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Therapeutic drug monitoring in patients on biologics – lessons from gastroenterology

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Abstract

Purpose of review—To give an overview on the role of therapeutic drug monitoring (TDM) of biologics in patients with inflammatory bowel disease (IBD).

Recent findings—Numerous prospective exposure-response relationship studies and post-hoc analyses of randomized controlled trials show a positive correlation between biologic drug concentrations and favorable clinical outcomes in IBD. These studies also demonstrate that higher drug concentrations appear to be needed to achieve more stringent objective therapeutic outcomes. Reactive TDM rationalizes the management of primary non-response and secondary loss of response to anti-tumor necrosis factor (anti-TNF) therapy and is more cost-effective when compared to empiric dose optimization. Furthermore, recent data suggest that proactive TDM, with the goal of targeting a threshold drug concentration, is associated with better therapeutic outcomes when compared to empiric dose escalation and/or reactive TDM of infliximab or adalimumab. Finally, proactive TDM can also efficiently guide infliximab de-escalation or discontinuation in patients with IBD in remission.

Summary—Reactive TDM is currently considered as standard of care, while proactive TDM is emerging as a new therapeutic strategy for better optimizing anti-TNF therapy in IBD. However, more data from prospective studies are needed before a wide implementation of TDM-based algorithms in real life clinical practice for newer biologics.

Keywords

inflammatory bowel disease; rheumatoid arthritis; psoriasis; biologics; immunogenicity; therapeutic drug monitoring; anti-TNF therapy; ustekinumab; vedolizumab

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Introduction

Biologic therapies are very effective for treating moderate to severe inflammatory bowel diseases (IBD), namely Crohn's disease (CD) and ulcerative colitis (UC). These agents include the tumor necrosis factor (TNF) inhibitors infliximab, adalimumab, certolizumab pegol and golimumab, the anti-integrin inhibitors vedolizumab and natalizumab, and the IL-12/23 p40 inhibitor ustekinumab [1, 2]. Unfortunately, not all patients respond to induction therapy, and many others lose response over time [3, 4]. Therapeutic drug monitoring (TDM) helps to explain these negative therapeutic outcomes can be attributed to either pharmacokinetic issues, characterized by low drug concentrations with or without the development of anti-drug antibodies (ADA), or a mechanistic failure in patients with adequate drug concentrations [5].

Numerous prospective exposure-response relationship studies and post-hoc analyses of randomized controlled trials show a positive correlation between biologic drug concentrations and favorable clinical outcomes in IBD [6-41*]. These studies in IBD also suggest that higher drug concentrations are required to achieve more stringent objective therapeutic outcomes (from clinical response to histologic remission) [42, 43]. On the other hand, low drug concentrations predispose to ADA formation and treatment failure [44-46].

Reactive TDM is defined as the evaluation of drug concentration and ADA levels in the setting of primary non-response or secondary loss of response (LOR) to a biologic agent. The use of reactive TDM has rationalized the management of these unwanted clinical outcomes [47-49] and is more cost-effective when compared to empiric dose escalation [50-52] (Figure 1). Patients who will benefit from more drug (low drug concentrations) are given it, and those patients who will benefit from another therapy (adequate drug concentrations or high ADA) are switched. Proactive TDM is defined as the evaluation of trough concentration and ADA levels with the goal of optimizing biological therapy to achieve a threshold drug concentration. Recent data suggest that proactive TDM is associated with better therapeutic outcomes when compared to empiric dose optimization and/or reactive TDM of anti-TNF therapy in IBD [53-59]. Proactive TDM can also effectively guide infliximab de-escalation [60, 61] or discontinuation [15, 62-64] in patients with IBD in remission TDM (Figure 2). However, there are perceived knowledge gaps regarding the role of TDM that have hampered the wide implementation of TDM-based algorithms in real-life clinical practice, as reflected also in some of the current guidelines and recommendations (Table 2) [65-70].

The goal of this review is to provide the most up to date information regarding the role of TDM for optimizing biologic therapy in IBD.

