

Practical Use of Therapeutic Drug Monitoring of Anti-TNF Therapy in IBD



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Anti-tumor necrosis factor (TNF) therapy has revolutionized the care of inflammatory bowel disease (IBD). However, 10-30% of IBD patients show no initial clinical benefit to anti-TNF therapy and over 50% after an initial response lose response over time. Some of this primary non-response and the majority of the secondary loss of response is due to sub-therapeutic drug concentrations and/or the development of anti-drug antibodies. Therapeutic drug monitoring (TDM) can better explain and guide the management of patients with a loss of response to anti-TNF therapy (reactive TDM). Reactive TDM has also been proven to be more cost-effective compared to empiric dose escalation of anti-TNF therapy based only on symptoms. Preliminary data demonstrate that proactive TDM with drug titration to a target concentration applied in patients showing clinical benefit can optimize anti-TNF therapy efficacy and cost. This review will focus on the role of TDM in guiding therapeutic decisions in IBD.

INTRODUCTION

Anti-tumor necrosis factor (TNF) therapy is the cornerstone of the treatment of patients with moderate to severe Crohn's disease (CD) and ulcerative colitis (UC).¹ Nevertheless, up to 30% of patients with inflammatory bowel disease (IBD) show no initial clinical benefit to anti-TNF therapy (primary non-responders) and over 50% lose response within the first year of therapy.^{2,3} Mechanisms underlying these undesired therapeutic outcomes involve pharmacokinetic or pharmacodynamic issues. The first are associated with inadequate drug concentrations due to the development of anti-drug antibodies or an

increased non-immune drug clearance, while the latter are related to a non-TNF driven inflammatory process.^{2,3}

Numerous exposure-response relationship studies have demonstrated that higher serum anti-TNF drug concentrations are associated with favorable objective therapeutic outcomes during both induction and maintenance therapy (Table 1).⁴⁻²⁴ On the other hand, low or undetectable drug concentrations are linked to anti-drug antibodies formation and treatment failure.^{3,25-27} These data suggest that in addition to 'treating-to-target' we should also be 'treating-to-trough' and that early proactive optimization of anti-TNF therapy may

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Figure 1. Proposed Algorithm for Reactive Therapeutic Drug Monitoring of Anti-TNF Therapy in Inflammatory Bowel Disease

Adapted from Papamichael and Cheifetz 2016.³

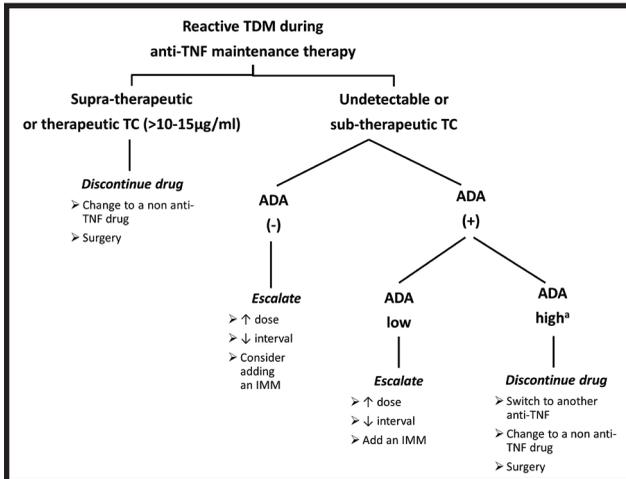


Figure Footnote 1. ^aFor antibodies to infliximab >8 µg/mL using ELISA²⁷ and >9.1 U/mL using the HMSA assay.⁸ ADA: antidrug antibodies; IMM: immunomodulator; TC: trough concentration; TDM: therapeutic drug monitoring; TNF: tumor necrosis factor

Figure 2. Proposed Algorithm for Proactive Therapeutic Drug Monitoring of Anti-TNF Therapy in Inflammatory Bowel Disease

