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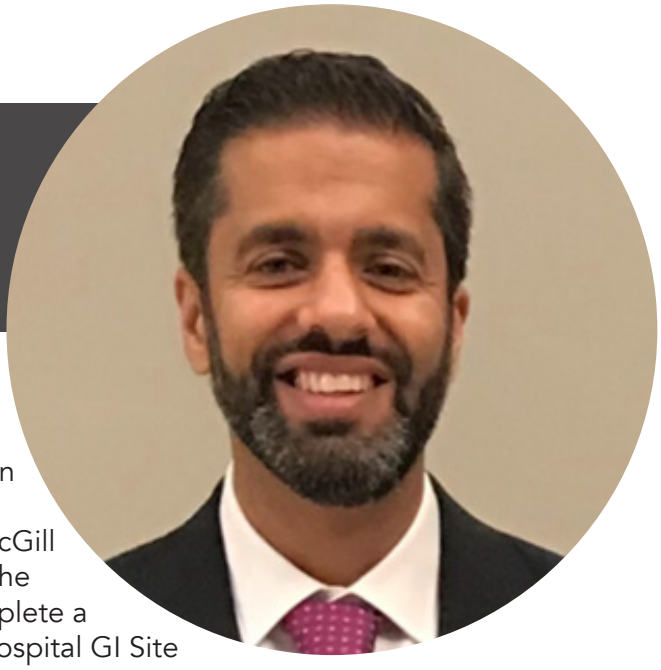

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THERAPEUTIC DRUG MONITORING OF BIOLOGICS IN INFLAMMATORY BOWEL DISEASE: WHERE HAS THE PENDULUM SWUNG?

Introduction

Biologics have revolutionized the management of patients with inflammatory bowel disease (IBD), in both ulcerative colitis (UC) and Crohn's disease (CD). There are several classes of biologics used to treat IBD, including monoclonal antibodies directed against TNF, integrin, IL12/23, and IL-23 monoclonal antibodies. Despite the effectiveness of anti-TNF medications, approximately 30% of patients are primary non-responders (PNR), and another 50% lose response over time (secondary loss of response [SLR]).[1] Therapeutic drug monitoring (TDM) provides a tool for biologic dose optimization by measuring drug trough concentrations and anti-drug antibodies (ADA). Drug concentrations are positively correlated to therapeutic benefits, but questions remain on how, when and for whom to perform TDM. Successful implementation is challenged by several factors such as variations in optimal drug targets, different types of drug detection assays, individual pharmacokinetics, and disease severity. Over recent years, various expert groups have provided guidelines on reactive TDM of anti-TNF therapies; however, a knowledge gap still exists on the role of proactive TDM, as well as reactive TDM for non-anti-TNF biologics. The most recent and comprehensive expert consensus statement published in the *American Journal of Gastroenterology* (AJG), attempted to fill this gap by advocating for the use of reactive TDM for anti-TNF medications, as well as for proactive TDM in certain scenarios.[1]

Biologic concentration targets and pharmacokinetics

Many exposure-response relationship studies have shown that higher biologic concentrations are associated with better therapeutic outcomes for IBD patients during both induction and remission.[1] The desirable thresholds vary depending on different therapeutic outcomes being investigated (i.e., clinical, biochemical, endoscopic, or histological remission) with higher concentrations typically being associated with more stringent endpoints.[1] The preponderance of data centers around anti-TNF medications, specifically infliximab and adalimumab. For example, the prospective PANTS study found that infliximab concentrations of >7 µg/mL and adalimumab concentrations of >12 µg/mL were associated with remission at weeks 14 and 54.[2] Features of high disease burden such as severe acute UC and fistulizing (perianal) CD likely require even higher thresholds.[3,]

There is significant inter- and intra-individual variability in the pharmacokinetics of biologic medications, particularly for anti-TNF medications. Patient-related covariates that are associated with increased clearance include male sex, increased body weight, immunogenicity, and increased inflammatory burden. Immunogenicity is increased in the absence of concomitant immunosuppressive medications, intravenous administration of drugs (versus subcutaneous), genetic factors (HLA-DQA1*05 carriage) and, most importantly, for anti-TNF medications (vs other biologics).[4,5] The concept of increased inflammatory load can be defined by severe active disease clinically, biochemically (increased C-reactive protein or fecal calprotectin [FCP] and decreased albumin) or endoscopically and is particularly important in the proactive TDM setting.

