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

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
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.\cite{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.\cite{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.\cite{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.\cite{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.\cite{18} Additional studies have demonstrated a positive correlation between reactive TDM and endoscopic remission in patients with IBD receiving biologics.\cite{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.\cite{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.\cite{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.\cite{24-29}

**Infliximab**

Infliximab (IFX) is a monoclonal antibody that binds to TNFα, an important inflammatory mediator in IBD, and neutralizes its effect.\cite{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.\cite{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.\cite{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.\cite{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.\cite{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.\cite{37} 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.\cite{38} 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.\cite{39}

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.\cite{40} However, it was determined that reactive TDM was associated with significant cost reduction.\cite{41} 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%).\cite{42}

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. 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. The remaining seven patients were reported to have high ADA and it was, therefore, recommended that they switch to a different biologic. 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. 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. 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.

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. 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. 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. This study concluded that there was a positive correlation between ADM serum drug concentration and clinical remission. However, a serum concentration threshold to discriminate patients by remission status could not be identified as there was a significant overlap. 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.

In the IMAgINE double-blind trial, the safety, efficacy, and pharmacokinetics of ADM were assessed in children. 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. In another prospective pediatric study, it was reported that among 65 patients, 60% achieved clinical/biomarker remission by week 24 without dose escalation. 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.

Ustekinumab and vedolizumab

Ustekinumab (UST) functions by inhibiting the activity of IL-22/23 through their common p40 subunit. Alternatively, vedolizumab (VDZ) is an antagonist that binds to the α4β7 integrin. 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. 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. 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. 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. Moreover, it was concluded that higher VDZ concentrations were also associated with higher rates of remission.

PROACTIVE THERAPEUTIC DRUG MONITORING

Proactive TDM employs a schedule of preemptive analysis of serum trough concentrations to accordingly adjust the patient's biologic dosage. 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. 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.[23] 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.[68] 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.[68,65] 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.[69] 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 trough 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. This study concluded that a greater ADM concentration at weeks 4 and 8 positively correlated with clinical/biomarker remission at week 24.

**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.

**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. 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. Furthermore, proactive TDM may be used to guide the de-escalation of biologics in patients with supratherapeutic drug concentration. This can be accomplished by dose reduction or increased time intervals, both of which may potentially decrease the cost of TDM. Additional cost reductions associated with proactive TDM have also been reported in the literature as a result of remission and fewer hospitalizations/surgeries.

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. 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. These potential inadvertent therapeutic level alterations may also be associated with a financial burden as a result of TDM changes. Most IBD patients are already consumed by frequent appointments and testing; therefore, it is important to consider the additional costs incurred by added testing. 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.

**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. Furthermore, pediatric studies assessing TDM within the literature are currently quite limited. Specific pediatric studies are essential to gain an increased understanding of the clinical pharmacokinetic and pharmacodynamic differences between adults and children.

Additionally, numerous studies have identified a positive correlation between improved clinical outcomes and higher anti-TNF concentrations. 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. 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. 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. This likely occurs because patients with analogous clinical phenotypes have different inflammatory pathways activated, and therefore do not respond to the same therapies. 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.
The time taken to receive patient trough level results in a central laboratory prior to IFX dose adjustment can also be challenging.[88] 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.[89]

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.[86,117] Thus, future research may be 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.

Financial support and sponsorship
Nil.

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.

