Editorial

Therapeutic drug monitoring in inflammatory bowel disease: too little too early?—comments on the American Gastroenterology Association Guideline

Heidi Y. Su, Mark G. Ward, Miles P. Sparrow

Department of Gastroenterology, Alfred Health and Monash University, Melbourne, Australia

Correspondence to: Miles P. Sparrow. Clinical Head IBD, Department of Gastroenterology, Alfred Health, 99 Commercial Road, Melbourne, VIC 3004, Australia. Email: m.sparrow@alfred.org.au.

Provenance: This is a Guest Editorial commissioned by Editor-in-Chief Jia-Fu Ji (Peking University School of Oncology & Beijing Cancer Hospital, Department of Gastrointestinal Surgery, Beijing, China).

Comment on: Feuerstein JD, Nguyen GC, Kupfer SS, *et al*. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology 2017;153:827-34.

Received: 02 December 2017; Accepted: 08 December 2017; Published: 19 December 2017.

doi: 10.21037/tgh.2017.12.05

View this article at: http://dx.doi.org/10.21037/tgh.2017.12.05

The management of inflammatory bowel disease (IBD) has advanced significantly in recent years, with increasing availability of biologic agents, the use of measurable objective biomarkers of inflammation (e.g., fecal calprotectin) and increasing use of therapeutic drug monitoring (TDM) to optimize individual therapies. IBD management has evolved towards a treat-to-target approach, of which TDM is an increasingly essential part. However, the clinical utilization of TDM varies globally and between institutions, and the ideal best practice use of TDM remains unclear. The recently published American Gastroenterology Association (AGA) TDM guideline attempted to address these issues for clinicians. It consisted of five recommendations on the use of TDM in IBD (1). Two of these recommendations considered anti-tumor necrosis factor (TNF)-α agents, with the remaining three relevant to thiopurines. Recommendations were not made on TDM of newer biologics agents such as vedolizumab and ustekinumab, due to the current paucity of data. The article was accompanied by a detailed technical review (2), a decision support tool (3), and a patient guide (4). The recommendations were developed by the AGA guideline panel, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. A literature review was performed in March 2016, and the panel met in February 2017 before finalizing the guideline.

We will address each of the five recommendations separately.

(I) In adults with active IBD treated with anti-TNF agents, the AGA suggests reactive TDM to guide treatment changes (Suggested trough concentration for infliximab ≥5 μg/mL, adalimumab ≥7.5 μg/mL, certolizumab ≥20 μg/mL)

The AGA guideline recommends reactive TDM in those with active IBD, either active symptoms confirmed by objective biomarkers, or asymptomatic patients with evidence of active inflammation on radiology and/or endoscopy. This is in keeping with the recent treat-to-target approach. Although there had been only a small number of studies, these showed better clinical response from reactive TDM than empiric dose escalation, which may also be cost-effective (2). Empiric dose escalation may be inappropriate in those with mechanistic failure or immune-mediated pharmacokinetic failure, who may benefit from an out of class or within class switch of therapy, respectively.

The guideline suggests target trough concentrations for use of infliximab at ≥5 μg/mL, adalimumab at ≥7.5 μg/mL, and certolizumab at ≥20 μg/mL in patients with active IBD during maintenance therapy. The authors acknowledged that the evidence on the optimal target trough

concentrations is limited. Unpublished data were used for the formulation of these guidelines, based on the proportion of patients achieving clinical remission above different thresholds (2). This is particularly relevant in the case of adalimumab, where the threshold was obtained from pooling the results of just 6 studies (232 patients). In a recent cross-sectional study in Crohn's disease, thresholds which discriminated between active disease and remission could be identified for infliximab, but not for adalimumab (5). The AGA recommended targets are higher than suggested from some of the previous studies, for example, a target of 3–7 µg/mL for infliximab in the TAXIT study (6). Higher target levels may be needed in certain patients, including those with secondary loss of response, ulcerative colitis, and perianal disease (7). Higher levels are likely to be needed to neutralize systemic inflammation and achieve deep remission with mucosal healing than levels required for clinical remission (5,8,9). More recently, since these guidelines were made, studies have suggested higher trough levels are also needed during induction (10,11). The guideline also noted a wide variation in lab testing of drug levels and anti-drug antibodies, therefore the same lab should be used for each patient for consistency, and, in particular, clinicians need to be aware of assay-specific target thresholds, as these may differ between kits.

The accompanied decision making tool outlines an algorithm for management in response to reactive TDM (3). Those with maintenance trough levels at or above the target may benefit from switching to a different drug class. Those with low or non-detectable drug trough levels and negative or low-titer anti-drug antibody may benefit from dose escalation and/or adding an immunomodulator (12). Those with low or non-detectable drug trough levels and high-titer anti-drug antibody may benefit from switching within or outside drug class.

