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How, When, and For Whom Should We Perform Therapeutic Drug Monitoring?

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Abstract

The implementation of therapeutic drug monitoring (TDM) in the inflammatory bowel disease (IBD) practice has evolved during the years. In the early days, the focus was merely on the *measuring* and reporting of drug concentrations. Later, these concentrations were considered in light of target concentrations that are related to clinical response. This did not only allow passively predicting a patient's future response, but it also triggered physicians and pharmacists to actively use the information to *optimize* the drug dosage to induce and maintain clinical response in the future. While reactive TDM, testing at time of loss of response, is widely accepted in practice especially for the anti-TNF antibodies, there is less data for the other monoclonal antibodies belonging to other classes. Besides reactive testing, there is a movement towards proactively adjusting biologic dosing to prevent loss of response in keeping with the tight control philosophy of IBD care. This review highlights the various assays available to measure drug concentrations and anti-drug antibodies as well as algorithmic approaches to TDM, the unmet needs and required studies to enable pharmacokinetics principles to be applied in the future.

Keywords: inflammatory bowel disease (IBD)

Abbreviations

ADA	antidrug antibody
CD	Crohn's disease
CDAI	Crohn's disease activity index
CRP	C-reactive protein
DBS	dried bloodspot
ELISA	enzyme-linked immunosorbent assay
EBE	empirical Bayes estimate
EHR	electronic health record
fCal	fecal calprotectin
FO SPR	fiber-optic surface plasmon resonance
HBI	Harvey-Bradshaw index
HMSA	homogenous mobility shift assay
HPLC	high-pressure liquid chromatography
HR	hazard ratio
IBD	inflammatory bowel disease
IL	interleukin
LoC	lab-on-a-chip
LF	lateral flow
MID3	model-informed drug design and development
MIPD	model-informed precision dosing
OR	odds ratio
PCDAI	pediatric Crohn's disease activity index
PD	pharmacodynamic
PK	pharmacokinetics
POC	point-of-care
PMS	partial Mayo score
RIA	radio-immunoassay
TC	trough concentration
TAT	turnaround time
TDM	therapeutic drug monitoring
TNF	tumor necrosis factor
TPMT	thiopurine S-methyltransferase
UC	ulcerative colitis
US FDA	United States Food and Drug Administration
6-MMP	6-methylmercaptopurine
6-TGN	6-thioguanine nucleotides

Introduction

The concept of Therapeutic Drug Monitoring (TDM) has received revived attention in inflammatory bowel diseases (IBD) with the introduction of monoclonal antibodies against tumor necrosis factor (TNF)-alpha. Clinicians have however applied TDM in their IBD patients long before the introduction of biological therapies. TDM refers to measuring the concentration of a drug or its metabolites to help individual dose adjustment in order to optimize efficacy and/or reduce toxicity and as such, is part of personalized patient care. TDM implies a relationship between the drug or metabolite concentration and outcome. In patients treated with cyclosporin A for acute severe ulcerative colitis (UC), drug concentrations between 150-350 ng/mL- the so-called therapeutic window- lead to the optimal ratio between efficacy and (renal, cardiovascular or neuro)toxicity (1). Thiopurine metabolite testing is also a well-established practice in many jurisdictions. The combination of thiopurine S-methyltransferase (TPMT) testing (before starting azathioprine) and 6-thioguanine nucleotides (6-TGN) and 6-methylmercaptopurine (6-MMP) metabolite testing (during maintenance) has shown to optimize response and decrease toxicity to the drug and is cost-effective as compared to standard dosing (2,3). Management of IBD entered a whole new dimension at the end of the last millennium with the development of biologic therapies that selectively block the inflammatory cascade. The first class of biologic agents targeting TNF-alpha dominated the field for almost 15 years. Later other classes of monoclonal antibodies blocking alpha4beta7 integrin and the interleukin (IL)-12/IL-23 pathway were introduced and nowadays biological agents are a major constituent of IBD management. Immunogenicity is an important downside of all biologic agents however. Immunogenicity refers to the concept that the body recognizes parts of the drug as non-self and the immune system develops antidrug antibodies (ADA). These ADA will block the binding site of the drug to the target and the formed ADA-drug immune complexes will interfere with drug

clearance leading to lower drug concentrations, which in turn, are associated with suboptimal response or loss of response. Hence has grown the belief that in patients treated with biological agents TDM may inform the clinician on what is going on with the drug and assist in his/her therapeutic actions. Distinction should be made between reactive TDM on one hand, in which testing is performed in the setting of loss of response or intolerance, and proactive TDM on the other hand, where the drug is titrated to a target drug concentration to prevent relapse.

In this review, we discuss the available techniques to measure drug concentrations and antidrug antibodies for monoclonal antibodies, we review the current evidence for reactive versus proactive TDM, and provide clinical guidance when and in whom to perform TDM. We conclude by providing a personal viewpoint on how the field should evolve to further improve patient care.