REFERENCES
1. El-Matary W, Leung S, Tennakoon A, Benchimol EI, Bernstein CN, Targownik LE. Trends of utilization of tumor necrosis factor antagonists in children with inflammatory bowel disease: A Canadian population-based study. Inflamm Bowel Dis 2020;26:134-8.
2. Feuerstein JD, Nguyen GC, Kupfer SS, Falek-Ytter Y, Singh S. American gastroenterological association institute guideline on therapeutic drug monitoring in inflammatory bowel disease. Gastroenterology 2017;153:827-34.
3. Vande Casteele N, Herfarth H, Katz J, Falek-Ytter Y, Singh S. 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.
4. Sparrow MP, Pamichael K, Ward MG, Riviere P, Laharie D, Paul S, et al. Therapeutic drug monitoring of biologics during induction to prevent primary nonresponse. J Crohns Colitis 2020;14:542-56.
5. Colombel JF, Narula N, Peyrin-Biroulet L. Management strategies to improve outcomes of patients with inflammatory bowel diseases. Gastroenterology 2017;152:351-61.
6. deBruyn JC, Jacobson K, El-Matary W, Wine E, Carroll MW, Goodhart C, et al. Early Serum Infliximab Levels in Pediatric Ulcerative Colitis. Front Pediatr 2021;9:1-9.
7. Huynh GH, Carroll MA, Griffith AM, El-Matary W, Petrova A, Prosser C, et al. IDeal – A multi-center prospective Infliximab Dose to Level pharmacokinetic study during induction in pediatric Crohn’s disease. J Crohn’s Colitis 2019;6:4.
8. Restellini S, Chao CY, Lakatos PL, Aruljothy A, Kherad O, Bitton A, et al. Therapeutic drug monitoring guides the management of Crohn’s patients with secondary loss of response to adalimumab. Inflamm Bowel Dis 2018;24:1531-8.
9. Kelly OB, O’Donnell S, Stempak JM, Steinhardt AH, Silverberg MS. Therapeutic drug monitoring to guide infliximab dose adjustment is associated with better endoscopic outcomes than clinical decision making alone in active inflammatory bowel disease. Inflamm Bowel Dis 2017;23:1202-9.
10. Pamichael K, Chefetz AS. Therapeutic drug monitoring in patients on biologics: Lessons from gastroenterology. Curr Opin Rheumatol 2017;29(5):446-53.

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   | 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 |
11. Shmais M, Regueiro M, Hashash JG. Proactive versus reactive therapeutic drug monitoring: Why, when, and how? Inflamm Intest Dis 2022;7:50–58.

12. El-Matary W, Walters TD, Huynh HQ, deBruyn J, Mack DR, Jacobson K, et al. Higher postinduction infliximab serum trough levels are associated with healing of fistulizing perianal Crohn’s disease in children. Inflamm Bowel Dis 2019;25:150–5.

13. Martins CA, Moss AC, Sobrado CW, Queiroz NS. Practical aspects of proactive TDM for anti-TNF agents in IBD: Defining time points and thresholds to target. Crohn’s & Colitis 360 2019;1:1–7.

14. Deora V, Kozak J, El-Kalla M, Huynh HQ, El-Matary W. Therapeutic drug monitoring was helpful in guiding the decision-making process for children receiving infliximab for inflammatory bowel disease. Acta Paediatr 2017;106:1863–7.

15. Albader F, Golovics PA, Gonczi L, Bessissow T, Afif W, Lakatos PL. Therapeutic drug monitoring in inflammatory bowel disease: The dawn of reactive monitoring. World J Gastroenterol 2021;27:6241–47.

16. Cheifetz A. Overview of therapeutic drug monitoring of biologic agents in patients with inflammatory bowel disease. Gastroenterol Hepatol 2017;3:5356–9.

17. Ricciuto A, Dhaliwal J, Walters TD, Griffiths AM, Church PC. Clinical outcomes with therapeutic drug monitoring in inflammatory bowel disease: A systematic review with meta-analysis. J Crohns Colitis 2018;12:302–15.

18. Lyles JL, Mulgund AA, Bauman LE, Su W, Fei L, Chona DL, et al. Effect of a practice-wide anti-TNF proactive therapeutic drug monitoring program on outcomes in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis 2021;27:482–92.

19. Colombel JF, Sandborn WJ, Allez M, Dupas JL, Dewit O, D’Haens G, et al. Association between plasma concentrations of certolizumab pegol and endoscopic outcomes of patients with Crohn’s disease. Clin Gastroenterol Hepatol 2014;12:423–31.

20. Chaparro M, Barreiro-de Acosta M, Garcia-Planella E, Domènech E, Bermejo F, Calvet X, et al. Outcome after a dose “de-intensification” strategy with anti-TNF drugs in patients with Crohn’s disease. Gastroenterol Hepatol 2016;39:255–60.

21. Velays FS, Kahn JG, Sandborn WJ, Feagan BG. A test-based strategy is more cost effective than empiric dose escalation for patients with Crohn’s disease who lose responsiveness to infliximab. Clin Gastroenterol Hepatol 2013;11:654–66.

