizumab trough concentration of ≥20 μg/mL
Golimumab	Unknown	There is a lack of sufficient evidence available to establish a target trough goal

[a]Studies used to derive different target trough concentrations were cross-sectional studies of patients on maintenance therapy in various stages of remission/response, to identify what proportion of patients were in remission (or not in remission), above and below specific thresholds. They were not specifically designed to evaluate patients who had a secondary loss of response.
[b]Details are available in accompanying Technical Review.

patients as having a mechanistic failure, because target trough concentrations are likely higher in this setting. During the induction phase, empiric dose escalation may be a reasonable alternative, unless immune-mediated pharmacokinetic failure is suspected. Therefore, based on the current evidence, the ability to provide guidance regarding reactive testing during induction is unknown.[1]

The target trough concentration is different for each of the biologic agents (Table 4).[1] The studies used to derive different target trough concentrations were cross-sectional studies of patients on maintenance therapy in various stages of clinical response or remission[10,13–23]; they were not specifically designed to evaluate patients who had a secondary loss of response. Based on the currently available evidence, the panel suggests target trough concentrations of ≥5 μg/mL for infliximab, ≥7.5 μg/mL for adalimumab, and ≥20 μg/mL for certolizumab pegol, to guide whether escalation of therapy may be beneficial (if trough is below this threshold) compared with switching therapy (to be considered if trough is above this threshold) to achieve clinical response in patients who are experiencing secondary loss of response on maintenance therapy.[1] It is important to note that for asymptomatic patients with ongoing endoscopic activity or with perianal disease who undergo reactive TDM, target trough concentrations may be higher, such that escalating index therapy may be a preferable option before switching therapies in these settings. It is also important to note that these are not uniform trough levels that need to be targeted for all patients regardless of clinical status. Data supporting these cutoffs were less robust for adalimumab than for infliximab.[1,5] Additionally, it remains unclear whether higher trough levels are required to achieve therapeutic effect in ulcerative colitis than in Crohn's disease. Data on golimumab are limited and not sufficient to provide a target trough level at this time.[1]

Based on this evidence and target trough concentrations, the panel developed an algorithm for how patients and physicians using shared decision making may respond to reactive TDM testing. Initially, only the trough concentrations should be assessed. If the level is at or above the target trough, then the patient may consider switching to a different drug class, although escalating index therapy may be a reasonable alternative (especially if reactive TDM is performed in asymptomatic patients with ongoing endoscopic activity, or in patients with perianal disease where target trough concentrations may be higher). In the presence of sufficient trough concentrations, results of antibody testing should not guide treatment decisions. If the trough concentration is low (below the suggested threshold, in patients with active IBD) and no anti-drug antibodies are present, then the index drug should be optimized using any of the following techniques: shortening the dosing interval and/or increasing the drug dose, and/or adding an immunomodulator agent. If there is no detectable drug (zero trough concentration) and high-titer anti-drug antibodies are present, then the patient should consider switching to a different drug within the class or to a different drug class. If there is no detectable drug and low-titer antibodies are present, then one can consider trying to optimize the index drug by shortening the dosing interval and/or increasing the drug dose, and/or adding an immunomodulator agent. Typically, optimizing the drug will be attempted before

changing to a different drug within the class or switching to a new drug class, although some might opt to change to a different drug within the class or switch to a new drug class. It should be noted that the reporting of anti-drug antibodies is variable between commercial assays, with some assays being very sensitive for detecting very-low-titer antibodies of limited clinical significance. Uniform thresholds for clinically relevant antibody titers are lacking. At this time, it is unclear how antibodies affect drug efficacy when both active drug and antibodies are detected. In cases of low trough concentrations and low or high anti-drug antibodies, the evidence to clarify optimal management is lacking.

Recommendation: In adult patients with quiescent IBD treated with anti-TNF agents, the AGA makes no recommendation regarding the use of routine proactive therapeutic drug monitoring. No recommendation, knowledge gap.