(II) In adult patients with quiescent IBD treated with anti-TNF agents, the AGA makes no recommendation regarding the use of routine proactive TDM

The benefits of routine proactive TDM in all patients with quiescent IBD are less certain and the subject of considerable debate. Prospective studies have failed to show clinical benefits of proactive TDM, whereas smaller retrospective have demonstrated improved outcomes. The TAXIT study did not find a significant difference in clinical and biochemical remission between proactive TDM-based dosing and clinically-based dosing, although patients in both groups had initial dose optimization prior to randomization, which may have affected the outcomes (6). There were however some signals supporting proactive TDM, with less rescue therapy needed, more achieving therapeutic trough levels, and a smaller proportion developing anti-drug antibodies in the TDM-based dosing group.

The TAILORIX study of biologic naïve luminal Crohn's disease patients receiving infliximab compared two groups where dose escalation was based on trough levels to one clinically-based dose escalation group. No differences between clinical and endoscopic outcomes at one year were found between groups, however the results may have been affected by the large proportion of the clinical care group receiving dose escalation (13). In contrast, two retrospective studies, predominantly from the one center, found better clinical outcomes with lower IFX discontinuation rates, lower immunogenicity rates and infusion reactions and even less IBD-related hospitalizations and surgeries in patients with proactive, rather than reactive, TDM (14,15). Prospective, multi-center studies replicating these results are required.

The AGA's lack of endorsement of proactive testing is in contrast to other recently published guidelines. The Australian consensus on TDM recommends proactive testing in the following situations: after successful induction at week 14, in those where a drug holiday is contemplated, and periodically during remission if the results would impact management (16). The recommendations to perform TDM after successful induction were made based on a post-hoc analysis form the ACCENT 1 cohort which showed higher clinical remission at 1 year in those with week 14 infliximab levels of ≥3.5 µg/mL (17). The rationale for recommending TDM prior to a drug holiday was based on a small retrospective study demonstrating improved outcomes in patients with undetectable ant-TNF levels prior to drug withdrawal (18). Similarly, the Building Research in Inflammatory Bowel Disease

Globally (BRIDGe) group also recommends TDM at least once during the first year of maintenance therapy, and following a drug holiday (19). The AGA justifies their caution in not recommending proactive TDM due to the limited evidence base and also concerns regarding high health costs, and potential inappropriate treatment changes in well patients in remission.

(III) In adult patients with IBD being started on thiopurines, the AGA suggests routine thiopurine methyltransferase (TPMT) testing (enzymatic activity or genotype) to guide thiopurine dosing [routine laboratory monitoring, including complete blood count (CBC), should be performed, regardless of TPMT testing results]

TPMT genetic polymorphisms are associated with low enzyme activity and an increased risk of leukopenic sepsis. Although homozygous low/absent TPMT enzymatic activity is only prevalent in 0.3% of the population, this test is inexpensive and can prevent serious, and potentially fatal, complications. Both genotype and phenotype can be performed, each with their own advantages and disadvantages. Genotype remains constant whereas phenotype can be influenced by exogenous factors including recent red blood cell (RBC) transfusion and some medications (including thiopurines themselves). However, within one genotype there can be a significant variation in enzyme activity such that some patients with a normal genotype can still have low phenotypic activity. For this reason we believe measuring phenotype allows for slightly better thiopurine dose individualization. The recent Dutch TOPIC study found significantly less severe hematological toxicity in TPMT heterozygotes receiving thiopurine dose reduction compared to when TPMT was not measured in this population (20). We agree with the views of the accompanying editorial emphasizing the importance of TPMT testing—"surely just do it?" (21). Although the guideline rated the quality of evidence supporting TPMT testing as low, we believe that for safety reasons this should be routinely adopted into current clinical practice. It is hoped that thiopurine pharmacogenomic testing in future will progress beyond TPMT testing alone. For example, testing for nucleoside diphosphate-linked moiety X-type motif 15 (NUDT15) polymorphism may help quantify the risk of thiopurine induced leukopenia in Asian populations where TPMT mutations are less common (22). Sensibly, the AGA guideline emphasizes the importance of routine laboratory monitoring, regardless of TPMT testing results, as myelosuppression is in fact most commonly seen in those with normal TPMT activity (23).