Exposure-outcomes relationship studies

Numerous exposure-outcomes relationship studies demonstrate that higher biologic drug concentrations, during both induction and maintenance therapy, are associated with better therapeutic outcomes in both CD and UC [6-41*]. Drug thresholds to target may vary depending on the IBD phenotype, investigated therapeutic outcome and type of TDM assay

used; and typically, higher concentrations are associated with more stringent outcomes [31, 42, 43, 71, 72]. These studies include adult populations as well as pediatrics (Table 1) [7-17]. Furthermore, though not discussed here, there are several exposure-response studies in other immune-mediated inflammatory diseases, such as rheumatoid arthritis, ankylosing spondylitis and psoriasis [35]. Though most of the data relates to anti-TNF therapies, all therapies have been shown to have positive exposure-outcome relationships. We have chosen to highlight only a few of the more recent studies.

A post-hoc analysis of the ACT-1 and 2 (A Safety and Efficacy Study for Infliximab in Patients with Active Ulcerative Colitis) RCTs showed that infliximab concentrations 18.6 µg/mL at week 2 and 10.6 µg/mL at week 6 were associated with an endoscopic improvement at week 8 [18*]. A post-hoc analysis of the TAILORIX (Drug-concentration versus Symptom-driven Dose Adaptation of Infliximab in patients with active Crohn's disease) RCT identified an infliximab threshold of 23.1 µg/mL at week 2 and 10 µg/mL at week 6 discriminating patients with early endoscopic remission at week 12 [19*]. The prospective PANTS (personalised anti-TNF therapy in Crohn's disease) study showed that the optimal week 14 drug concentrations associated with remission at both week 14 and week 54 were 7 mg/L for infliximab and 12 mg/L for adalimumab [20*]. A recent prospective study showed that a vedolizumab trough concentration cut-off of 16.55 µg/ml at week 14 predicted drug persistence within the first year of therapy [40]. The VISIBLE 1 (Efficacy and Safety of Vedolizumab Subcutaneously (SC) as Maintenance Therapy in Ulcerative Colitis) RCT showed that the proportion of patients receiving vedolizumab SC for maintenance who achieved clinical remission increased with increasing vedolizumab exposure from 50% (quartile 1) to 83% (quartile 4). Similarly, the proportion of patients with endoscopic improvement increased with increasing exposure from 50% (quartile 1) to 89% (quartile 4) [41*]. The prospective multi-center LOVE-CD (LOW countries VEdolizumab in CD) study, including 110 patients with active CD who received open-label vedolizumab (300 mg) infusions at weeks 0, 2, and 6, and every 8 weeks thereafter through week 52, showed that serum concentrations of vedolizumab >10 µg/ml at week 22 were associated with endoscopic remission at week 26 [39]. A recent systemic review and meta-analysis showed that in patients with UC, week 6 vedolizumab trough concentrations 18.5-20.8 µg/mL, and maintenance trough concentrations 9-12.6 µg/mL were associated with favorable clinical outcomes [37]. In addition, a recent post-hoc analysis of the UNIFI (A Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Participants With Moderately to Severely Active Ulcerative Colitis) RCT identified a target concentration threshold 3.7µg/mL at week 8 for achievement of clinical response at week 8 and a target concentration threshold 1.3µg/mL for clinical remission at week 44 [38*].

Reactive therapeutic drug monitoring

Reactive TDM has rationalized the management of LOR to anti-TNF therapy in IBD. It can stratify patients with subtherapeutic drug concentrations who will respond to dose escalation from those patients who already have enough drug exposure and would benefit from an alternative mechanism of medication from those patients with high ADA that cannot be overcome with dose optimization [47-49]. Yanai et al. showed that at the time of LOR,

infliximab concentrations $>3.8 \mu\text{g/mL}$ and adalimumab concentrations $>4.5 \mu\text{g/mL}$ identify patients who probably have a mechanistic failure and benefit more from changing out-of-class than dose escalation or switching within drug class [47]. Furthermore, Roblin et al. showed that adalimumab concentrations $>4.9 \mu\text{g/mL}$ are associated with failure to a second anti-TNF, thus helping to identify patients likely failing adalimumab due to pharmacodynamic issues who would benefit from a non-anti-TNF agent [49]. Additionally, several studies have demonstrated that reactive TDM is more cost-effective [50-52] and is associated with higher rates of endoscopic remission when compared to empiric infliximab dose optimization [74]. Thus, we recommend reactive TDM in patients who develop LOR to anti-TNF therapy. A suggested reactive TDM-based algorithm for optimizing infliximab therapy in IBD is depicted in Figure 3. As adequate drug concentrations suggest a loss mechanistic effect, in practice we do not abandon infliximab or adalimumab unless drug concentrations are greater than 10-15 $\mu\text{g/ml}$.