22. Negoeceu DM, Enns EA, Swanhorst B, Baumgartner B, Campbell JP, Osterman MT, et al. Proactive vs reactive therapeutic drug monitoring of infliximab in Crohn’s disease: A cost-effectiveness analysis in a simulated cohort. Inflamm Bowel Dis 2020;26:103–11.

23. Steenholtz C, Brynskov J, Thomsen OØ, Munk-JK, Fallborg J, Christensen LA, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn’s disease who lose response to anti-TNF treatment: A randomised, controlled trial. Gut 2014;63:919–27.

24. Papamichael K, Casteele NV, Ferrante M, Gils A, Cheifetz A. Therapeutic drug monitoring during induction of anti-tumor necrosis factor therapy in inflammatory bowel disease: Defining a therapeutic drug window. Inflamm Bowel Dis 2017;23:1510–5.

25. Davidov Y, Ungar B, Bar-Yoseph H, Carter D, Haj-Natour O, Yavzori M, et al. Association of induction infliximab levels with clinical response in perianal Crohn’s disease. J Crohns Colitis 2016;11:549–55.

26. Papamichael K, Van Stappen T, Vande Casteele N, Gils A, Billiet T, Tops S, 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.

27. Kobayashi T, Suzuki Y, Motoya S, Hirai F, Ogata H, Ito H, et al. First trough level of infliximab at week 2 predicts future outcomes of induction therapy in ulcerative colitis-results from a multicenter prospective randomized controlled trial and its post hoc analysis. J Gastroenterol 2016;51:241–51.

28. Brandse JF, Mathot RA, van der Kleij D, Rispens T, Ashraf Y, Janse JM, et al. Pharmacokinetic features and presence of anti-drug antibodies associated with response to infliximab induction therapy in patients with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol 2016;14:251–8.

29. Papamichael K, Baert F, Tops S, Van Assche G, Rutgeerts P, Veirmeir S, et al. Post-induction adalimumab concentration is associated with short-term mucosal healing in patients with ulcerative colitis J Crohns Colitis 2017;11:53–59.

30. Talley NJ, Abreu MT, Achkar JP, Bernstein CN, Dubinsky MC, Hanauer SB, et al. An evidence-based systematic review on medical therapies for inflammatory bowel disease. Am J Gastroenterol 2011;106:22–5.

31. Kolho KL. Therapeutic drug monitoring and outcome of infliximab therapy in pediatric onset inflammatory bowel disease. Front Pediatr 2021;8:1–6.

32. Akobeng AA, Sandborn WJ, Bickston SJ, Chande N, Shackleton LM, Nelson S, et al. Tumor necrosis factor-alpha antagonists twenty years later: What do cochrane reviews tell us?. Inflamm Bowel Dis 2014;20:2132–41.

33. Gisbert JP, Panés J. Loss of response and requirement of infliximab dose intensification in Crohn’s disease: A review. Am J Gastroenterol 2009;104:760–7.

34. Paul S, Del Teideco E, Marotte H, Rinaudo-Gaajou M, Moreau A, Philip JM, et al. Therapeutic drug monitoring of infliximab and mucosal healing in inflammatory bowel disease: A prospective study. Inflamm Bowel Dis 2013;19:2568–76.

35. Afif W, Loftus EV Jr, Faubion WA, Kane SV, Brunning DH, Hanson KA, et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. Am J Gastroenterol 2010;105:1133–9.

36. Chaparro M, Panes J, Garcia V, Manosa M, Esteve M, Olga M, et al. Long-term durability of infliximab treatment in Crohn’s disease and efficacy of dose “escalation” in patients losing response. J Clin Gastroenterol 2011;45:113–8.

37. Rutgeerts P, Sandborn W, Feagan B, Reinisch W, Olson A, Johannes J, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med 2005;353:2462–76.

38. Grossberg LB, Papamichael K, Feuerstein JD, Siegel CA, Ullman TA, Cheifetz AS. Survey study of gastroenterologists’ attitudes and barriers toward therapeutic drug monitoring of anti-TNF therapy in inflammatory bowel disease. Inflamm Bowel Dis 2018;24:191–7.

39. Adedokun OJ, Xu Z, Padgett L, Blank M, Johannes J, Griffiths A, et al. Pharmacokinetics of infliximab in children with moderate-to-severe ulcerative colitis: Results from a randomized, multicenter, open-label, phase 3 trial. Inflamm Bowel Dis 2013;19:2753–62.