(IV) 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 (suggested target 6-thioguanine (6-TGN) between 230–450 pmol/8×10^8 RBCs when used as monotherapy. Optimal cutoff when used in combination with anti-TNF agents is uncertain)

Reactive testing of thiopurine metabolites in those with active IBD or suspected toxicity is recommended. Retrospective studies, and meta-analyses, have consistently found improved clinical outcomes in patients with therapeutic 6-TGN levels (24). In our anecdotal (and unpublished) experience, 6-TGN levels in the range of 300–400 pmol/8×10^8 RBCs are associated with the best benefit to risk ratio. Testing of thiopurine metabolites also helps identify metabolic subgroups such as 6-methylmercaptopurine (6-MMP) "shunters" (who may benefit from dose reduction and the addition of low dose allopurinol), and truly refractory patients with therapeutic levels but active disease who require a change of agent. Perhaps the most practical use of thiopurine metabolite testing is for the detection of non-adherence. The guideline acknowledges that these recommended 6-TGN levels are for patients on thiopurine monotherapy. Optimal 6-TGN levels for patients on combination therapy remain uncertain, although recent pharmacokinetic studies have suggested that lower 6-TGN levels may be sufficient to optimize anti-TNF levels and outcomes in patients on combination therapy (25).

(V) In adult patients with quiescent IBD treated with thiopurines, the AGA suggests against routine thiopurine metabolite monitoring

The AGA guideline does not recommend routine thiopurine metabolite monitoring in those with quiescent IBD. Two randomized controlled trials did not find benefit of routine

testing compared to standard weight-based dosing, although these studies had methodological limitations (2). The guideline suggests that regular routine testing of thiopurine metabolites may add time and expense, without providing benefit. However, the authors of the accompanied technical review acknowledged the potential benefit of routine testing for identifying certain subgroups and guiding subsequent management decisions. Perhaps future studies will show that these patients may benefit from early treatment interventions prior to developing active disease or thiopurine related adverse events.

Appropriately, the guideline has taken into consideration the risks and benefits of an intervention, patients' values and preferences, and resource utilization. Given this suitably holistic and pragmatic view, and the limited current evidence base to support proactive TDM in particular, these recommendations are conservative, and, as with any guidelines, may not be applicable to all patients. With the rapidly evolving field of IBD, it should be anticipated that future TDM guidelines will be produced and/or revised, and will be quite different from this current version. Well-designed prospective studies of proactive TDM are a research priority. When performed, it is likely that these will confirm the validity of proactive TDM in certain circumstances, e.g., after induction or before de-escalation of therapy. Higher target trough concentrations are likely to be recommended in the future as treatment goals move towards deeper levels of remission. Future individualization of TDM will hopefully lead to different target levels for remission during induction and maintenance, and perhaps different recommendations for Crohn's disease and ulcerative colitis. Phenotypic individualization of TDM is already occurring with the emerging recognition of the need for higher levels in patients with perianal Crohn's disease and hopefully this trend will continue. Similarly, the increasing understanding of the effect of pregnancy on drug metabolism and pharmacokinetics may lead to specific recommendations for TDM in pregnancy in future guidelines. Drug level testing for newer biologics such as vedolizumab and ustekinumab will become commercially available in the near future, and pending the strength of data TDM recommendations for these agents may be incorporated into future guidelines. Results from studies utilizing rapid point of care assays and complex dashboard pharmacokinetic algorithms are also eagerly anticipated.

For now, reactive TDM has the strongest clinical evidence base for both thiopurines and anti-TNF agents and its use should be considered standard of care for IBD clinicians. Although not recommended for routine care of all patients, proactive testing may also be appropriate in some cases (such as patients with aggressive disease phenotypes), and should be considered on an individual basis. Hopefully, ongoing research in this rapidly evolving field will confirm the validity, or lack thereof, of proactive TDM testing for future guidelines.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Feuerstein JD, Nguyen GC, Kupfer SS, et al. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology 2017;153:827-34.
2. Vande Casteele N, Herfarth H, Katz J, et al. American Gastroenterological Association Institute Technical Review on the Role of Therapeutic Drug Monitoring in the Management of Inflammatory Bowel Diseases. Gastroenterology 2017;153:835-57.e6.
3. Association AG. Therapeutic Drug Monitoring in Inflammatory Bowel Disease: Clinical Decision Support Tool. Gastroenterology 2017;153:858-9.
4. Association AG. Therapeutic Drug Monitoring in Inflammatory Bowel Disease: A Patient Guide. Gastroenterology 2017;153:860-1.
5. Ward MG, Warner B, Unsworth N, et al. Infliximab and adalimumab drug levels in Crohn's disease: contrasting associations with disease activity and influencing factors. Aliment Pharmacol Ther 2017;46:150-61.
6. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide

