Review Article

Therapeutic drug monitoring for biological medications in inflammatory bowel disease

Rachel C. Cogan, Basem W. El-Matary, Wael M. El-Matary

Section of Pediatric Gastroenterology, Department of Pediatric and Child Health, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada

Abstract

Therapeutic drug monitoring (TDM) is the measurement of serum drug concentrations and anti-drug-antibodies (ADA) for biologic therapies used to treat inflammatory bowel disease (IBD). The aim of this article is to review the current literature concerning reactive and proactive TDM for both adults and children with IBD. Although optimal trough concentration windows for some of these medications are not well defined, there is mounting evidence to suggest that reactive TDM is associated with favorable therapeutic outcomes, including less immunogenicity, greater drug exposure, and a decreased risk of treatment failure. Moreover, while the exact mechanism of loss of response is not fully elucidated, the vast majority of studies have reported a decreased incidence of nonresponse and secondary loss of response when TDM is implemented. Proactive TDM, while even less understood in the literature, employs a schedule of preemptive analysis of serum trough concentrations to accordingly adjust the patient's biologic dosage. Proactive TDM may decrease the need for IBD-related surgery/hospitalization, and therefore merits future studies of investigation.

Keywords: Adalimumab, anti-TNF, inflammatory bowel disease, infliximab, proactive, reactive, therapeutic drug monitoring

Address for correspondence: Dr. Wael M. El-Matary, Professor of Pediatric and Child Health, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, AE 408 Children's Hospital, Health Sciences Centre, 840 Sherbrook St., Winnipeg, Manitoba, R3A 1S1, Canada.
E-mail: welmatary@exchange.hsc.mb.ca

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INTRODUCTION

The introduction of biologics has revolutionized the management of inflammatory bowel disease (IBD), and their utilization has substantially increased over the last two decades. A recent pediatric study from Canada showed that utilization of anti-tumor necrosis factor (anti-TNF) agents, in patients with Crohn's disease (CD), increased from 13% in 2010 to 60% in 2016, and from 4.9% to 25.5% in patients with ulcerative colitis (UC).[1] Despite their efficacy, a substantial number of patients with IBD do not respond or lose response to biologics, which may be related to suboptimal drug concentrations and/or development of anti-drug antibodies (ADA).[2-4] Therapeutic drug monitoring (TDM) of biologics through measuring their trough serum levels and ADA has emerged as a useful tool to optimize the utilization of these medications and improve patient outcomes. Several factors may affect trough concentrations of these medications, including disease subtype, extent, phenotype, degree of inflammation, serum albumin, concomitant immunomodulator, patient's sex, and body mass index.[5-7] In clinical care, TDM can

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be performed proactively or reactively. In reactive TDM, serum drug level and presence of ADA are measured in patients receiving a biological agent, in response to evidence of active disease or incomplete response to the biologic that is confirmed with objective evidence via endoscopy, biochemically, or radiographically.[8-11] Proactive TDM means systematic measurement of trough concentrations with ADA with the goal of optimizing and adjusting drug dose and concentration, to a target drug concentration in patients with clinical response/remission.[12-14]

REACTIVE THERAPEUTIC DRUG MONITORING

Reactive TDM is a specialized method of drug therapy that involves the measurement of serum drugs and/or ADA to ensure drug efficacy.[15,16] This measurement allows clinicians to confirm therapeutic exposure and optimize the treatment of the respective biologic. This is especially vital following loss of response as it aids in avoiding unnecessary dose intensification or switching medications. Furthermore, reactive TDM can help to clarify the specific mechanism of loss of response which can serve to further guide clinician's decisions regarding the best course of treatment.[17] For example, a study assessing ADA by comparing a pre-TDM group (108 patients) and a post-TDM group (206 patients) found that the latter was at a lower risk of anti-TNF loss of response related to ADA.[18] Additional studies have demonstrated a positive correlation between reactive TDM and endoscopic remission in patients with IBD receiving biologics.[19] However, several studies investigating the benefits of reactive TDM have also demonstrated its value in identifying patients who have been administered supratherapeutic doses of anti-TNFs. Upon identification, dose reduction can be considered to reduce dose-dependent side effects, such as infection, and reduce costs.[20] Furthermore, several studies have indicated that reactive TDM is more cost-effective than the standard practice of empiric dose escalation as it aids in efficiently determining which patients would benefit from dose escalation or alternatively changing therapy.[21-23] For effective clinical outcomes, it has been suggested that reactive TDM be performed early during induction because higher serum anti-TNF concentrations during induction is associated with more favorable therapeutic outcomes, including less immunogenicity, greater drug exposure, and a decreased risk of treatment failure.[24-29]