40. Carman N, Mack DR, Benchimol EI. Therapeutic drug monitoring in pediatric inflammatory bowel disease. Curr Gastroenterol Rep 2018;20:1–13.

41. Choi SY, Kang B, Lee JH, Choe YH. Clinical use of measuring trough levels and antibodies against infliximab in patients with pediatric inflammatory bowel disease. J Chest Surg 2017;11:55–61.

42. Stein R, Lee D, Leonard MB, Thayu M, Denson LA, Chuang E, et al. Serum infliximab, antidrug antibodies, and tumor necrosis factor predict sustained response in pediatric Crohn’s disease. Inflamm Bowel Dis 2016;22:1370–7.

43. Wasan SK, Kane SV. Adalimumab for the treatment of inflammatory bowel disease. Expert Rev Gastroenterol Hepatol 2011;5:679–84.

44. Hu S, Liang S, Guo H, Zhang D, Li H, Wang X, et al. Comparison of the inhibition mechanisms of adalimumab and infliximab in treating tumor necrosis factor α-associated diseases from a molecular view. J Biol Chem 2013;288:27059–67.

45. Rutgeerts P, Van Assche G, Sandborn WJ, Wolf DC, Geboes K, Colombel JF, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn’s disease: Data from the EXTEND trial. Gastroenterology 2012;142:1102–11.
46. Chiu YL, Rubin DT, Vermeire S, Louis E, Robinson AM, Lomax KG, et al. Serum adalimumab concentration and clinical remission in patients with Crohn's disease. Inflamm Bowel Dis 2013;19:1112-22.

47. Karmiris K, Paintaud G, Noman M, Magdelaine–Beuzelin C, Ferrante M, Degene D, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. Gastroenterology 2009;137:1628-40.

48. Rueemmele FM, Rosh J, Faulion WA, Dubinsky MC, Turner D, Lazar A, et al. Efficacy of adalimumab for treatment of perianal fistula in children with moderately to severely active Crohn's disease: Results from IMAgINE 1 and IMAgINE 2. J Crohns Colitis 2018;12:1249-54.

49. Sharma S, Eckert D, Hyams JS, Mensing S, Thakkar RB, Robinson AM, et al. Pharmacokinetics and exposure–efficacy relationship of adalimumab in pediatric patients with moderate to severe Crohn's disease: Results from a randomized, multicenter, phase-3 study. Inflamm Bowel Dis 2015;21:783-92.

50. Rinawi F, Ricciuto A, Church PC, Frost K, Crowley E, Walters TD, et al. Association of postinduction adalimumab exposure with subsequent clinical and biomarker remission in children with Crohn's disease. Inflamm Bowel Dis 2021;27:1079-87.

51. Sandborn W, Gasink C, Gao LL, Blank MA, Johans J, Guzzo C, et al. Influence of co-medications on the clinical outcomes in patients with ulcerative colitis or Crohn's disease. J Crohns Colitis 2016;10:1437-44.

52. Adedokun OJ, Xu Z, Gasink C, Jacobsin D, Szapary P, Johans J, et al. Pharmacokinetics and exposure response relationships of ustekinumab in patients with Crohn's disease. Gastroenterology 2018;154:1660-71.

53. Soufflet N, Boschetti G, Roblin X, Cuerq C, Wiltiet N, Charlois AL, et al. Concentrations of ustekinumab during induction therapy associate with remission in patients with Crohn's disease. Clin Gastroenterol Hepatol 2019;17:2610-2.

54. Rosario M, Dirks NL, Gastonguay MR, Fasanmade AA, Wyant T, Parikh A, et al. Pharmacokinetics and pharmacodynamics of vedolizumab in patients with ulcerative colitis and Crohn's disease. Aliment Pharmacol Ther 2015;42:188-202.

55. Vermeire S, Loftus E, Colombel J, Feagan B, Sandborn W, Sands B, et al. Long-term efficacy of vedolizumab for Crohn's disease. J Crohns Colitis 2017;11:412-24.

56. Rosario M, Abhyankar B, Sankoh S, Dirks N, Lasch K, Sandborn W. Relationship between vedolizumab pharmacokinetics and endoscopic outcomes in patients with ulcerative colitis. J Crohns Colitis 2015;9:546.