A recent RCT, showed that patients with LOR and antibodies to a first anti-TNF benefit from the use of azathioprine in combination with the second anti-TNF. In these patients the addition of azathioprine was associated with a significant reduction in the risk of developing ADA, low drug concentrations and LOR to a second anti-TNF [73**]. Thus, if patients develop ADA to one anti-TNF, the addition on an immunomodulator (IMM) (or proactive TDM) should be recommended with the use of a second anti-TNF. This becomes even more clinically relevant in patients with a genetic predisposition for developing ADA [75]. Though the data for reactive TDM for new biologics is only theoretical at this time, though based on exposure-response studies, makes sense.

Proactive therapeutic drug monitoring

Proactive TDM for optimizing medications is not a new concept. It has been used for cyclosporine and tacrolimus in treating UC and in solid organ transplantation as well as with various antibiotics (gentamycin and vancomycin). The goal of proactive TDM is to improve response rates and prevent secondary LOR by targeting drug concentrations which are considered to be in the optimal therapeutic range. Proactive TDM of anti-TNF therapy has been associated with better therapeutic outcomes when compared to empiric dose escalation and/or reactive TDM in IBD including a lower risk of relapse, improved clinical remission rates, higher rates of mucosal healing as well as less treatment failure, need for IBD-related surgery or hospitalization, risk of ADA and serious infusion reactions [53-59]. Most recently, the PAILOT (Paediatric Crohn's disease Adalimumab-Level-based Optimisation Treatment) RCT randomized 80 biological-naïve children with luminal CD who responded to adalimumab induction therapy to proactive TDM or reactive TDM. This study met its primary endpoint and showed that the steroid-free clinical remission rate at week 72 was higher in children undergoing proactive compared to those undergoing reactive TDM [32 (82%) vs. 19 (46%), $p<0.001$, respectively] [57**]. Furthermore the proactive TDM group had a higher rate of the stringent composite remission (defined as corticosteroid-free clinical remission, C-reactive protein $<0.5 \text{ mg/dL}$ and fecal calprotectin $<150 \text{ mg/g}$) throughout week 8 to 72 when compared to those undergoing reactive TDM [16/38 (42%) vs. 5/40 (12%), $p=0.003$, respectively] [57**]. Interestingly, in this study 90% of the proactive group required dose-optimization compared to almost 60% of the reactive group.

Furthermore, a recent 3-year prospective observational study showed that proactive TDM compared to empirical dosing is associated with a significant reduction in the risk of treatment failure (hazard ratio [HR]: 0.51; 95% confidence interval [CI]: 0.27-0.92; $p=0.037$), IBD-related surgery (HR: 0.14; 95%CI: 0.03-0.65; $p=0.012$) and hospitalization (HR: 0.38; 95% CI: 0.17-0.87; $p=0.022$) [58].

Proactive TDM can also be applied to better guide biologic withdrawal or de-escalation in patients in remission [60-63]. A recent observational study showed that in IBD patients in clinical remission infliximab de-escalation based on TDM (when infliximab concentrations at the time of de-escalation were higher than 7 $\mu\text{g/mL}$) was associated with less relapse compared to only clinically-based infliximab de-escalation [60]. In our clinical practice, dose de-escalation is typically performed patients in stable clinical remission with an infliximab concentration > 15 $\mu\text{g/mL}$. Following dose de-escalation, patients should continue to be followed with proactive TDM to maintain adequate infliximab concentrations and avoid relapse [61].