Infliximab

Infliximab (IFX) is a monoclonal antibody that binds to TNFα, an important inflammatory mediator in IBD, and neutralizes its effect.[30] Since receiving approval from the FDA in 1998 and 2011 for CD and UC, respectively, IFX has become one of the main therapeutic agents used for treating IBD.[31,32] In addition, IFX is typically the first choice for treating perianal fistulizing Crohn's disease (pfCD), as numerous studies have proven its efficacy. However, approximately 50% of patients eventually lose response to the drug, and approximately 13% of patients are reported to lose response every year.[33] Numerous studies have demonstrated that reactive TDM is beneficial for determining if the patient has developed ADA and if the current drug administration levels are optimal. A prospective interventional study demonstrated a strong positive correlation between dose intensification following loss of response and mucosal healing.[34] Interestingly, while most authors suggested switching therapies for patients with high ADA and low IFX trough levels, this study found that IFX dose intensification in association with azathioprine therapy resulted in half of their patients achieving clinical remission within 8 weeks.[34-36] Additionally, a retrospective study investigated the rates of endoscopic remission in patients who either had dose adjustments based on clinical decision making alone or TDM IFX dose escalation. It was found that TDM-guided dose escalation was associated with higher post-adjustment levels, higher endoscopic remission rates, and fewer relapses.[9] Moreover, data from prospective studies have been able to confirm certain advantages of reactive TDM with IFX. In a randomized, double-blind, placebo-controlled study, 121 patients received 5 mg/kg of IFX, 122 patients received 10 mg/kg of IFX, and 121 patients received a placebo at weeks 0, 2, 6, and then every 8 weeks until week 46.[37] It was reported that 69.4% of the 5-mg/kg group and 61.5% of the 10-mg/kg group demonstrated clinical improvement as compared to 37.2% of patients in the placebo group.[37]

On the contrary, it is also important to note that some studies have determined that reactive TDM makes little impact. In a systematic review and meta-analysis examining the effectiveness of reactive TDM, it was concluded that existing evidence is not sufficient to support the notion that TDM improves clinical remission rates.[17] However, it was determined that reactive TDM was associated with significant cost reduction.[17] Alternatively, a study surveying members of the American College of Gastroenterology concluded that the majority of clinician's concerns with reactive TDM are regarding barriers to insurance coverage (77.9%), out-of-pocket patient costs (76.4%), and the time taken to obtain results following obtainment of the serum sample (38.5%).[38]

While studies assessing pediatric TDM are limited, the majority of available literature suggests that similar to adults, children exhibit a positive correlation between serum

IFX level and clinical remission.[14,39,40] A retrospective study assessing pediatric TDM reported that of their 39 patients who had a poor response to IFX therapy, 32 regained response following dose intensification.[41] The remaining seven patients were reported to have high ADA and it was, therefore, recommended that they switch to a different biologic.[41] However, this study also reported that one of the patients with high ADA regained response following drug intensification, thus suggesting that ADA may be transient in nature.[41] Moreover, a prospective study was able to confirm findings from adult studies as it concluded that of the 77 pediatric CD patients, the 66 who were able to complete 12 months of IFX therapy had higher serum IFX levels and lower ADA during induction.[42] Furthermore, this study highlighted the importance of measuring serum TNF-α as it reported that the patients who were able to complete therapy also had a greater change in serum TNF-α from baseline to 10 weeks.[42]