At this time, the relative benefit vis-à-vis harms of routine proactive TDM in patients with quiescent IBD treated with anti-TNF therapy is uncertain. Although a benefit is biologically conceivable (presence of exposure−response relationship between trough concentration and clinical and endoscopic response, inter-individual variability in pharmacokinetics, especially the negative impact of anti-drug antibodies on drug clearance and efficacy), there is concern for harm, especially due to premature switching away from index therapy (due to limited understanding of significance of low-titer anti-drug antibodies, resulting in inconsistent interpretation of anti-drug antibody titers and trough concentrations). While selective use of proactive TDM after careful consideration may be beneficial, current evidence supporting routine, proactive TDM is limited and the overall benefits of this strategy remain uncertain. Therefore, because of this knowledge gap and need for further studies, no recommendation can be made regarding this question.

There were no RCTs or comparative observational studies comparing a priori proactive TDM for achieving remission and thus, indirect evidence was utilized. The single RCT on this topic was the TAXIT (Trough Concentration Adapted Infliximab Treatment) study by Vande Casteele et al,[24] in which all patients were first dose optimized to achieve an infliximab trough of 3−7 μg/mL. Once this target was reached, patients were randomized to proactive TDM vs no TDM. While initial dose optimization in a subset of patients with low trough concentrations resulted in an increase in the proportion of patients achieving clinical and biochemical remission, once the initial dose optimization was achieved with TDM, the proportion of patients achieving remission at 1 year with routine proactive TDM vs no TDM was not different (RR, 1.04; 95% CI, 0.88−1.24).[24] While this study indicates that an initial TDM for dose optimization may be beneficial, further routine repeated TDM (eg, before every dose of infliximab) does not show any additional benefit at 1 year. This study provided only indirect evidence to answer the question of routine TDM because all patients were initially optimized to a goal trough of 3−7 μg/mL. There was no comparator arm in this initial drug optimization phase and, therefore, while the findings indicate an increase in proportion of patients in remission who had low drug levels optimized and a cost savings by dose reduction in those with a supratherapeutic trough concentration, the true effects of these changes long-term from routine proactive TDM remain unknown.[1,24] This study does not answer the question regarding the benefit of a one-time routine proactive TDM or timing of drug optimization on clinical outcomes. One important finding of the TAXIT study was that at 1 year, the patients who did not receive proactive TDM had higher rates of anti-drug antibodies and undetectable infliximab trough levels. This might presumably increase the risk of disease flares and treatment failure in the long term. However, given the limited duration of follow-up in the TAXIT study, the evidence to answer this is unknown. In another single-center, retrospective observational study by Vaughn et al,[25] patients who underwent routine proactive TDM before each infliximab infusion were less likely to discontinue infliximab due to disease flares or infusion reaction compared with patients who did not undergo TDM.

Overall, the evidence from the TAXIT study was considered very low quality due to very serious indirectness and imprecision from the wide CIs and summary estimate near unity. Similarly, evidence from Vaughn et al[25] was also very low quality due to the retrospective design of this study and that patients were selected for routine proactive TDM, which may have resulted in significant selection bias. Additionally, the limited data on direct patient-relevant clinical outcomes limit the strength of the evidence from this study and its overall generalizability.[1]

Post-hoc analysis from clinical trials of induction therapy of anti-TNF drugs indicates an exposure−response relationship and patients with higher trough levels between weeks 4 and 14 were more likely to achieve remission.[1] This is further supported by the data from Vande Casteele et al,[24] who noted that uniform dose optimization resulted in an increase in proportion of patients in clinical remission (from 65% pre-optimization to 88% post-optimization). While this supports the notion that early optimization of therapy based on proactive TDM testing can be helpful, the magnitude of benefit for patient-important outcomes, long-term benefit over reactive TDM, and frequency of assessments in proactive TDM are unclear.[1]

Routine proactive TDM may not be without harm. Because target trough concentrations for asymptomatic patients under routine care are unclear and the significance of low-titer anti-drug antibodies is unclear, testing can lead to therapeutic dilemmas and inappropriate treatment changes, particularly due to premature switching to different drugs in patients who are otherwise in remission. Also, the frequency with which TDM needs to be repeated for routine proactive TDM and after a drug-dosing change is also unclear. The cost associated with this is variable based on the different assay costs, as well as downstream costs of treatment changes. Additional well-designed RCTs with direct patient-relevant outcomes from routine proactive TDM compared with no TDM are still needed to answer whether routine proactive TDM should be performed and, if it is performed, how often TDM should be checked.[1]

Recommendation: In adult patients with IBD being started on thiopurines, the AGA suggests routine TPMT testing (enzymatic activity or genotype) to guide thiopurine dosing. Conditional recommendation, low quality of evidence.
Comment: Routine laboratory monitoring, including complete blood count (CBC), should be performed, regardless of TPMT testing results.