Proactive TDM can also be used to support the concept of ‘optimized monotherapy’ instead of using combination anti-TNF therapy with an IMM (thiopurines or methotrexate) which poses a risk for serious and opportunistic infections and lymphoma [76]. Two recent observational studies showed that proactive TDM-based infliximab monotherapy is as effective as infliximab combination therapy with an IMM [77, 78]. This concept is further reinforced by a recent post-hoc analysis of the SONIC (Study of Biologic and Immunomodulator Naive Patients in Crohn Disease) RCT which demonstrated that patients stratified by infliximab concentration quartiles have comparable outcomes regardless of concomitant azathioprine [79**]. In our clinical practice, we perform proactive TDM, typically optimized monotherapy, with infliximab and adalimumab. For infliximab our goal threshold is typically 5-10 $\mu\text{g/mL}$, but in certain scenarios may be as high as 15 for infliximab. For adalimumab, our goal threshold is typically >10 $\mu\text{g/mL}$. If not performing optimized monotherapy with anti-TNF, patients with IBD should be on a concomitant IMM to decrease ADA and improve outcomes.

However, before a wide implementation of TDM-based algorithms in real life clinical practice, several knowledge gaps need to be addressed, including when to measure biologic drug concentrations (peak vs. intermediate vs. trough; induction vs. post-induction concentrations) and what are the optimal drug concentrations to target (depending on the therapeutic outcome, IBD phenotype and type of TDM assay used). Moreover, the detection, quantification and interpretation of ADA can be challenging depending largely on the analytical properties of the assay used [80]. For example, the previously established cutoff of 8 $\mu\text{g/ml}$ with the first-generation enzyme-linked immunosorbent assay (ELISA) seems to correspond to the cutoff of 374 ng/ml with the second-generation ELISA and a cutoff of 119 ng/ml in the ready-to-use ELISA kit [81]. Additionally, more data from well-designed prospective studies and RCTs are also needed. For example, the NOR-DRUM (NORwegian DRUG Monitoring) randomised, open, controlled, parallel-group, comparative, multi-centre, national, superiority, phase IV study will aim to assess the effectiveness of TDM in patients with rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, UC, CD and psoriasis. Participants will be randomised 1:1 to either TDM of infliximab (intervention group) or to

standard treatment with infliximab without TDM (control group) [82]. Finally, future perspectives to better optimize TDM include the incorporation of pharmacokinetic dashboard models and the use of rapid point of care assays for an early drug optimization [83, 84].

Conclusion

Many studies show the positive correlation of drug concentrations and outcomes. Currently, reactive TDM is considered the standard of care, while proactive TDM is emerging as a new therapeutic strategy for better optimizing anti-TNF therapy in IBD. However, more data from prospective studies are needed before a wide implementation of TDM-based algorithms in real life clinical practice for newer biologics.

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Abbreviations:

TDM	therapeutic drug monitoring
IBD	inflammatory bowel disease
ADA	anti-drug antibody
CD	Crohn's disease
UC	ulcerative colitis
ELISA	enzyme-linked immunosorbent assay
TNF	tumor necrosis factor
ADA	anti-drug antibodies
SAE	serious adverse events
HR	hazard ratio
CI	confidence interval
LOR	loss of response
IMM	immunomodulator.

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Key points

- There is a positive correlation between biologic drug concentrations and favorable therapeutic outcomes in inflammatory bowel disease (IBD).
- Reactive therapeutic drug monitoring (TDM) can efficiently guide the management of patients with primary non-response and secondary loss of response to anti-tumor necrosis factor (anti-TNF) therapy in IBD and has been proven more cost-effective when compared to empiric dose escalation.
- Preliminary data suggest that proactive TDM of anti-TNF therapy is associated with better therapeutic outcomes when compared to empiric dose optimization and/or reactive TDM in IBD.
- Proactive TDM can efficiently guide infliximab de-escalation or discontinuation in patients with IBD in remission.