Adapted from Papamichael and Cheifetz 2016.³

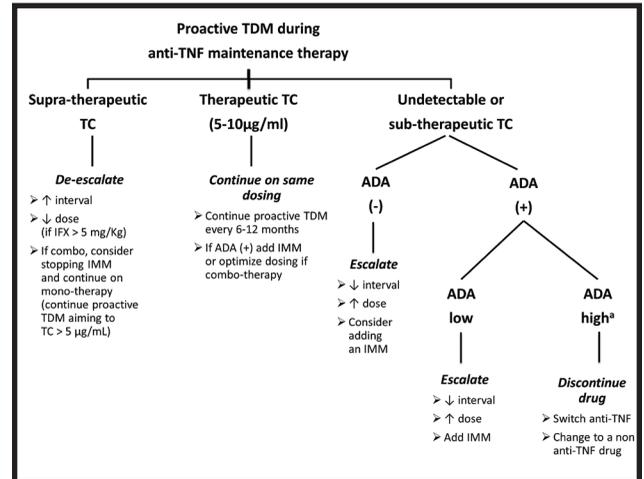


Figure Footnote 2. ^aFor antibodies to infliximab >8 µg/mL using ELISA²⁷ and >9.1 U/mL using the HMSA assay.⁸ ADA: antidrug antibodies; IMM: immunomodulator; TC: trough concentration; TDM: therapeutic drug monitoring; TNF: tumor necrosis factor; IFX: infliximab

achieve better long-term therapeutic outcomes.

Therapeutic drug monitoring (TDM), defined as the evaluation of serum drug concentrations and anti-drug antibodies, has rationalized the management of IBD patients who lose response to anti-TNF therapy and improved therapeutic decision making. Reactive TDM allows for more individualized treatment (personalized medicine) when a secondary loss of response occurs. Moreover, it better directs care and prevents unnecessary drug exposure in patients who are unlikely to respond to more anti-TNF therapy.³

Preliminary data show that proactive TDM with drug titration to a target trough concentration applied in patients in clinical response or remission can improve the efficacy and potentially cost-effectiveness of anti-TNF therapy.^{28,29} Proactive TDM may also be useful to better guide therapeutic decisions in other clinical scenarios, such as re-introduction of anti-TNF therapy after a drug holiday³⁰ or discontinuation of anti-TNF therapy in patients achieving deep remission.^{31,32} This review will focus on the practical role of TDM of anti-TNF therapy in clinical practice.

Reactive TDM

Reactive TDM can better explain and guide the management of loss of response to anti-TNF therapy

in IBD and has been proven to be more cost-effective than standard-of-care.³³⁻³⁵ Patients with sub-therapeutic or undetectable drug concentrations and no anti-drug antibodies benefit more from escalation of treatment (by increasing the dose or decreasing the interval) compared to those switched to another anti-TNF agent.³⁶ Moreover, higher drug concentrations after dose escalation are associated with re-capturing clinical response and improved clinical outcomes.³⁷⁻³⁹ On the contrary, patients with therapeutic or supra-therapeutic drug concentrations benefit more when changing out of class to a drug with a different mechanism of action, as there is probably a shift to non-TNF driven disease.³⁶ A recent study showed that infliximab and adalimumab trough concentration of >3.8 and >4.5 µg/mL, respectively, measured at the time of loss of response distinguished patients who had a better long-term outcome from alternative therapies compared to those who escalated the anti-TNF therapy or switched to another anti-TNF agent.⁴⁰ However, considering the lower response rate to a subsequent biologic, the limited pharmacological options, and the lack of a clear drug threshold, in practice we typically dose optimize to drug concentrations of >10-15 µg/mL before stopping infliximab or adalimumab. On the other hand, patients with high anti-drug antibodies do better when

switched to another anti-TNF rather than further dose escalation.³⁶ Vande Casteele and colleagues, showed that patients with antibodies to infliximab >9.1 U/ml when loss of response occurred had a 3.6 times higher risk to fail a subsequent infliximab dose optimization.⁸ There are several laboratories that offer TDM and it is critically important to understand the assay and how the

antibodies are recorded (Table 2). A proposed treatment algorithm for using reactive TDM for anti-TNF therapy is shown in Figure 1.