The guideline panel conditionally recommends routine TPMT testing before starting a thiopurine based on low-quality evidence. While available evidence suggests that there may not be significant benefit of this strategy over empiric weight-based dosing at a population level, a very small subset of patients who are homozygous for TPMT are at risk for considerable harm due to severe neutropenia and infections, if treated with empiric weight-based dosing.

There are 3 RCT studies comparing TPMT testing to no testing with empiric weight-based thiopurine dosing.[26–28] Genotype was utilized in 2 studies and enzymatic activity in 1 study. In these studies, patients with a normal enzyme/genotype started full-dose thiopurine, while those with intermediate enzymatic activity/heterozygous genotype had a 50% dose reduction. Those with low/absent enzyme activity or homozygous genotype were not given the drug or were given a reduced dose at 0−10% of the initiation dose. In the 1145 patients included in the studies, only 0.17% (n = 2) were homozygous. Hematologic adverse events and treatment discontinuation were used as surrogate outcomes for benefits of TPMT testing. There was no significant difference in either outcome based on TPMT testing, with the relative risk of hematologic events of 0.94 (95% CI, 0.59−1.50) and treatment discontinuation of 1.09 (95% CI, 0.94−1.27). Additionally, there was also no significant difference in clinical remission in these groups based on TPMT checking (RR, 1.03; 95% CI, 0.84−1.27). However, if an individual is intermediate enzymatic activity/heterozygous genotype or homozygous genotype/low enzymatic activity, then TPMT testing to guide dosing was associated with an 89% risk reduction of hematologic adverse events.[26–28] Therefore, although the risk of harm from not testing a TPMT level before initiating therapy is minimal in most cases, there is considerable risk of harm in the 0.3% patients who are homozygous genotype or have low/absent TPMT enzymatic activity. While this risk may be mitigated by routine laboratory CBC checking, adherence to regular monitoring in clinical practice is suboptimal.[29] It is therefore important to continue to perform routine laboratory monitoring with CBC and liver enzyme monitoring after starting a thiopurine regardless of the TPMT testing results.[1]

The evidence supporting this recommendation was considered low quality due to the indirectness of the surrogate outcomes studied—hematologic adverse events and treatment discontinuation. Additionally, the evidence was further rated down for serious imprecision given the wide CIs crossing unity and the low event rate.

Recommendation: In adult patients treated with thiopurines with active IBD or adverse effects thought to be due to thiopurine toxicity, the AGA suggests reactive thiopurine metabolite monitoring to guide treatment changes. Conditional recommendation, very low quality of evidence.
Comment: When measuring thiopurine metabolite monitoring in patients with active IBD-related symptoms, we suggest a target 6-thioguanine (6-TGN) cutoff between 230 and 450 pmol/8 × 10^8 red blood cells (RBCs) when used as monotherapy; optimal 6-TGN cutoff when thiopurines are used in combination with anti-TNF agents is uncertain.

The panel conditionally recommends in favor of reactive testing of thiopurine metabolites in patients with active IBD based on very low quality evidence. There were no RCTs available to answer this question. In a retrospective observational study of 60 patients with active IBD treated with thiopurines, response to therapy was categorized based on whether patients received treatment concordant with TDM algorithm vs treatment discordant with TDM algorithm.[30] The TDM algorithm suggested thiopurine dose optimization if their 6-TGN level was low (<230 pmol/8 × 10^8 RBCs) and switching to a different medication if 6-TGN level was adequate. Patients who received algorithmic-concordant care were significantly more likely to respond to a therapeutic change compared with patients who received algorithm-discordant care (RR, 5.15; 95% CI, 1.82−14.56).[30]

Overall, the level of evidence was very low quality due to observational study design, imprecision from the small study size, and indirectness from the study comparison groups.[1]

The target 6-TGN metabolite cutoff between 230 and 450 pmol/8 × 10^8 RBCs when used as monotherapy is based on limited studies.[1] The 6-TGN levels ≥230 pmol/8 × 10^8 RBCs were associated with 40% higher rates of remission (RR, 1.4; 95% CI, 1.2−1.6) compared with levels <230 pmol/8 × 10^8 RBCs. However, it is unclear whether this target 6-TGN concentration applies when thiopurines are used in combination with anti-TNF agents, where one of the reasons for combination therapy is to reduce the risk of immunogenicity, rather than independently targeting remission. Although lower targets have been suggested, current evidence fails to identify a target threshold.[1]