Adalimumab

Adalimumab (ADM) is a fully human anti-TNF monoclonal antibody. Since receiving approval from the FDA for CD in 2007 and UC in 2012, ADM has been shown to induce and sustain IBD remission by bivalently binding to TNF and forming complexes that prevent TNF from activating receptors at the cell's surface.[43,44]

In the EXTEND trial, the safety and efficacy of adalimumab through endoscopic healing, as indicated by induced and maintained mucosal healing, was assessed.[45] This study reported that based on the Crohn's disease endoscopic index of severity, 52% of the ADM group was in remission compared to 28% in the placebo group.[45] It was, therefore, concluded that mucosal healing was more likely in those undergoing reactive TDM with ADM. In the Clinical Assessment of Adalimumab Safety and Efficacy Studied as Induction Therapy in Crohn's Disease (CLASSIC) placebo-controlled dose-ranging study, clinical remission was assessed in patients receiving three different ADM doses.[46] This study concluded that there was a positive correlation between ADM serum drug concentration and clinical remission.[46] However, a serum concentration threshold to discriminate patients by remission status could not be identified as there was a significant overlap.[46] Furthermore, a prospective follow-up study determined that introducing ADM following IFX non-response resulted in sustained clinical benefit, as demonstrated by two-thirds of the patients during the follow-up approximately 2 years later.[47]

In the IMAgINE double-blind trial, the safety, efficacy, and pharmacokinetics of ADM were assessed in children.[48,49] It was concluded that in children with pfCD, ADM induced fistula closure within the first 12 weeks of treatment and that these results were sustained for over 5 years.[48] In another prospective pediatric study, it was reported that among 65 patients, 60% achieved clinical/biomarker remission by week 24 without dose escalation.[50] It was also reported that ADM trough levels at weeks 4 and 8 of 22.5 and 12.5 μg/mL, respectively, were good predictors of remission at week 24.[50]

Ustekinumab and vedolizumab

Ustekinumab (UST) functions by inhibiting the activity of IL-22/23 through their common p40 subunit.[51] Alternatively, vedolizumab (VDZ) is an antagonist that binds to the α4β7 integrin.[52] There currently exists limited data regarding the use of UST and VDZ for TDM because non-anti-TNF have yet to be thoroughly investigated in this respect. However, evidence from numerous studies suggest a potential role for UST and VDZ in TDM in the future. For instance, in one prospective study, it was reported that higher UST serum concentrations positively correlated with rates of endoscopic remission and efficacy endpoints.[53] Another prospective observational study assessing UST reported that of their 32 patients, 63% achieved a steroid-free clinical remission wherein the trough levels were 10.0, 5.0, and 1.6 μg/mL at weeks 4, 8, and 16, respectively.[54] Furthermore, in an analysis of five randomized, placebo-controlled clinical studies assessing VDZ, it was reported that fixed dosing of VDZ was effective for obtaining clinical remission and that the pharmacokinetic parameters were similar in patients with either moderate to severe UC or CD.[55] In an analysis of the GEMINI open-label study investigating the safety of VDZ, it was reported that among 693 patients, week 6 trough levels of 37.1 μg/mL was recognized as the earliest time at which VDZ concentrations were indicative of clinical remission at weeks 14 and 52.[56,57] Moreover, it was concluded that higher VDZ concentrations were also associated with higher rates of remission.[58]

PROACTIVE THERAPEUTIC DRUG MONITORING

Proactive TDM employs a schedule of preemptive analysis of serum trough concentrations to accordingly adjust the patient's biologic dosage.[59] In a study designed to determine gastroenterologists' attitudes toward TDM of anti-TNF therapy in clinical practice, it was determined that among 403 gastroenterologists, 66% utilized TDM for primary nonresponse, 90.1% utilized TDM for secondary loss of response, and only 36.6% used TDM proactively.[38] However, recent studies suggest that proactive TDM may allow for the detection of subtherapeutic drug levels,

which would otherwise lead to immunogenicity or a subsequent loss of response.[60] Proactive TDM can be implemented during the induction, post-induction phase, or during the maintenance phase if the patient remains asymptomatic with no evidence of active disease.[11] This early optimization may have significant clinical advantages such as decreasing the need for IBD-related surgery/hospitalization and increasing drug durability.[61,62]