dosing for patients with inflammatory bowel disease. Gastroenterology 2015;148:1320-9.e3.
7. Yarur AJ, Kanagala V, Stein DJ, et al. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. Aliment Pharmacol Ther 2017;45:933-40.
8. Ungar B, Levy I, Yavne Y, et al. Optimizing Anti-TNF-α Therapy: Serum Levels of Infliximab and Adalimumab Are Associated With Mucosal Healing in Patients With Inflammatory Bowel Diseases. Clin Gastroenterol Hepatol 2016;14:550-7.e2.
9. Yarur AJ, Jain A, Hauenstein SI, et al. Higher Adalimumab Levels Are Associated with Histologic and Endoscopic Remission in Patients with Crohn's Disease and Ulcerative Colitis. Inflamm Bowel Dis 2016;22:409-15.
10. Papamichael K, Van Stappen T, Vande Casteele N, et al. Infliximab Concentration Thresholds During Induction Therapy Are Associated With Short-term Mucosal Healing in Patients With Ulcerative Colitis. Clin Gastroenterol Hepatol 2016;14:543-9.
11. Davidov Y, Ungar B, Bar-Yoseph H, et al. Association of Induction Infliximab Levels With Clinical Response in Perianal Crohn's Disease. J Crohns Colitis 2017;11:549-55.
12. Ungar B, Kopylov U, Engel T, et al. Addition of an immunomodulator can reverse antibody formation and loss of response in patients treated with adalimumab. Aliment Pharmacol Ther 2017;45:276-82.
13. D'Haens GR, Vermeire S, Lambrecht G, et al., editors. Drug-Level Based Dosing Versus Symptom-Based Dose Adaptation in Patients with Crohn's Disease: A Prospective, Randomized Multicenter Study (TAILORIX). San Diego: Digestive Disease Week, 2016.
14. Vaughn BP, Martinez-Vazquez M, Patwardhan VR, et al. Proactive therapeutic concentration monitoring of infliximab may improve outcomes for patients with inflammatory bowel disease: results from a pilot observational study. Inflamm Bowel Dis 2014;20:1996-2003.
15. Papamichael K, Chachu KA, Vajravelu RK, et al. Improved Long-term Outcomes of Patients With Inflammatory Bowel Disease Receiving Proactive Compared With Reactive Monitoring of Serum Concentrations of Infliximab. Clin Gastroenterol Hepatol 2017;15:1580-8.e3.
16. Mitrev N, Vande Casteele N, Seow CH, et al. Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases. Aliment Pharmacol Ther 2017;46:1037-53.
17. Cornillie F, Hanauer SB, Diamond RH, et al. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. Gut 2014;63:1721-7.
18. Ben-Horin S, Chowers Y, Ungar B, et al. Undetectable anti-TNF drug levels in patients with long-term remission predict successful drug withdrawal. Aliment Pharmacol Ther 2015;42:356-64.
19. Melmed GY, Irving PM, Jones J, et al. Appropriateness of Testing for Anti-Tumor Necrosis Factor Agent and Antibody Concentrations, and Interpretation of Results. Clin Gastroenterol Hepatol 2016;14:1302-9.
20. Coenen MJ, de Jong DJ, van Marrewijk CJ, et al. Identification of Patients With Variants in TPMT and Dose Reduction Reduces Hematologic Events During Thiopurine Treatment of Inflammatory Bowel Disease. Gastroenterology 2015;149:907-17.e7.
21. Sanderson JD. TPMT Testing Before Starting Azathioprine or Mercaptopurine: Surely Just Do It? Gastroenterology 2015;149:850-3.
22. Chao K, Wang X, Cao Q, et al. Combined Detection of NUDT15 Variants Could Highly Predict Thiopurine-induced Leukopenia in Chinese Patients with Inflammatory Bowel Disease: A Multicenter Analysis. Inflamm Bowel Dis 2017;23:1592-9.
23. Colombel JF, Ferrari N, Debuysere H, et al. Genotypic analysis of thiopurine S-methyltransferase in patients with Crohn's disease and severe myelosuppression during azathioprine therapy. Gastroenterology 2000;118:1025-30.
24. Moreau AC, Paul S, Del Tedesco E, et al. Association between 6-thioguanine nucleotides levels and clinical remission in inflammatory disease: a meta-analysis. Inflamm Bowel Dis 2014;20:464-71.
25. Yarur AJ, Kubiliun MJ, Czul F, et al. Concentrations of 6-thioguanine nucleotide correlate with trough levels of infliximab in patients with inflammatory bowel disease on combination therapy. Clin Gastroenterol Hepatol 2015;13:1118-24.e3.

doi: 10.21037/tgh.2017.12.05

Cite this article as: Su HY, Ward MG, Sparrow MP. Therapeutic drug monitoring in inflammatory bowel disease: too little too early?—comments on the American Gastroenterology Association Guideline. Transl Gastroenterol Hepatol 2017;2:113.