Reactive TDM

Reactive TDM is completed in the context of biologic PNR, partial response or loss of response (LOR) to treatment to provide guidance for drug optimization. If the drug concentration is inadequate in the absence anti-drug antibodies (ADA), dose optimization is needed, whereas, if the drug concentration is high or with the presence of high ADA, biologic switching is needed (**Figure 1**).[6] Yanai et al demonstrated that in patients with LOR infliximab concentrations of >3.8 µg/µ, and adalimumab concentrations of >4.5 µg/mL were suggestive of treatment failure and that switching biologic class may be beneficial.[7] Kelly et al demonstrated that using reactive TDM to guide infliximab dose optimization was superior to empirical dose optimization in terms of achieving endoscopic remission and cost-effectiveness.[8] When performing reactive TDM to guide clinical decisions, it is important to ensure that the drug concentration is optimized before discontinuing the first biologic. Several studies show subsequent inferior response to a second-line biologic, hence for LOR in both infliximab and adalimumab, discontinuation should not be considered until a drug of at least 10-20 µg/mL is achieved.[1,9] In the absence of high-quality data, this range is set higher than the standard infliximab concentration target (5-10 µg/mL) or the adalimumab concentration target (> 8-12 µg/mL), primarily to

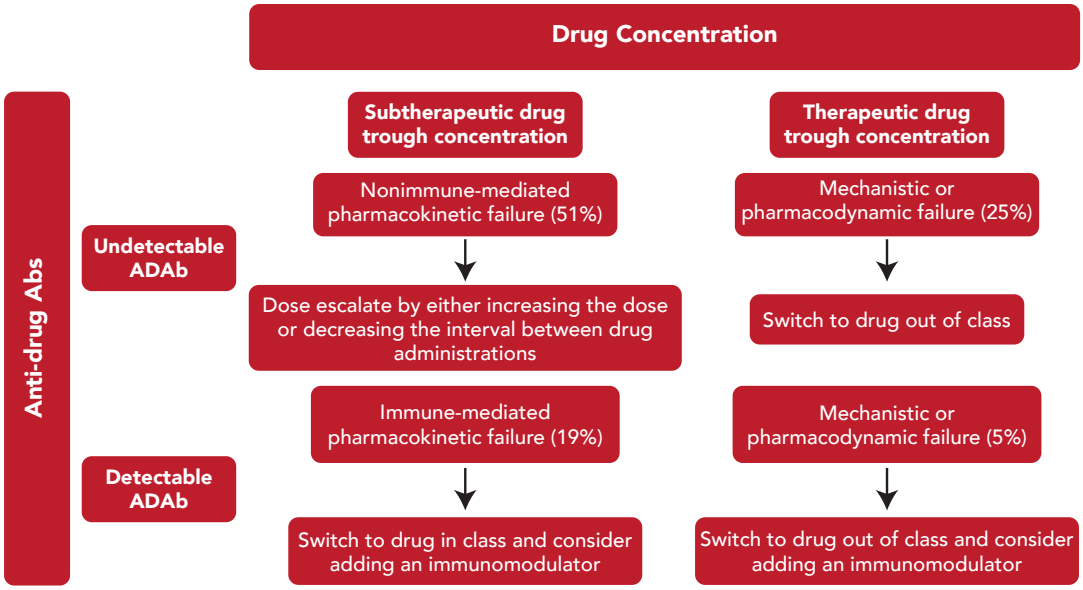

Figure 1. *Therapeutic drug monitoring at secondary LOR (Vande Casteele N, et al. Gastroenterology 2017); adapted from Vande Casteele N, et al. Gastroenterology 2017*

avoid unnecessary withdrawal of the biologic.[1] Most recommendations and guidelines are in favour of using reactive TDM in PNR and LOR to anti-TNF biologics.[3,10]