Infliximab

In recent years, proactive TDM has been compared to reactive TDM in various studies investigating the clinical benefits or lack thereof. In a cohort study using IFX, proactive and reactive TDM were compared. It was found that the patients who underwent TDM every 6 months had a higher IFX concentration, lower ADA levels, and were more likely to remain on IFX at 5 years.[22] In another prospective comparative study, proactive TDM with IFX trough levels between 3 and 7 μg/mL for CD and between 5 and 10 μg/mL for UC, resulted in a decreased need for surgery and higher rates of mucosal healing, compared to the reactive control group.[63] Furthermore, a retrospective cohort study compared patients receiving reactive testing alone with patients receiving proactive IFX following reactive testing for either an infusion reaction or a loss of response.[64,65] It was concluded that the latter group was associated with greater drug persistence and fewer hospitalizations.[65] Additionally, 24% of patients receiving proactive treatment following reactive testing underwent dose de-escalation without negative impact.[64]

Similarly, in the Trough level Adapted Infliximab Treatment (TAXIT) randomized controlled trial comparing proactive care and standard care, 27% of patients receiving proactive treatment underwent dose de-escalation.[65] The primary endpoint of this study, which was clinical and biochemical remission at 1 year, did not reach significance between the two groups; however, it was determined that proactive care is associated with fewer IBD flares, less rescue therapy, and fewer undetectable IFX trough concentrations.[16,65] In a similar retrospective study, the control group was not initially dose optimized and the patients were followed for a duration greater than 1 year. This observational study concluded that the probability of patients remaining of IFX up to 1 year was similar for both groups; however, exceeding 1 year, the probability favored proactive TDM.[66] The prospective TAILORIX randomized controlled trial (tailored treatment with infliximab for active luminal Crohn's disease) also had inconclusive results, as increasing the dose of IFX based on serum drug concentrations did not yield significantly different results than increasing the IFX dose based on symptoms alone.[67]

Comparable to the management of adult IBD, IFX is the standard therapeutic agent used to treat pediatric IBD.[68] In a prospective observational cohort study for pediatric patients, it was reported that week-14 IFX trough levels predicted week-54 IFX outcomes and that early drug monitoring during induction resulted in a decreased loss of response.[69] In a retrospective cohort study, IFX discontinuation, ADA, and infusion reactions were compared for patients under the age of 25 receiving either proactive or standard care.[70] A difference in serum tough level was reported; however, there was no difference in the therapeutic outcomes.[70] It is hypothesized that the main advantage of proactive TDM is aiding in the recognition of drug non-responders rather than actually increasing the longevity of IFX use.[61] Another retrospective cohort study analyzing proactive IFX amongst children found that after 52 weeks, there was no significant difference between the patients treated proactively and reactively.[71] This study further hypothesized that patients under 10 years old require a more intensive treatment regimen when compared to older pediatric patients, as the likelihood of developing ADA is higher in patients under 10 years old.[71] Another pediatric study using a precision dosing dashboard reported that 80% of patients on a standard dose of IFX were predicted to require a shorter interval schedule than what the standard dose label indicated.[72] Furthermore, a multicenter inception cohort study assessed pre-maintenance trough IFX levels to predict the healing of pfCD in children at 24 weeks. This study reported that higher trough IFX levels positively correlated with the healing of pfCD and that a level of 12.7 μg/mL best predicted healing at 24 weeks.[12]