Proactive TDM

Recent data demonstrate that proactive TDM can optimize efficacy and potentially cost of anti-TNF

Table 1. Serum Anti-TNF Concentration Thresholds During Induction and Maintenance Therapy Associated with Favourable Objective Therapeutic Outcomes in Inflammatory Bowel Disease

Drug	Time Point of TDM	TC Threshold (µg/ml)	Therapeutic Outcome	TDM Assay	Ref.
IFX	Induction (w2)	≥28.3	Mucosal healing (w10-14)	ELISA	(5)
IFX	Induction (w6)	≥15	Mucosal healing (w10-14)	ELISA	(5)
IFX	Induction (w6)	>6.6	Endoscopic response ^a (w8)	RIA	(6)
IFX	Post-induction (w14)	>2.5	Colectomy-free survival	ELISA	(9)
IFX	Post-induction (w14)	≥2.1	Early mucosal healing	ELISA	(5)
IFX	Maintenance	>6.8	Normal CRP (≤5mg/L)	ELISA	(7)
IFX	Maintenance	>2.8	Normal CRP (≤5mg/L)	HMSA	(12)
IFX	Maintenance	>0.6	Normal CRP (≤0.3mg/dL)	ELISA	(18)
IFX	Maintenance	>7.3	Normal FC (<250mg/g)	ELISA	(20)
IFX	Maintenance	>1.1	Normal FC (<300µg/g)	ELISA	(18)
IFX	Maintenance	>8.3	Mucosal healing	HMSA	(21)
IFX	Maintenance	>5	Mucosal healing	ELISA	(7)
IFX	Maintenance	≥3	Mucosal healing	ELISA	(22)
IFX	Maintenance	>4	Mucosal healing	ELISA	(18)
ADM	Post-induction (w4)	≥7.5	Mucosal healing (w10-14)	ELISA	(10)
ADM	Maintenance	>6.6	Normal CRP (≤5mg/L)	ELISA	(7)
ADM	Maintenance	>5.9	Normal CRP (≤0.3mg/dL)	ELISA	(19)
ADM	Maintenance	>5.9	CRP normalization	ELISA	(23)
ADM	Maintenance	>7.1	Mucosal healing	ELISA	(7)
ADM	Maintenance	>4.9	Mucosal healing	ELISA	(24)
ADM	Maintenance	>8.1	Mucosal healing	HMSA	(17)
CZP	Post-induction (w8)	>23.3	Endoscopic response and remission (w10)	ELISA	(11)

^aDefined as ≥ one point reduction in the endoscopic Mayo score

ELISA: enzyme-linked immunosorbent assay; **HMSA:** homogeneous mobility shift assay; **TC:** trough concentration; **CRP:** C-reactive protein, **FC:** fecal calprotectin; **TNF:** tumor necrosis factor; **IFX:** infliximab; **ADM:** adalimumab; **w:** week; **TDM:** therapeutic drug monitoring; **CZP:** certolizumab pegol; **RIA:** Radioimmunoassay; **Ref.:** references

Table 2. Therapeutic Drug Monitoring Assays for Measuring Anti-Drug Antibodies⁴⁵⁻⁵⁷

Type	Drug-tolerant	ADA Titer	Laboratories Using Commercial Kits or in-House Developed Assays for TDM
ELISA ^a	No	µg/mL	Theradiag/Alpha, France; Grifols, Spain; Matriks Biotek, Turkey; Immundiagnostik AG, Germany; Miraca, USA; R-Biopharm AG, Germany
ELISA ^b	Yes	ng/mL	KU Leuven, Belgium
AHLC	Yes	µg/mL	Tel-Aviv University, Israel
HMSA	Yes	U/mL	Prometheus, USA
ECLIA	Yes	ng/mL	LabCorp/Esoterix, USA; Janssen, USA
RIA	No	U/mL	Sanquin, Netherlands; Biomonitor A/S, Denmark
SRA LC-MS/MS	Yes	U/mL	Mayo Clinic, USA
Bioassays ^c	Yes	NA	Biomonitor A/S, Denmark (RGA); Israel Institute of Technology, Haifa, Israel (ITBR)