Although most of the current evidence on reactive TDM is based on anti-TNF biologics, there is a definite exposure-outcome relationship that has been observed both clinically and endoscopically with non-anti-TNF medications. Higher serum concentrations of vedolizumab and ustekinumab are associated with better therapeutic response but the rates of immunogenicity are significantly lower, which may obviate the need for TDM for these non-anti-TNF medications.[23] In summary, there is little data to support routine clinical use of reactive TDM with these medications in the setting of LOR.[11,12]

Proactive TDM

The role of proactive TDM is to enhance response rates and prevent treatment failure by determining whether the biologic dose is optimized during induction and maintenance therapy. Although this is theoretically logical, the data from multiple randomized control trials (RCTs) has been mixed. The PAILOT RCT study comparing the response to adalimumab induction between the reactive and proactive TDM groups, in children with luminal Crohn's disease, showed that the latter group had higher steroid-free clinical remission rates at week 72 (46% vs 82%, p<0.001).[13]

Multiple other RCTs have failed to show a benefit of proactive TDM, although there were methodological concerns with these studies. The TAXIT (Trough Level Adapted Infliximab Treatment) study was a one-year RCT that did not show superiority of TDM based dosing over routine clinical management in achieving clinical remission, but it was associated with fewer flares over the course of treatment.[15] Importantly, all patients were dose optimized to 3-7 µg/ml prior to initiation into the study, which could explain the lack of benefit for maintenance TDM based dosing. The TAILORIX (Tailored Treatment With Infliximab for Active Crohn's Disease) trial was another one year RCT found that proactive trough-level–based dose intensification was not superior to dose intensification based on symptoms alone.[16] Long delays in treatment optimization and the inability to achieve adequate trough concentrations in 50% of the proactive group could again explain the lack of benefit with proactive TDM in this study. A recent meta-analysis of nine studies (n=1405 patients) by Nguyen et al failed to show a benefit of proactive TDM to avoid treatment failure with anti-TNF therapy.[14]

Recommendations made for routine use of proactive TDM by various medical societies have been vague due to insufficient data (**Table 1**). There is no data on the use of proactive TDM with non-anti-TNF medications. Given the conflicting data, a more nuanced approach is recommended, rather than proactive TDM for all anti-TNF medications. Proactive TDM should be considered during or post-induction in patients with high inflammatory burden to avoid low drug concentrations and increased immunogenicity. In addition, proactive TDM for the pediatric population may be more important given patient/dosing heterogeneity. During maintenance therapy, a tiered approach of proactive monitoring of inflammatory activity (FCP) is recommended, followed by TDM in those patients with active inflammation (an early reactive approach during monitoring).[19]

Consensus /Guidelines	Recommendations	
	Reactive TDM	**Proactive TDM**
The American Gastroenterological Association (AGA) 2017[7]	Recommended for active IBD patients on anti-TNFs	Not recommended for patients on anti-TNFs with quiescent disease
AJG consensus 2021[1]	Recommended for all biologics	Strong recommendations were made for performing proactive TDM for patients on anti-TNFs.
British guidelines 2019[25]	Recommends incorporation of TDM conjunctively to aid decision to alter treatment (either dose or drug change)	Measurement of drug level and ADA in all IBD patients 2-4 weeks post induction, as good practice recommendation
European Crohn's and Colitis Organization (ECCO) 2020[26]	Insufficient evidence to support the use of TDM for LOR in CD patients	Insufficient evidence to support the use of TDM for CD patients on anti-TNF in remission
Australian guidelines[27]	Recommended in patients in clinical remission following anti-TNF therapy induction	Inconsistent evidence. TDM should be performed for patients in stable remission only if results are likely to impact clinical management.