57. Rosario M, French JL, Dirks NL, Sankoh S, Parikh A, Yang H, et al. Exposure–efficacy relationships for vedolizumab induction therapy in patients with ulcerative colitis or Crohn's disease. J Crohns Colitis 2017;11:921-9.

58. de Almeida Martins C, Moss AC, Sobrado CW, Queiroz NS. Practical aspects of proactive TDM for anti-TNF agents in IBD: Defining time points and thresholds to target. Crohns & Colitis 360 2019;1:17.

59. Lee SD, Shivashankar R, Quirk D, Zhang H, Telliez JB, Andrews J, et al. Infliximab dose and dosage regimens in pediatric IBD patients: A new approach for predicting secondary loss of efficacy. Inflamm Bowel Dis 2019;25:1079-87.

60. Jongsma MM, Winter DA, Huynh HQ, Norsa L, Hussey S, Kolho KL, et al. Infliximab induction and maintenance therapy in refractory Crohn's disease. Inflamm Bowel Dis 2021;27:1026-37.

61. Lega S, Phan BL, Rosenthal CJ, Gordon J, Haddad N, Pittman N, et al. Proactively optimized infliximab monotherapy is as effective as combination therapy in IBD. Inflamm Bowel Dis 2019;25:134-41.

62. Dubinsky MC, Phan BL, Singh N, Rabizadeh S, Moull DR. Pharmacokinetic dashboard-recommended dosing is different than standard of care dosing in infliximab-treated pediatric IBD patients. Inflamm Bowel Dis 2017;19:215-22.

63. Papamichail K, Juncadella A, Wong D, Rakowsky S, Sattler LA, Campbell JP, et al. Proactive therapeutic drug monitoring of adalimumab is associated with better long-term outcomes compared with standard of care in patients with inflammatory bowel disease. J Crohns Colitis 2019;13:976-81.

64. Papamichail K, Cheifetz AS, Melmed GY, Irving PM, Vande Casteele N, Kozuch PL, et al. Appropriate therapeutic drug monitoring of biologic agents for patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2018;16:1415-23.

65. Papamichail K, Osterman MT, Siegel CA, Melmed GY, Dubinsky MC, Colombel JF, et al. Using proactive therapeutic drug monitoring of anti-tumor necrosis factor therapy in inflammatory bowel disease: From an old concept to a future standard of care?. Gastroenterology 2018;154:1201-2.