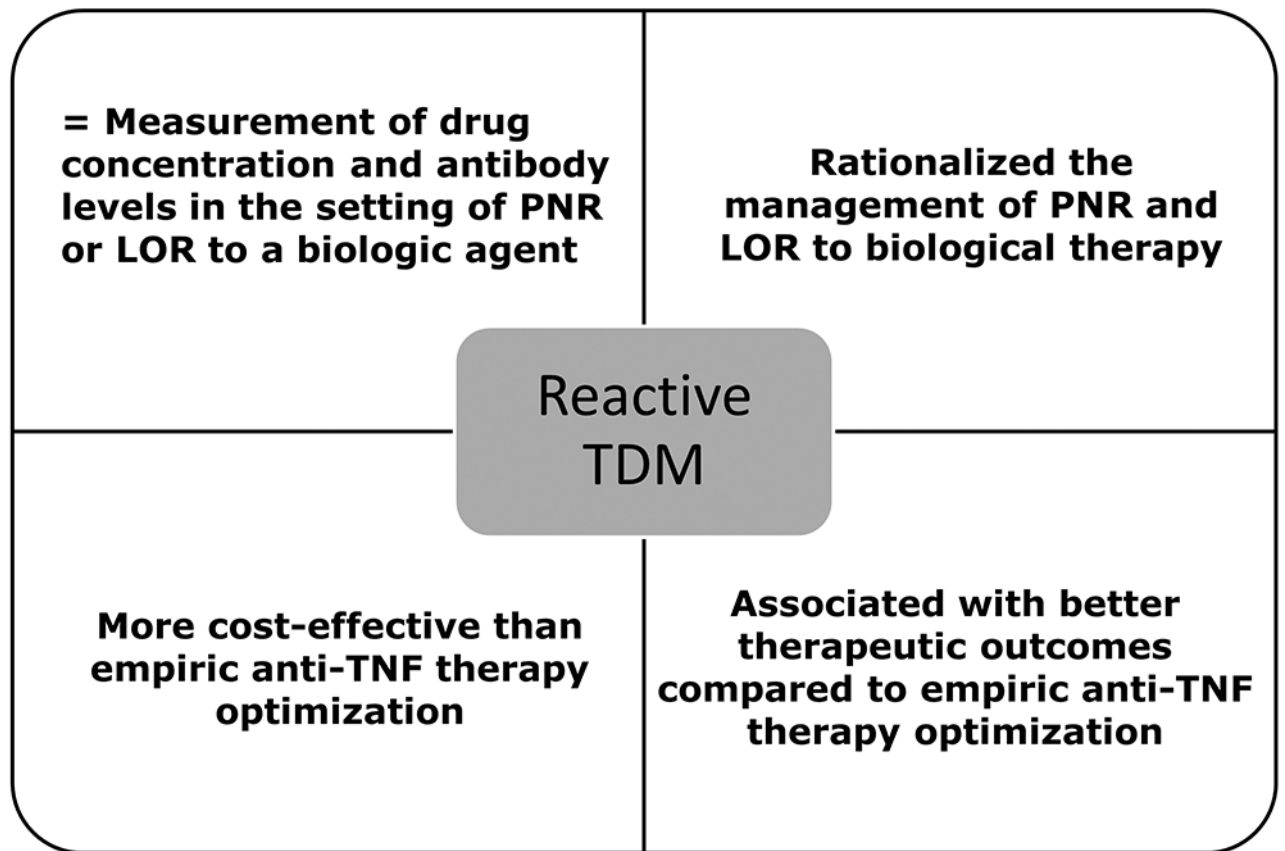


Figure 1.

Definition and role of reactive therapeutic drug monitoring of anti-TNF therapy in inflammatory bowel disease.

PNR: primary non-response, LOR: loss of response; TDM: therapeutic drug monitoring; TNF: tumor necrosis factor.

