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American Gastroenterological Association Technical Review on the Role of Therapeutic Drug Monitoring in the Management of Inflammatory Bowel Diseases

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Therapeutic drug monitoring (TDM), which involves measurement of drug or active metabolite levels and anti-drug antibodies, is a promising strategy that can be used to optimize inflammatory bowel disease therapeutics. It is based on the premise that there is a relationship between drug exposure and outcomes, and that considerable inter-individual variability exists in how patients metabolize the drug (pharmacokinetics) and the magnitude and duration of response to therapy (pharmacodynamics). Therefore, the American Gastroenterological Association has prioritized clinical guidelines on the role of TDM in the management of inflammatory bowel disease. To inform these clinical guidelines, this technical review was developed in accordance with the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework for interventional and prognostic studies, and focused on the application of TDM for biologic therapy, specifically anti-tumor necrosis factor−α agents, and for thiopurines. Focused questions address the benefits and risks of a strategy of reactive TDM (in patients with active inflammatory bowel disease) to guide treatment changes compared with empiric treatment changes, and the benefits and risks of a strategy of routine proactive TDM (during routine clinical care in patients with quiescent disease) compared with no routine TDM. Additionally, the review addresses the benefits and risks of routine measurement of thiopurine methyltransferase enzyme activity or genotype before starting thiopurine therapy compared with empiric weight-based dosing and explores the performance of different trough drug concentrations for anti−tumor necrosis factor agents and thiopurines to inform clinical decision making when applying TDM in a reactive setting. Due to a paucity of data, this review does not address the role of TDM for more recently approved biologic agents, such as vedolizumab or ustekinumab.

During the last decade, the approach to treating inflammatory bowel diseases (IBD) has evolved from controlling symptoms and achieving clinical remission to decreasing progressive bowel damage and disability through the timely and optimal use of biologic therapies and/or immunomodulator agents. One emerging strategy in optimizing the use of biologics is therapeutic drug monitoring (TDM), which involves measuring serum drug concentration (typically at trough) and anti-drug antibodies (ADAbs).[1] The proposed rationale for TDM is that a systematic and algorithmic assessment of drug concentration (and ADAb) can help objectively evaluate potential reasons for failure of therapy and define next steps in management, and proactively provide opportunities for optimizing therapy to maximize chances of treatment success. This is based on clinical observations, including the presence of an exposure−response relationship in which serum drug concentration determines the magnitude of the clinical response; inter-individual variability in drug clearance through both immune-mediated (formation of neutralizing ADAb) and non−immune-mediated mechanisms (associated with high inflammatory burden), which contribute to differences in drug concentration; and concept of mechanistic failure, in which, despite adequate drug exposure at site of receptor, some patients may not respond to a particular class of biologics due to differences in underlying disease pathophysiology.[2–4] A similar concept of TDM also applies to thiopurines, wherein thiopurine methyltransferase (TPMT) enzyme activity (or genotype) influences drug metabolism and concentration of drug metabolites, 6-thioguanine (6-TGN) and 6-methylmercaptopurine (6-MMP), which have been variably associated with drug efficacy and safety.[5,6]

However, despite increasing adoption of TDM in clinical practice, there is limited synthesis of evidence and a lack of guidance on the benefits, risks, and overall approach to TDM in the management of IBD. Therefore, the American Gastroenterological Association (AGA) has prioritized this topic for the generation of clinical guidelines.

Abbreviations used in this paper: ADAb, anti-drug antibody; AGA, American Gastroenterological Association; AZA, azathioprine; CBC, complete blood count; CD, Crohn's disease; CI, confidence interval; CRP, C-reactive protein; ECLIA, electrochemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HMSA, homogenous mobility shift assay; IBD, inflammatory bowel disease; 6-MMP, 6-methylmercaptopurine; 6-MP, 6-mercaptopurine; RCT, randomized controlled trial; RIA, radioimmunoassay; RR, relative risk; TDM, therapeutic drug monitoring; 6-TGN, 6-thioguanine; TNF, tumor necrosis factor; TPMT, thiopurine methyltransferase; UC, ulcerative colitis.