Adalimumab

In a retrospective cohort study involving 311 CD patients and 71 UC patients, the long-term outcome of those who received ADM proactively was compared to those who received ADM reactively.[73] This study provided evidence that proactive TDM with ADM may be associated with a reduced risk of treatment failure when compared to the control group.[73] Furthermore, in the Pediatric Crohn's Disease Adalimumab Level-based Optimization Treatment (PAILOT) randomized controlled trial of 78 pediatric patients ranging from 6 to 18 years old, it was investigated whether proactive ADM monitoring was associated with higher rates of clinical remission.[74] In this study, the primary end point of sustained corticosteroid-free clinical remission at all visits (week 8–72) was achieved by 82% of patients in the proactive group and 48% of patients in the reactive group.[75] These results suggest that proactive ADM monitoring may result in higher rates of clinical remission in pediatric patients. Furthermore, a recent

prospective pediatric study investigated the relationship between early ADM trough levels and CD remission at week 24.[50] This study concluded that a greater ADM concentration at weeks 4 and 8 positively correlated with clinical/biomarker remission at week 24.[50]

Vedolizumab and ustekinumab

To date, there are no studies comparing proactive and reactive TDM with either VDZ or UST. Future studies to obtain sufficient data are required before these non-anti-TNFs and others can become part of the clinical practice for proactive TDM.[76]

Proactive TDM: Benefits and drawbacks

While studies regarding proactive TDM are less robust than those for reactive TDM, it is evident that proactive TDM may provide significant benefits for those with moderate to severe UC and CD. Data demonstrate that proactive TDM improves the efficacy of anti-TNFs by ensuring drug administration in the optimal range.[65] This drug titration to a target trough level may minimize subtherapeutic and supratherapeutic doses, thus reducing the risk of ADA development and adverse side effects, respectively.[77-79] Furthermore, proactive TDM may be used to guide the de-escalation of biologics in patients with supratherapeutic drug concentration[76,80] This can be accomplished by dose reduction or increased time intervals, both of which may potentially decrease the cost of TDM.[21,23,81] Additional cost reductions associated with proactive TDM have also been reported in the literature as a result of remission and fewer hospitalizations/surgeries.[9]

While proactive TDM provides promise to become the future standard of care for treating IBD, it has its drawbacks. Currently, the frequency with which proactive TDM should be applied and the optimal therapeutic trough windows are incompletely understood within the literature.[82] Furthermore, long-term stability cannot be assumed because external factors such as patient weight change or increased drug excretion from diarrheal illnesses cannot be predicted.[83] These potential inadvertent therapeutic level alterations may also be associated with a financial burden as a result of TDM changes.[84] Most IBD patients are already consumed by frequent appointments and testing; therefore, it is important to consider the additional costs incurred by added testing.[85,86] However, these potential costs must be compared to those that are associated with a change in therapy due to a loss of response or an IBD flare.[84]

CURRENT KNOWLEDGE GAP

Reactive TDM is routinely recommended for biologics in the treatment of IBD. Table 1 summarizes the current suggested tough levels of biologics to maintain remission in children and adults with IBD. On the contrary, current literature shows significant promise for proactive TDM becoming the future standard of care. However, a gap of knowledge regarding proactive TDM currently exists as some aspects remain incompletely understood.

The majority of studies that investigated proactive TDM are retrospective in nature and are, therefore, subject to an increased potential of selection bias and suboptimal control.[92,93] Furthermore, pediatric studies assessing TDM within the literature are currently quite limited.[94] Specific pediatric studies are essential to gain an increased understanding of the clinical pharmacokinetic and pharmacodynamic differences between adults and children.[95,96]

Additionally, numerous studies have identified a positive correlation between improved clinical outcomes and higher anti-TNF concentrations.[97-99] However, it remains uncertain whether mucosal healing occurs as a result of higher drug concentrations or if mucosal healing occurs secondary to decreased disease activity, fecal loss, or another primary factor.[100] Future research would be required to make this clarifying distinction regarding the effects of TDM.