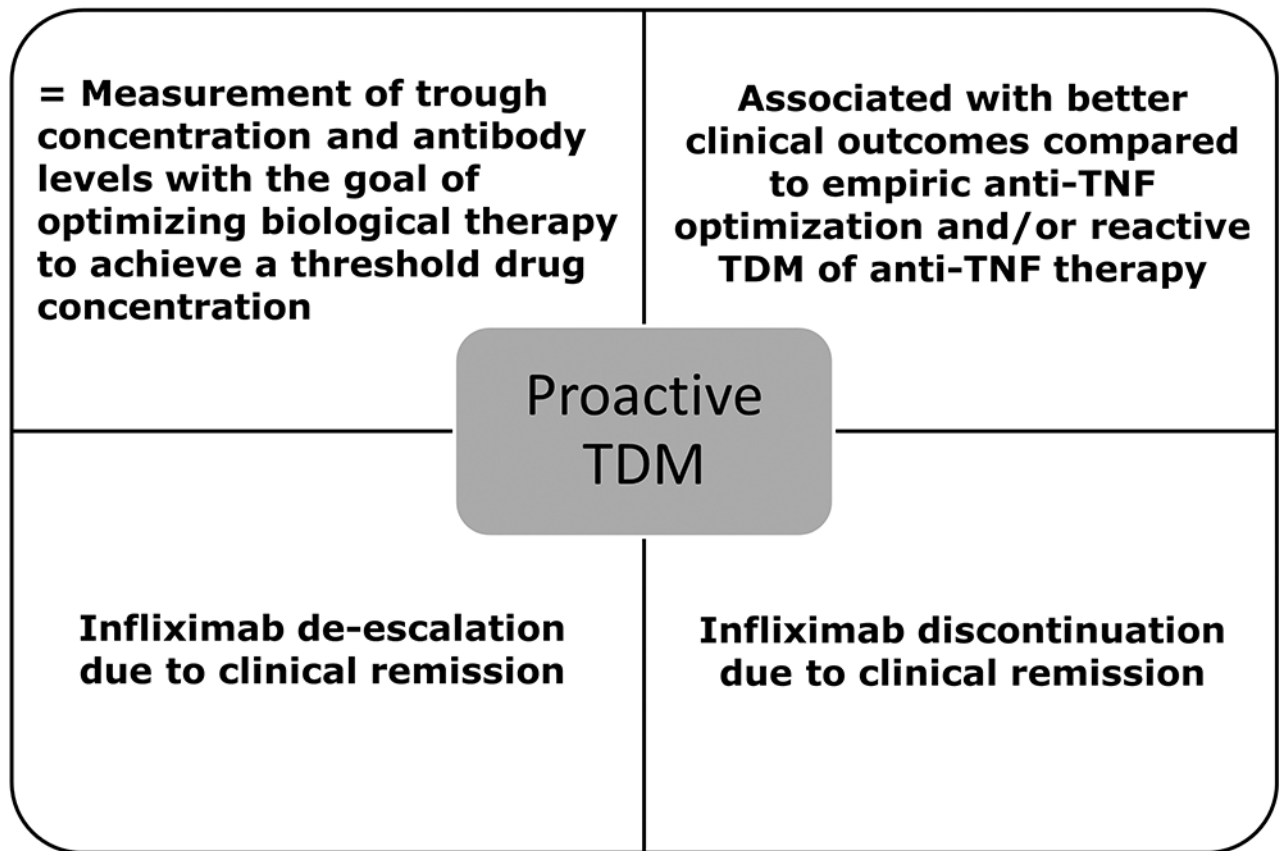


Figure 2.
Definition and role of proactive therapeutic drug monitoring of anti-TNF therapy in inflammatory bowel disease.
TDM: therapeutic drug monitoring; TNF: tumor necrosis factor.