Techniques to Measure drug concentrations

TDM of biologicals is traditionally based on trough concentrations (TC), requiring sample collection just before the next administration of the drug. To facilitate an appropriate implementation of TDM of the self-administered biologicals, dried bloodspot (DBS) and other microsampling techniques may be used.^{4,5} Evidence supporting the role of TDM based on intermediate and peak concentrations is limited but emerging.^{6,7} Besides an appropriate timing, attention must also be paid to correct sample collection, preparation, storage and shipment.⁸

Many research groups and companies have developed assays for the quantification of biological drugs (and antibodies towards them) in patient's serum. The solid-phase enzyme-linked immunosorbent assay (ELISA) is the most commonly used format. Given its ease of use and automatization, it is the typical format of the commercially available assays.

Drug assays employ the drug as a calibrator. Drug titers are thus expressed in absolute units (mg/L) and can be directly compared between different assays. Various attempts were undertaken to compare different drug assays and generally showed a good correlation.⁸ However, it remains preferable to only compare results obtained with the same assay.

As for the drug ELISA, two binding sites must be available for capture and detection of ADA. If ADA are already bound to the drug in the patient's serum, the bivalency is compromised, the bridge between the capture and detection antibody cannot be formed, and the ADA cannot be quantified. Therefore, only the excess of free ADA fraction can be quantified. Kopylov *et al.* developed an ELISA using an antihuman λ -chain antibody for detection, which does not require ADA to have a free binding site for detection, making the assay less sensitive to the presence of drug.⁹ In addition, Gils *et al.* validated the use of their infliximab ELISA for the quantification of the CT-P13 biosimilar.¹⁰ To date, the clinical benefits of drug-tolerant and drug-resistant assays over drug-sensitive assays remain unclear and may depend on the clinical context.¹¹

Laboratory quantification services use ELISAs or the more labor-intensive fluid-phase formats like the radio-immunoassay (RIA) and the high-pressure liquid chromatography (HPLC)-based homogenous mobility shift assay (HMSA). Other formats have been developed as well.¹²⁻¹⁵

ADA assays use a monoclonal ADA as a calibrator and ADA titers are thus expressed in relative units (e.g. ng/mL equivalents of the calibrator antibody) and cannot be directly compared between different assays. Vague categorizations as “low”, “intermediate” and “high” ADA have been used to facilitate assay-independence of the dose optimization algorithms. The implementation of universal calibrators for quantifying ADA has been proposed to facilitate inter-laboratory harmonization of ADA measurements.^{16,17}

Reactive Testing: What is the Evidence?

Reactive testing is performed in the setting of loss of response or intolerance to a monoclonal antibody. Knowing the TC of the drug and the presence of possible ADA will help the clinician in deciding about dose optimization or switching to a different agent within or out of the class (**Figure 1**). The concept of reactive testing is supported by pivotal studies – mainly with anti-TNF-alpha agents – which have shown associations between serum drug concentrations and clinical response, remission and endoscopic healing. Most therapeutic target trough concentrations have been determined through post-hoc analysis. There are few prospective studies that have attempted to adequately escalate patient to a specified trough concentration and shown improved long-term outcomes. In addition, the strategies to manage results of reactive testing have not been prospectively validated (i.e. does all ADA positivity need to result in switching agent – can this be optimized?). Similarly, trough concentrations may be different for different disease phenotypes (acute severe UC, perianal fistulizing CD). Recent prospective studies (**Table 1**) and *post-hoc* analyses of randomized controlled trials (**Table 2**) show that higher serum drug concentrations are indeed associated with better therapeutic outcomes regarding both maintenance and probably even more important during and early after induction therapy when the inflammatory burden and consequently drug clearance is high ⁽⁴⁴⁻⁴⁸⁾ (Table 3). This exposure-response relationship is often depicted as quartile analyses where increasing quartiles of drug concentrations are correlated to better clinical response and remission rates, more endoscopic healing and lower C-reactive protein (CRP) and fecal calprotectin (*f*Cal) levels. This correlation between exposure and response has been demonstrated for all anti-TNF-alpha agents (infliximab, adalimumab, golimumab

and certolizumab pegol) but also for vedolizumab and ustekinumab. Although fewer real-world data are available for the latter, the data led investigators to apply the same practice of measuring drug levels and antibodies also for the non-anti-TNF-alpha biological therapies and to optimize therapy in case of low levels. Where optimal cut-off values have been proposed for the different anti-TNF-alpha agents, this is at the moment less clear for vedolizumab and ustekinumab. Cut-off values may also be different depending on the desired outcome.