A patient's clinical, immunological, pharmacokinetic, microbiological, and genetic markers currently play the most significant role in determining the course and aggressiveness of TDM used.[101] However, these markers do not accurately predict if the patient will respond to a specific therapy. Primary anti-TNF non-response has been reported to occur in 10%–40% of cases and secondary non-response has been reported in up to 50% of instances.[102,103] This likely occurs because patients with analogous clinical phenotypes have different inflammatory pathways activated, and therefore do not respond to the same therapies.[104-106] IBD patients would significantly benefit from the development of new prognostic tools that can inform physicians about a patient's specific IBD activity and likely response to therapy. Different disease phenotypes, severity, and extent, may respond differently to different drug concentrations, but these points have not been adequately explored. Factors for calculating the dose, such as weight versus body surface area in male patients versus female patients, also need more clarification. Another challenge for the future will be implementing this personalized IBD treatment in a way that does not significantly exacerbate the high costs already associated with anti-TNF treatment.[107]

Table 1: Data displaying the optimal trough levels during induction and maintenance therapy for various anti-TNF and non-anti-TNF drugs to achieve clinical remission

Biologic	CD		UC	
	Induction	Maintenance	Induction	Maintenance
Infliximab[87]	>20.4 μg/mL	1.5–15 μg/mL	>15.3 μg/mL	2.1–15 μg/mL
Adalimumab[88-90]	>15 μg/mL	≥12.5 μg/mL	>13.85 μg/mL	>6.6 μg/mL
Ustekinumab[53,88]	3–7 mg/mL	1.4–3 mg/mL	3–7 mg/mL	1.1–3 mg/mL
Vedolizumab[91]	>16 μg/mL	>14 μg/mL	>17 μg/mL	>14 μg/mL

The time taken to receive patient trough level results in a central laboratory prior to IFX dose adjustment can also be challenging.[38] Currently, commercially available ELISA-based IFX quantification kits are used to optimize treatments following the infusion approximately 6–8 weeks later.[108] However, emerging evidence indicates that point-of-care anti-TNF assays can be utilized to make immediate and informed clinical decisions.[109] This can ultimately improve biologic efficacy, reduce adverse effects associated with both supratherapeutic or subtherapeutic dosing, and further instigate more proactive and cost-effective patient care.[110-112]

Current proactive research is primarily limited to studies involving IFX and ADA, whereas literature involving other biologics such as VDZ and UST is scarce.[113,114] Future research would be required to determine what else, aside from receptor saturation, influences the clinical outcomes associated with VDZ.[115] While some studies involving UST have demonstrated a clear association between UST concentration and clinical remission, further research is required to refine the therapeutic dose threshold necessary for endoscopic remission.[53,116] Furthermore, VDZ and UST dose escalation has proven to be successful in reobtaining clinical response and remission; however, data have not been published specifically in the context of TDM.[53]

Additionally, current research has determined that various human leukocyte antigen (HLA) alleles are responsible for approximately 10%–33% and 64%–100% of the total genetic risk for CD and UC, respectively.[88,117] Thus, future research maybe beneficial in using molecular markers to aid in the discernment of UC and CD. Interestingly, the HLA-DRB1*0103 and HLA-B*52 alleles are associated with both CD and UC; therefore, future research would also be useful for explaining, in part, why the two forms of IBD concur at an incidence greater than projected by chance alone.[118] A genome-wide association study determined that the HLA-DQA1*05 allele increased the risk of ADA development by twofold in patients with CD.[87] Moreover, patients with the HLA-DQA1*05 allele being treated with IFX displayed immunogenicity rates of 92% at 1 year.[87] Future studies should investigate the immunogenicity rates in individuals with the HLA-DQA1*05 allele being treated with alternative biologics and the presence of any other immunogenicity-predictive immune markers to different biologics.

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Conflicts of interest

Wael El-Matary has consulted to Abbvie, Janssen, Merck Pharmaceuticals, has received speaker fees from Abbvie and had investigator-initiated research support from Janssen. No conflicts for the other two authors.

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