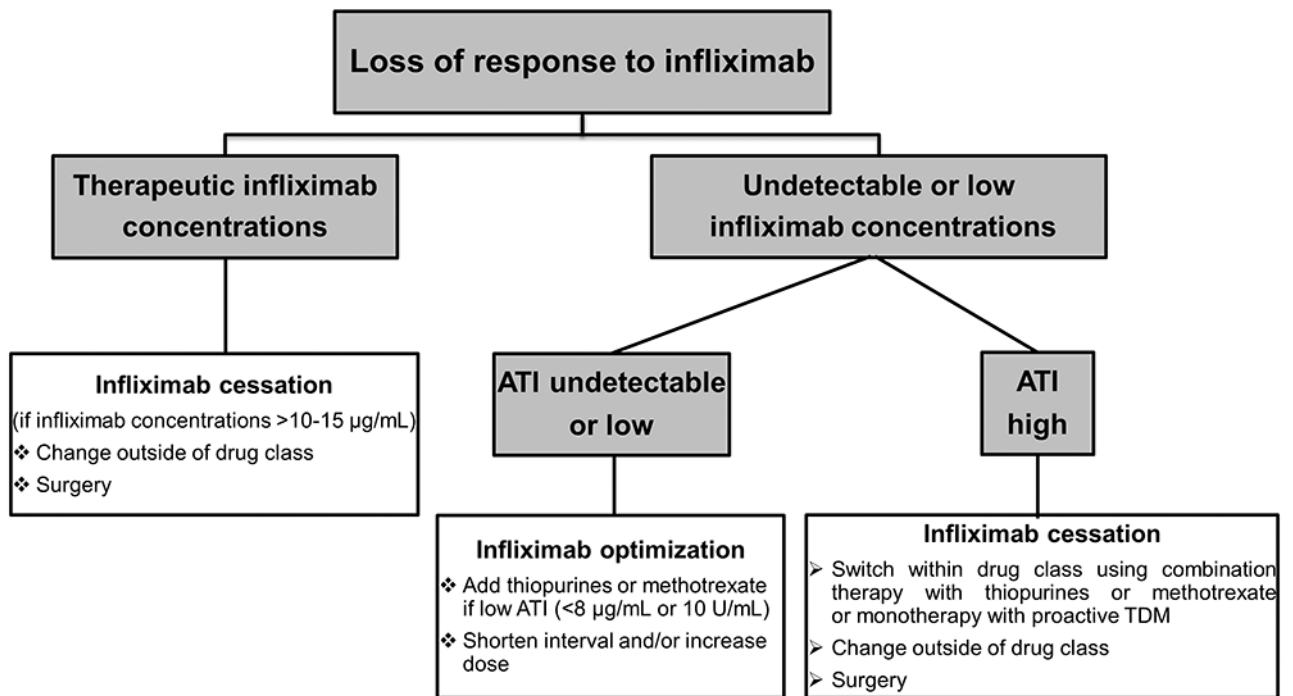


Figure 3.

Reactive therapeutic drug monitoring-based algorithm for optimizing infliximab therapy in inflammatory bowel disease.

ATI: antibodies to infliximab; TDM: therapeutic drug monitoring.

Table 1.

Exposure-outcome relationship data of infliximab in pediatric IBD.

IBD type	Treatment time point	Threshold (µg/mL)	Therapeutic outcome and time point	TDM assay	Ref.
CD	Induction (w2)	>9.2	Clinical remission (w14)	ELISA	7
CD	Induction (w2)	26.7	Clinical response (w14)	ELISA	8
CD	Induction (w6)	>2.2	Drug retention beyond one year of treatment	ELISA	7
CD	Induction (w6)	18	CRP<0.5 mg/dL	ELISA	8
CD	Induction (w6)	15.9	Clinical response (w14)	ELISA	8
CD	Induction (w6)	>8.3	Clinical remission (w14)	ELISA	9
CD/UC	Induction (w6)	>9.8	CRP <0.5 mg/dL	ELISA	10
CD	Post-induction (w10)	9.1	Drug retention (w52)	HMSA	11
CD	Post-induction (w14)	>12.7	Fistula response (w24)	ELISA	12
CD/UC	Post-induction (w14)	>5.5	Clinical remission (w54)	HMSA	13
CD/UC	Post-induction (w14)	>2	ESR <18 mm/hr	ELISA	10
CD/UC	Post-induction (w14)	>3.1	Sustained clinical remission	ELISA	14
CD	Maintenance	2.5	Relapse after drug withdrawal for remission	ELISA	15
CD	Maintenance	>4.9	Biochemical remission	ELISA	16
CD	Maintenance	>5	Mucosal healing	ELISA	16
CD/UC	Maintenance	>5.4	Endoscopic remission	ELISA	17
CD/UC	Maintenance	>1.6	ESR <18 mm/hr	ELISA	10

ELISA: enzyme-linked immunosorbent assay; HMSA: homogeneous mobility shift assay; CRP: C-reactive protein, FC: fecal calprotectin; TDM: therapeutic drug monitoring; CD: Crohn's disease; UC: ulcerative colitis; Ref.: reference; w: week; hr: hour.