66. Grassmeier MK, Langmann AF, Langmann P, Treiber M, Thaler MA, Luppa PB. Dynamics of serum concentrations of antibodies to infliximab: A new approach for predicting secondary loss of response in inflammatory bowel diseases. Therap Adv Gastroenterol 2021;14:17562848211037849. doi: 10.1177/17562848211037849.
treatments in inflammatory bowel disease. Br J Clin Pharmacol 2020;80:1165-75.
80. Lucidarme C, Peticcollin A, Brochard C, Siproudhis L, Dewit M, Landemaine A, et al. Predictors of relapse following infliximab de-escalation in patients with inflammatory bowel disease: The value of a strategy based on therapeutic drug monitoring. Aliment Pharmacol Ther 2018;49:147-54.
81. VandeCastelee N, Gilis A. Pharmacokinetics of anti-TNF monoclonal antibodies in inflammatory bowel disease: Adding value to current practice. J Clin Pharmacol 2015;55:39-50.
82. Gibson, DJ, Ward MG, Rentisch C, Friedman AB, Taylor KM, Sparrow MP, et al. Review article: Determination of the therapeutic range for therapeutic drug monitoring of adalimumab and infliximab in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2020;51:612-28.
83. Ma C, Battar R, Jairath V, Van Castele N. Advances in therapeutic drug monitoring for small-molecule and biologic therapies in inflammatory bowel disease. Curr Treat Options Gastroenterol 2019;17:127-45.
84. McNeill R, Barclay M. Cost-effectiveness of therapeutic drug monitoring in inflammatory bowel disease. Curr Opin Pharmacol 2020;55:41-6.
85. Hazratjee N, Agito M, Lopez R, Lashner B, Rizk M. Hospital readmissions in patients with inflammatory bowel disease. Am J Gastroenterol 2013;108:1024-32.
86. Rakowsky ST, Feuerstein JD. Highs and lows of proactive therapeutic drug monitoring in Crohn’s patients. Dig Dis Sci 2021;66:3226-7.
87. Cheifetz AS, Abreu MT, Afif W, Cross RK, Dubinsky MC, et al. Linkage of Crohn’s disease to the major histocompatibility complex region is detected by multiple non-parametric analyses. Gut 1999;44:519-26.
88. Lucafò M, Curci D, Bramuzzo M, Alvisi P, Martelossi S, Silvestri T, et al. Serum adalimumab levels after induction are associated with long-term remission in children with inflammatory bowel disease. Front Pediatr 2021;9:1-9.
89. Papamichael K, Gilis A, Rutgeerts P, Levesque BG, Vermeire S, Sandborn WJ, et al. Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD: Evolution in the definition and management of primary nonresponse. Inflamm Bowel Dis 2015;21:182-97.
90. Zorzi F, Monteleone I, Sarra M, Calabrese F, Marafini I, Cretella M. Distinct profiles of effector cytokines mark the different phases of Crohn’s disease. PLoS One 2013;8:1-10.
91. Verdier J, Bégue B, Cerf-Bensussan N, Ruemmele FM. Compartmentalized expression of TH1 and TH17 cytokines in pediatric inflammatory bowel diseases. Inflamm Bowel Dis 2012;18:1260-6.
92. Areya R, Neurath MF. Mechanisms of molecular resistance and predictors of response to biological therapy in inflammatory bowel disease. Lancet Gastroenterol Hepatol 2018;3:790-802.
93. van der Valk ME, Mangen MJ, Leenders M, Dijkstra G, van Bodergraven AA, Fidder HH, et al. Healthcare costs of inflammatory bowel disease have shifted from hospitalisation and surgery towards anti-TNFalpha therapy: Results from the COIN study. Gut 2014;63:72-9.
94. afonso J, Lopes S, Gonçalves R, Caldeira P, Lago P, Tavares de Sousa H, et al. Proactive therapeutic drug monitoring of infliximab: A comparative study of a new point-of-care quantitative test with two established ELISA assays. Aliment Pharmacol Ther 2016;44:684-92.
95. Taddio A, Prim D, Bojescu E, Segura J, Pfeiffer M. Point-of-care therapeutic drug monitoring for precision dosing of immunosuppressive drugs. J Appl Lab Med 2020;5:738-61.
96. Van Stappen T, Bollen L, Vande Casteele N, Papamichael K, van Assche G, Ferrante M, et al. Rapid test for infliximab drug concentration allows immediate dose adaptation. Clin Transl Gastroenterol 2016;7:1-7.
97. Dutzer D, Nasser Y, Berger A, Robin X, Paul S. New thresholds need to be defined when using point of care assays to monitor infliximab trough levels in IBD patients. Aliment Pharmacol Ther 2016;44:684-92.
98. Srinivasan A, Ding NS, van Langenberg D, De Cruz P. Therapeutic drug monitoring in inflammatory bowel disease: Optimising therapeutic effectiveness of biologics. In: Sheng Ding N, De Cruz P, editors. Biomarkers in Inflammatory Bowel Diseases. Springer; 2019. p. 243-55.
99. Restellini S, Khanna R, Afif W. Therapeutic drug monitoring with ustekinumab and vedolizumab in inflammatory bowel disease. Inflamm Bowel Dis 2018;24:2165-72.
100. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2013;369:699-710.
101. Rosario M, Dirks NL, Milich C, Parikh A, Bargfrede M, Wyant T, et al. A review of the clinical pharmacokinetics, pharmacodynamics, and immunogenicity of vedolizumab. Clin Pharmacokinet 2017;56:1287-301.
102. Painchart C, Brabant S, Duveau N, Nachury M, Desreuix P, Branche J, et al. P360 Trough levels and antibodies to ustekinumab...
are not correlated to response to ustekinumab treatment in Crohn’s disease patients. ECCO 2017;11:260-1.

117. Satsangi, J, Welsh KJ, Bunce M, Julier C, Farrant JM, Bell JI, et al. Contribution of genes of the major histocompatibility complex to susceptibility and disease phenotype in inflammatory bowel disease. Lancet 1996;347:1212-7.

118. Ahmad T, Marshall SF, Jewell D. Genetics of inflammatory bowel disease: The role of the HLA complex. World J Gastroenterol 2006;12:3628-35.