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Objectives of the Review

This technical review addresses the following focused clinical questions on different strategies of TDM with biologics and thiopurines to improve patient outcomes:

1. In biologic-treated patients with active IBD, what are the benefits and risks of reactive TDM (in response to active disease) to guide treatment decisions over a strategy of empiric treatment changes? If TDM is adopted, what is the association between different target drug concentrations and clinical outcomes?
2. In biologic-treated patients with quiescent IBD, what are the benefits and risks of routine proactive TDM-guided dose adaptation?
3. What are the benefits and risks of routine measurement of TPMT enzyme activity or genotype, before starting thiopurines, over empiric weight-based dosing?
4. In thiopurine-treated patients with active IBD or suspected to have thiopurine-related toxicity, what are the benefits and risks of reactive TDM with measurement of 6-TGN and 6-MMP levels, to guide treatment decisions over a strategy of empiric treatment changes? If TDM is adopted, what target 6-TGN cutoff is optimal for improving clinical outcomes?
5. In thiopurine-treated patients with IBD on standard weight-based therapy, what are the benefits and risks of routine proactive TDM-guided dose adaptation?

The results of this technical review were used to inform the development of the accompanying clinical guidelines on TDM in IBD. Of note, we focused on anti-tumor necrosis factor (TNF)-α agents only when reviewing TDM for biologics, and no distinction was made between monotherapy and combination therapy in this setting. While the same concepts may apply to other biologics (eg, vedolizumab and ustekinumab), their mechanism of action is distinct from anti-TNF agents and, at this point, there are very limited published data on the role of TDM for these agents to inform guidelines. Therefore, non–anti-TNF biologics are not discussed in these guidelines. Similarly, due to limited use, the technical review team and the guideline panel, with the approval of the AGA Governing Board, opted not to synthesize evidence on the role of TDM for methotrexate, cyclosporine, and tacrolimus.

Methods

Overview

This technical review and the accompanying guideline were developed using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework.[7] The members of the technical review panel were selected by the AGA Clinical Guidelines Committee based on their clinical content and guidelines methodological expertise and went through a thorough vetting process for potential conflicts of interest. Through an iterative process, and in conjunction with the guideline panel, the participants developed focused clinical questions on the role of TDM for anti-TNF agents and thiopurines deemed relevant for clinical practice that the guideline would address. After the focused questions were approved by the AGA Governing Board (in December 2015), the technical review team formulated the clinical questions, identified relevant patient-important outcomes, systematically reviewed and summarized the evidence for each outcome across studies, and then rated the quality of the evidence across all outcomes for each clinical question.

Formulation of Clinical Questions

Using the PICO format, which frames a clinical question by defining a specific population (P), intervention (I), comparator (C), and outcomes (O), the team finalized 5 questions (Table 1). The first set of PICOs focused on TDM for anti-TNF agents, and the second set of PICOs on TDM for thiopurines. Questions focused on comparing different strategies of TDM classified as reactive TDM or routine proactive TDM. *Reactive TDM* is defined as TDM performed in response to active IBD (ongoing active inflammation based on biochemical, endoscopic, or radiologic assessment, usually with symptoms) after a period of quiescent disease, or continued inflammation without achieving remission with index therapy; of note, a small fraction of patients, especially those with active Crohn's disease (CD) (active inflammation) may be asymptomatic, and the concept of reactive TDM also applies to those patients. *Routine proactive TDM* was defined as TDM performed in patients regardless of clinical status (generally in quiescent disease) periodically as part of routine clinical care. The comparator strategy relied on empiric treatment changes—for anti-TNF agents, this focused on a stepwise approach of empiric escalation of therapy or switching to different treatment agents within or outside the index class (ie, with same putative mechanism of action or with a different mechanism of action). Potentially relevant patient-important outcomes were considered and rated in terms of importance through consensus; clinical remission was considered critical for decision making, whereas mucosal healing (endoscopic remission), serious adverse events, cost, drug or metabolite concentration, and patient convenience were considered important outcomes. The panel recognized limitations of using a clinical disease activity as an outcome measure, especially for CD, but still believed that in the current context, it is the most consistently reported outcome in clinical practice and is important for patients.

Search Strategy and Study Selection Criteria

The literature search was performed on March 6, 2016, and details of the search strategy are reported in the Supplementary Material. Studies were selected for inclusion based on PICO theme. Due to lack of high-quality randomized controlled trials (RCTs) informing each question, the study selection and data synthesis approach were customized for each question. For PICO #1 (reactive TDM) and PICO #2 (routine proactive TDM), for anti-TNF agents, we included RCTs, comparative observational studies, or cohort studies in adults with IBD, with either active IBD or quiescent disease, treated with anti-TNF agents, who underwent TDM (ie, measurement of drug levels and/or ADAbs). Due to the paucity of high-quality RCTs and observational comparative studies for