^aFirst-generation; ^bAffinity-capture-elution methodology; ^cFunctional immune-based assays

ELISA: enzyme-linked immunosorbent assay; **RIA:** radioimmunoassay; **HMSA:** homogeneous mobility shift assay; **ECLIA:** electro-chemiluminescence immunoassay; **RGA:** reporter-gene assay; **AHLC:** antihuman lambda chain antibody; **U:** units; **TDM:** therapeutic drug monitoring; **ADA:** antidrug antibodies; **ITBR:** infliximab-tumor necrosis factor binding reduction ratio; **NA:** not applicable; **SRA LC-MS/MS:** Selective Reaction Monitoring Liquid Chromatography Mass Spectrometry/Mass Spectrometry.

therapy.^{28,29} An observational study from our center was the first to show significantly greater infliximab durability in IBD patients in clinical remission who underwent proactive TDM and dose optimization to a therapeutic trough concentration of 5 to 10 µg/mL when compared to patients receiving empiric dose escalation and/or reactive TDM.²⁸ Subsequently, the landmark Trough Concentration Adapted Infliximab Treatment (TAXIT) trial demonstrated that proactive TDM to a target concentration of 3-7 µg/mL was associated with less need for rescue therapy and a higher rate of detectable drug concentrations compared to clinically-based dosing.²⁹ Moreover, this randomized controlled trial showed that during the initial optimization phase dose escalation in patients with CD and a suboptimal infliximab concentration significantly increased the number of patients in clinical remission with a concomitant decrease in CRP levels.²⁹ A proposed treatment algorithm for using proactive TDM for anti-TNF therapy is shown in Figure 2.

Though the above studies relate to patients in the maintenance phase of anti-TNF therapy, exposure-response relationship studies show that higher drug concentrations during, or early after, the induction phase are associated with improved therapeutic outcomes

(Table 1). These data imply that early optimization, even during induction therapy, may better optimize the efficacy of anti-TNF therapy. In fact, moderate to severely active patients with significant inflammatory burden are likely to benefit the most from proactive TDM as they have an increased drug clearance which predisposes to lower drug concentrations and development of anti-drug antibodies. Although clinically relevant drug thresholds can vary based on the assay used and the therapeutic outcome of interest, we typically aim for post-induction concentrations > 10 µg/mL both for infliximab and adalimumab.

Another aspect of proactive TDM is to guide treatment de-escalation in patients with supra-therapeutic drug concentrations through dose reduction, interval prolongation and/or withdrawal of an immunomodulator (IMM). The rationale for this treatment de-escalation is to potentially maximize both safety and cost-effectiveness of anti-TNF therapy. In our study, 15% of patients either stopped or de-escalated infliximab therapy based on TDM without any negative impact on their long-term clinical outcomes.²⁸ Similarly, 27% of patients in the TAXIT trial underwent dose de-escalation resulting in a significant reduction of

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treatment costs without any deterioration of remission rates.²⁹ Another study showed that the great majority (90%) of patients with trough concentration $>8 \mu\text{g}/\text{mL}$ who de-escalated infliximab therapy to a target concentration of a 3 to 7 $\mu\text{g}/\text{mL}$ remained in deep remission after a median follow up of 8 months.⁴¹ Recently, a prospective study of 80 consecutive patients with IBD in clinical remission demonstrated that a TDM-based de-escalation approach was superior to blind adjustments of infliximab therapy based on symptoms and CRP.⁴²

