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Q1 Q2 Therapeutic Drug Monitoring in Inflammatory Bowel Disease

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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 Q6 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 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,

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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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.

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 ≥0.5 μg/mL was considered optimal. Patients with a trough ≥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 ≥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 (≥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 antibodies, especially with undetectable trough concentrations, are generally persistent and neutralizing. In this setting, especially with undetectable drug, there may be

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.