Table 1. *Recommendations on TDM by various expert groups; courtesy of Waqqas Afif, MD and Arti Woncha-um, MD*

Proactive TDM should also be considered in the setting of biologic dose de-escalation or withdrawal of immunosuppressive medications in patients on combination therapy. Lucidarme et al showed that the use of trough levels to guide infliximab dose de-escalation (with a concentration of >7 µg/mL) was associated with a reduced risk of relapse compared to clinical guidance alone.[20] Withdrawal of immunosuppressive medications has been shown to decrease infliximab trough concentrations by approximately 2 µg /mL over the course of two years, indicating that patients with borderline trough concentrations should be optimized prior to withdrawal.[21] In addition, optimizing anti-TNF monotherapy through proactive TDM may obviate the need for concomitant immunosuppressive therapy.[22]

Future of TDM

Reactive and proactive TDM measures drug trough and ADA concentrations and informs only two components of an individual's multi-factorial pharmacokinetic (PK) interactions and are prone to lag between testing and dose adjustment. In recent years, a dashboard software-guided dosing system (**Figure 2**) has been developed to determine an individual's precise target trough level, incorporating TDM with population PK data, individual factors (such as sex and weight) and other clinical parameters (such as serum albumin and C-reactive protein).[24] The PRECISION trial demonstrated higher rates of sustained clinical remission after 1 year (88% vs 64%, p=0.017), as well as lower median fecal calprotectin levels in the precision group (p=0.031), when using the Bayesian dashboard software system compared to standard dosing.[20] A greater understanding of how the drug PK varies during the treatment cycle may also feed into the development of the dashboard system by considering TDM testing at different points of the dosing cycle, allowing more opportunities to perform TDM-based dose adjustment by finding the optimal point in time to measure the drug level other than at the trough (i.e., trough vs peak, induction vs post-induction).[1,24] Other areas to consider as part of the future development of the dashboard system include: genetics, where carriers of HLA-DQA1*05 are more likely to develop ADA; mode of drug administration (subcutaneous vs intravenous); and new technology for TDM point-of-care home testing, which will allow more rapid decision-making.[24] TDM represents a small part of the dashboard, but moving towards a more personalized approach it will still play an important role in the foreseeable future with anti-TNF medications.

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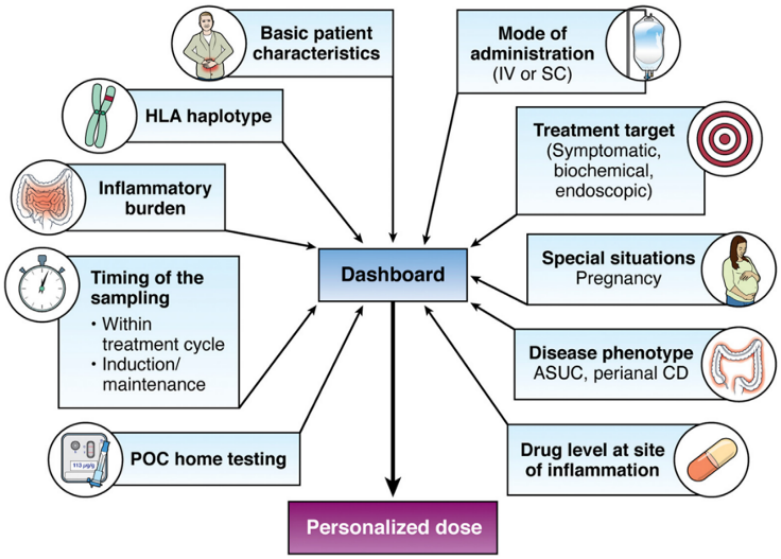

Figure 2. *Personalized dosing in IBD (image from Irving et al, Gastroenterology 2022).*

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