Potential harms associated reactive TDM testing include the additional burden of intensified laboratory monitoring necessary with each dose adjustment and the potential for delaying alternative effective therapies in patients not responding to thiopurines.[1]

Recommendation: In adult patients with quiescent IBD treated with thiopurines, the AGA suggests against routine thiopurine metabolite monitoring. Conditional recommendation, very low quality of evidence.

The guideline panel conditionally recommended against routine testing of thiopurine metabolites in patients with quiescent IBD. There were 2 RCT trials of 107 patients on azathioprine that investigated routine thiopurine metabolite

monitoring to achieve a 6-TGN concentration of 250−400 pmol/8 × 10^8 RBCs compared with standard weight-based dosing determined by TPMT testing.[31,32] There was no significant difference in the rate of achieving clinical remission (RR, 1.44; 95% CI, 0.59−3.52) or serious adverse events (RR, 1.20; 95% CI, 0.50−2.91) with routine thiopurine metabolite monitoring compared with standard dosing.[31,32] Of note, these studies were not performed in patients on combination therapy with anti-TNF agents and provided limited ability to optimize thiopurine therapy (only thiopurine dose escalation was permitted in patients with 6-TGN <230 pmol/8 × 10^8 RBCs and alternative strategies such adding allopurinol was not permitted). Therefore, data from these studies cannot be extrapolated to the management of thiopurines when used in combination with an anti-TNF agent.[1]

The evidence supporting this recommendation was very low. Neither study achieved their recruitment target resulting in a concern for high risk of bias. Additionally, the quality of the studies was downgraded for having both serious inconsistency ($I^2 > 50\%$) and imprecision (wide CIs).[1]

Potential harms associated with this strategy include the additional burden of intensified laboratory monitoring necessary with each dose adjustment and the potential for delaying alternative effective therapies in patients not responding to thiopurines. Therefore, based on the current evidence, the benefit of routine TDM over standard weight-based thiopurine dosing is uncertain.[1]

Summary

These practice guideline recommendations for TDM in IBD were developed using the GRADE framework and in adherence with the standards for guideline development set forth by the Institute of Medicine for the creation of trustworthy guidelines.[6,7] The current evidence supports the use of reactive TDM to guide treatment changes in patients with active IBD who are being treated with anti-TNF agents or thiopurines. However, there is insufficient evidence to inform on the use of routine proactive TDM with anti-TNF agents in patients with quiescent disease. For thiopurines, routine proactive thiopurine metabolite monitoring is not recommended in patients with quiescent IBD. Current evidence supports testing for TPMT enzyme or genotype before initiation of a thiopurine. However, this is not a replacement for routine laboratory monitoring with CBC and liver enzymes after starting therapy with a thiopurine. To further provide guidance on how to implement this guideline in practice, a clinical decision support tool on when to perform TDM and how to interpret TDM when patients are taking an anti-TNF agent or a thiopurine has been provided.[33]

There are several knowledge gaps in TDM that have been identified for which prospective observational and RCTs are warranted, which have been highlighted in the Technical Review that accompanies this guideline.[1] It is unclear whether TDM should be performed during induction therapy in patients with suboptimal response (as opposed to empiric dose escalation) and, if it is performed, what the target trough concentrations should be. Similarly, target trough concentrations when performed in the reactive setting in patients on maintenance therapy with different agents is unclear, and whether it should be different based on disease phenotype, disease state, and treatment target (clinical remission vs mucosal healing). Further studies are also needed to better define clinically meaningful vs insignificant anti-drug antibodies, based on titers and/or persistence on repeated testing, and at which titers can anti-drug antibodies be suppressed before needing to change drug therapies. Additionally, well-designed RCTs are needed that compare routine proactive TDM vs reactive TDM, and empiric dosing changes on patient relevant outcomes, and also the frequency and timing of proactive TDM. Finally, as newer biologic agents are approved, the use of TDM to optimize these drugs will need to be evaluated.

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Conflicts of interest
The authors disclose no conflicts.