Table 2.

Current recommendations and guidelines from medical societies/organizations as well as expert groups.

Medical society / organization or expert group	Method	Reactive TDM	Proactive TDM	Ref.
AGA	GRADE	In adults with active IBD treated with anti-TNF agents reactive TDM to guide treatment changes is suggested. <i>(Conditional recommendation, very low quality of evidence)</i>	In adult patients with quiescent IBD treated with anti-TNF agents, no recommendation regarding the use of routine proactive TDM is made. <i>(Knowledge gap)</i>	65
BSG	GRADE	Treatment options for failure of initial anti-TNF therapy (increase dose, shorten dosage interval, switch to alternative anti-TNF, or switch to different drug class) may be informed by the clinical context and by measurement of serum drug and ADA concentrations. <i>(Weak recommendation, low-quality evidence)</i> . Patients with LOR to anti-TNF therapy may have serum drug and ADA concentrations measured to inform appropriate changes in treatment. <i>(Weak recommendation, moderate-quality evidence)</i>	All IBD patients should be reviewed 2-4 weeks after completing loading doses of anti-TNF therapy to assess response and optimize maintenance dosing based on clinical response and measures such as serum drug and ADA concentrations, blood inflammatory markers, fecal biomarkers or endoscopy. <i>(Good practice recommendation)</i>	66
ECCO	GRADE	In CD patients who have lost response to an anti-TNF agent, there is currently insufficient evidence to recommend for or against the use of reactive therapeutic drug monitoring to improve clinical outcomes. <i>(Weak recommendation, low-quality evidence)</i>	In CD patients in clinical remission under anti-TNF treatment, there is currently insufficient evidence to recommend for or against the use of proactive TDM to improve clinical outcomes as compared to routine care. <i>(Weak recommendation, moderate-quality evidence)</i>	67
Australian IBD, consensus Working Group	Modified Delphi	TDM should be performed in patients with secondary loss-of-response to guide clinical decision-making	In patients in clinical remission following anti-TNF therapy induction, TDM should be considered to guide management. TDM should be considered periodically in patients in clinical remission if the results are likely to impact management	68
CAG	GRADE	In patients with CD who have a suboptimal clinical response to anti-TNF induction therapy or LOR to maintenance therapy, we suggest regimen intensification informed by TDM. <i>(Conditional recommendation, very-low-quality evidence)</i>	N/A	69
BRIDGE	Modified Delphi	It is appropriate to order drug/antibody concentration testing for all anti-TNFs in patients with confirmed LOR. It is appropriate to order drug/antibody concentration testing of anti-TNFs at the end of induction in PNRs.	It is appropriate to order drug/antibody concentration testing at least once during maintenance for patients on all anti-TNFs. It is appropriate to order drug/antibody concentration testing in responders at the end of induction for all anti-TNFs.	42
ACG	GRADE	In patients with moderately to severely active UC who are responders to anti-TNF therapy and now losing response, we suggest measuring serum drug levels and ADA (if there is not a therapeutic level) to assess the reason for loss of response. <i>(Conditional recommendation, very low quality of evidence)</i>	N/A	70

AGA: American Gastroenterological Association; IBD: inflammatory bowel disease; TDM: therapeutic drug monitoring; TNF: tumor necrosis factor; LOR: loss of response; ADA: anti-drug antibodies; N/A: not applicable; GRADE: Grading of Recommendations Assessment, Development and Evaluation; BSG: British Society of Gastroenterology; PNRs: primary non-responders; CAG: Canadian Association of Gastroenterology; UC: ulcerative colitis; CD: Crohn's disease; ACG: American College of Gastroenterology; BRIDGE: Building Research n IBD Globally; IBD: inflammatory bowel disease; ECCO: European Crohn's and colitis organization.