Editorial

Re: American Gastroenterological Association Institute Guideline on therapeutic drug monitoring in inflammatory bowel disease

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The recently published American Gastroenterological Association (AGA) guideline on therapeutic drug monitoring (TDM) in inflammatory bowel disease (IBD) provides important and useful perspectives for individuals caring for and managing individuals with IBD and also for researchers focusing on this area (1). The guideline reviews key aspects of the roles that TDM increasingly has in the management of individuals with IBD and highlights key concepts. It also illustrates that many of these areas are supported by scanty evidence. Consequently, this also serves to prompt further study that might expand the evidence base accordingly.

The management of IBD in children and adults includes the achievement of prompt diagnosis along with focused and targeted therapeutic interventions. Disease monitoring and assessment of disease activity are required to ensure the success of therapies. The advent of more specific and less invasive biomarkers of inflammation, such measurement of faecal calprotectin, has provided opportunities to monitor disease closely and as frequently as indicated (2). The last 2 decades have seen numerous advances in the therapeutic approaches to the management of IBD, driven in part by the arrival of a number of new therapeutic agents, especially the biologic drugs infliximab and adalimumab (3). Alongside these developments has been an increasing desire to utilise standard therapies better and more effectively. Furthermore, there is increasing emphasis upon clear treatment goals: moving beyond clinical remission and resolution of symptoms to mucosal healing (MH). It is clear that the establishment of MH enables one to modify the course of the disease, whilst reducing the risks of hospitalisation, surgery and disease exacerbations (4,5).

Paramount in the desire to utilise therapeutic agents effectively has been the recognition that monitoring of drug levels (or other indicators) may enable smarter and safer use of drugs. This is especially relevant for the thiopurines and the biologic drugs, but also for other medical therapies such as methotrexate or tacrolimus (not covered further here). It may also prove to be important in the way other biologic drugs are utilised in the future (but there are not yet data available).

The thiopurines, azathioprine and 6-mercaptopurine, are typically used as long-term maintenance drugs to maintain remission. The metabolism of these agents is now well-documented (6). Along with assessment of the thiopurine methyl transferase activity, which enables more individualised initial dosing, measurement of two metabolites permits customisation of the dosage. These metabolites are 6-thioguanine nucleotide (TGN) and 6-methyl-mercaptopurine (MMP). Optimization of 6-TGN levels to the therapeutic range of 235–450 pmol/8×10^8 red blood cells is associated with remission (7). Furthermore, low levels suggest insufficient drug dosage or indicate non-adherence and high levels are associated with increased risk of bone marrow suppression. In contrast, measurement of 6-MMP levels does not guide efficacy, but can assist in avoidance of adverse effects. Very high levels of this metabolite (>6,000 pmol/8×10^8 red blood cells) are associated with increased risk of hepatotoxicity. In addition, a high 6-MMP in conjunction with low 6-TGN suggests shunting—this would prompt a therapeutic change with the additional of allopurinol. TDM in the case of thiopurines,

therefore, can enhance drug efficacy, whilst potentially limiting adverse effects.

In the context of the biologic drugs infliximab and adalimumab, TDM focuses upon drug levels and anti-drug antibody levels. Adequate levels of the active drug are required to achieve therapeutic response: namely suppression of tumour necrosis factor (TNF)-α activity. Antidrug antibody (ADA) levels (which can be observed in drug-naïve individuals, but typically develop after dosing has been commencing), can interfere with the therapeutic activity of the agent, by binding to the active antibody thereby preventing it's expected activity. The development of ADA may be more pronounced in individuals with low drug levels, variable drug levels (as seen with periodic dosing of infliximab) and in those who have received the drug for longer periods of the time (thereby contributing to secondary loss of response).

The AGA guideline specifies target levels of infliximab and adalimumab that are associated with clinical outcomes (1). These levels are relevant to children and adults alike. Further, the guidelines refer to issues related to the assessment of these trough levels and the consequent decision-making steps. The guideline also details issues related to the assessment of ADA. Namely, the available assays do not provide consistent results. Consequently, assessment of anti-drug antibodies will need to be more regional and patient specific.

One aspect that is not highlighted in the guideline is the role of combination therapy (an immunomodulator in combination with the biologic agent). This has typically meant the concurrent use of a thiopurine or methotrexate. One of the key roles of this approach is to reduce immunogenicity and thereby maintain efficacy of the biologic drug. The use of combination therapy is associated with more prolonged remission and enhanced drug efficacy in adults and children (8,9). In contrast, combination therapy may be associated with increased adverse effects, including skin damage/disease and lymphoproliferative conditions. Recent work has illustrated that a 6-TGN level of at least 125 pmol/8×10^8 red blood cells was associated with higher infliximab levels (10). Similarly, lower dose methotrexate appears to also be sufficient in combination therapy (11). Lower doses of the immunomodulatory used in combination likely leads to reduced risks of adverse side-effects.

Although the rationale of the above concepts is relevant to children/adolescents as well as adults, it is important to note that less data on the role of TDM is available in children to date. A recent Canadian study provided interesting retrospective data on the role of TDM in the use of infliximab in 73 children managed in two Canadian sites (12). Trough levels were measured on 107 occasions, 24 due to concerns about poor response (reactive) and 83 for routine monitoring. Trough levels were suboptimal on 38 occasions. Subsequent management changes included reducing the frequency of infliximab dosing with consequent improved disease activity.

Infliximab trough levels and ADA were assessed on 93 occasions in 45 children in a second report published this year (13). Although the number of subtherapeutic levels was not stated by the authors, trough levels were clearly associated with clinical disease activity scores and serum inflammatory markers [for instance, C-reactive protein (CRP)], indicating response to infliximab. ADA were shown in all 12 occasions that infliximab levels were undetectable. An earlier Dutch study evaluated trough levels and ADA in 39 children, most of whom had Crohn disease (14). More than a third of these children had sub-therapeutic trough levels, whilst four had ADA. In this patient series, trough levels were also associated with serum CRP levels (as a marker of inflammation). Together these case series provide support for TDM in children with IBD managed with infliximab. They are also consistent with the general concepts iterated in the recent consensus guideline.

The overall conclusions of the guideline were also evident in a recent consensus statement formulated by a group of Australian investigators (15). This manuscript undertook to assess the approach of 22 individual practitioners to aspects of TDM in IBD. This statement covered management aspects in addition to those considered in the AGA guideline.

Both the recent AGA guideline (1) and the recent consensus statement encompassed a review of and reference to the available relevant literature. Most of the comments and recommendations provided were based upon low quality data. Although in some cases this was due to data sourced from retrospective studies or small groups of patients (low quality), this also reflects that there is an absence of data covering/guiding decision making in many key areas. This should be considered by investigators internationally as aspects that require further study: findings arising from such essential work should directly impact on management processes eventually leading to enhanced patient outcomes (short and long term).

In conclusion, this recently-published guideline provides a useful overview and commentary on the evolving field

of TDM. This document sets a framework for clinical management. Finally, this document highlights important gaps in current knowledge in this important aspect of the care of individuals with IBD.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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