Regarding IMM withdrawal as a de-escalating therapeutic strategy, our study showed that drug retention was similar between patients in clinical remission on mono- or combo-therapy who achieved an infliximab concentration of $\geq 5 \mu\text{g}/\text{mL}$, suggesting that 'optimized monotherapy' is feasible in this group of patients.²⁸ This is in line to another study which demonstrated that in patients receiving combination therapy, those with infliximab trough concentration $>5 \mu\text{g}/\text{mL}$ at the time of IMM discontinuation have a decreased risk for dose escalation, IBD-related surgery and drug cessation due to loss of response.⁴³ Furthermore, it was previously shown that although patients who continued to receive combination therapy had higher median trough infliximab concentration and lower CRP levels than those who discontinued IMM, no clear clinical benefit of combo-therapy was observed beyond 6 months.⁴⁴

Another potential role of proactive TDM is when anti-TNF therapy needs to be discontinued for reasons other than loss of response or adverse event (e.g. pregnancy, patient preference, health insurance issues) as preliminary evidence suggests that low or undetectable drug concentrations at the time of drug discontinuation are associated with sustained clinical remission after anti-TNF withdrawal.^{31,32} Subsequently, when re-starting anti-TNF therapy after a drug holiday, a recent retrospective study showed that the absence of antibodies to infliximab and detectable infliximab trough concentrations after the first dose were associated with fewer infusion reactions and a better long-term response, respectively.³⁰

TDM Assays

There are several assays available for TDM of anti-TNF therapy, and currently none of them can be considered as the gold standard (Table 2).⁴⁵⁻⁵⁷ The choice of assay

in clinical practice typically depends on cost, local availability and physician's preference and expertise. Recent data suggests that commonly used assays are generally comparable regarding drug concentrations, in contrast to anti-drug antibodies that still largely depend on the analytical properties of the assay used (Table 2). Consequently, clinically relevant thresholds of low or high titer anti-drug antibodies can vary among the currently available assays, making it difficult to compare results across studies. It is important to understand the assay used to avoid misinterpretations and erroneous therapeutic decisions, particularly as anti-drug antibodies can be reported in various ways that may make titers appear high and clinically significant when, in fact, they are not (Table 2). Recent data suggest that a new era in TDM is imminent as accurate, affordable, and easily accessible point-of-care testing and software-decision support tools that will incorporate a predictive pharmacokinetic model based on patient and disease characteristics are already underway.⁵⁸

Limitations

Before TDM can be widely applied into everyday clinical practice there are still several barriers that have to be overcome. These include out-of-pocket cost and health insurance reimbursement issues, time lag from collecting a serum sample to the result of the test, accurate interpretation and application of the results based on the assay used, and the optimal timing of serum sampling. Furthermore, additional data from well-designed prospective studies with a long-term follow up concerning all available biologics during both maintenance and induction therapy are urgently needed.

Despite these limitations, TDM appears to improve outcomes and the care of patients with IBD. A panel consisting of members of the Building Research in Inflammatory Bowel Disease Globally research alliance (BRIDGE; www.BRIDGEIBD.com), and recognized leaders in the field of TDM in IBD has recently published recommendations that helps clinicians on the appropriate timing and best way to interpret and respond to TDM results depending on the specific clinical scenario.⁵⁹

CONCLUSIONS

A TDM-based therapeutic strategy is likely to emerge as the new standard-of-care of utilizing biologics in IBD. Numerous studies demonstrate the association of adequate drug concentrations and improved clinical outcomes including objective measures of inflammation. Reactive TDM better directs care in those patients losing response to anti-TNF and is more cost-effective than empiric dose escalation. Additionally, although data are still limited, proactive, rather than reactive, TDM may prove even more effective in optimizing biologic therapies and the treatment of IBD. Nevertheless, before a TDM-based therapeutic approach can be widely implemented in clinical practice, several barriers should be first overcome regarding the type and cost of the assay used, optimal time of serum sampling and interpretation and application of the results. ■

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Potential Competing Interests

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