The empiric approach to secondary loss of response by intensifying treatment and only when this is unsuccessful, switch to another biological, is frequently suboptimal and puts the patient at risk for allergic reactions or high costs. Therefore, a TDM-based strategy may be advantageous. First, it avoids giving even more drug to a patient who does not need intensification (in case of high concentrations) and second, it does not put patients at risk for infusion reactions in those who may have developed high titer antibodies. Reactive TDM can indeed be helpful to distinguish between immunogenic, pharmacokinetic and pharmacodynamic loss of response. In a randomized single-blind study from Denmark, 69 patients with loss of response to infliximab were randomized to infliximab dose intensifications (n=36) or interventions based on serum infliximab and infliximab antibody levels using an algorithm (n=33). Outcomes of the study included CDAI response at week 12 and costs. The treatment costs per patient were 34% lower when using a TDM-based algorithm compared with routine infliximab intensification without affecting clinical response rates.⁴⁹ A French prospective study in 52 IBD patients with secondary loss of response to infliximab found that restoration of infliximab drug concentrations after dose escalation was correlated with achieving mucosal healing in both CD and UC.⁵⁰

Data on reactive TDM for vedolizumab are scarce. A systematic review and meta-analysis by Peyrin-Biroulet *et al.* showed that the pooled incidence rates of loss of response to

vedolizumab were 47.9 per 100 person-years of follow up among patients with CD and 39.8 per 100 person-years of follow up among patients with UC.⁵¹ Dose intensification restored response to the drug in 53.8% of secondary non-responders. A Belgian study assessed the effect of vedolizumab dose intensification on serum TC and regain of response in 62 patients with secondary loss of response to vedolizumab. After dose escalation, median (IQR) TC increased from 8.8 (5.1-13.5) µg/ml (T0) to 19 (11.9-22.9) µg/ml (T1) and 23.1 (15.5-28.4) µg/ml (T2) (all $p < .0001$). Regain of biological and clinical response was observed in 44% and 59% of patients respectively but was not associated with an increase in TC.⁵² More data are needed to support the wide use of reactive TDM also for vedolizumab.

For ustekinumab, although the results of the UNITI, IM-UNITI and UNIFI phase 3 programs all support an exposure-response relationship⁴³, there are yet no data that support reactive TDM in patients losing response to ustekinumab induction. A number of studies are underway which look at different optimization protocols including STARDUST (NCT03107793; every 4 week [q4w] dosing); POWER (NCT03782376; IV reinduction) and RESCUE (intravenous reinduction + q8w versus intravenous reinduction + q4w). The results of these studies are needed before firm recommendations can be given on how and when to optimize treatment with ustekinumab.

Proactive testing and dose optimization : What is the Evidence?

The utility of proactive TDM and dose optimization in IBD everyday clinical practice remains still debatable.⁵³⁻⁵⁶ Moreover, there is increasing evidence for the beneficial role of proactive TDM of the anti-TNF-alpha agents infliximab and adalimumab over empiric dosing optimization and/or reactive TDM, although most of this derives from retrospective studies.⁵⁷⁻⁶⁵

Primary endpoints for all three prospectively evaluated proactive dose optimization algorithms were clinical outcomes (CD activity index [CDAI], Harvey-Bradshaw index [HBI], pediatric CDAI and/or partial Mayo score [PMS]) whether or not combined with biochemical remission (CRP), corticosteroid-free remission, endoscopic improvement (reduction in active fistulas, absence of ulcers) and/or absence of need for bowel resection or abscess.^{57,58,64} The TAILORIX algorithm combined pharmacokinetic (PK) monitoring (i.e., drug concentrations) and pharmacodynamic (PD) monitoring (i.e., *f*Cal concentrations) while other algorithms only considered PK monitoring.³² In each study, dose optimization was allowed in the control arm, but the criteria differed. TAXIT and TAILORIX compared TC monitoring with biomarker monitoring, and PAILLOT compared proactive TDM with reactive TDM. In the proactive PAILLOT arm, doses were intensified based on TC regardless of disease activity, while in the reactive arm, doses were intensified base on clinical and biological loss of response only when the adalimumab TC was below 5 mg/L. Also, dose optimization strategies differed between the studies. While TAILORIX only allowed dose escalation, TAXIT and PAILLOT also allowed dose de-escalations. Many additional differences occurred between the studies, including sample size, blinding to study allocation, follow-up period, inclusion criteria, *etc.*

Apart from the study by Assa *et al.* and some secondary endpoints in the study by Vande Casteele *et al.*, results have been mostly disappointing. One explanation for the lack of statistical significance in TAILORIX was the high number of dose optimizations in the control arms that were driven by nonspecific symptoms, as demonstrated by normal drug and biomarker levels in these patients. In addition, the target TC was not aligned with the aimed outcome. A TC of 3 mg/L as used in TAILORIX may suffice for targeting clinical response, it may be too low when aiming for absence of ulceration.

A recent observational study demonstrated that proactive TDM of infliximab compared to conventional non-TDM based management was independently associated with less surgeries [odds ratio (OR): 0.36; 95% confidence interval (CI): 0.13–0.95; $p=0.039$] and higher rates of mucosal healing (OR: 3.26; 95%CI: 1.68–6.31; $p<0.001$). Furthermore, it showed that proactive TDM significantly decreased a composite unfavorable outcome (defined as surgery, hospitalization, treatment failure and no mucosal healing) compared to conventional non-TDM based management (OR: 0.358; 95%CI: 0.188-0.683; $p=0.002$).⁶¹

A retrospective single-center study showed that at least one proactive TDM compared to lack of any proactive measure was associated with higher drug persistence.⁵⁹ A large retrospective multi-center study reported that proactive TDM was associated with less treatment failure, IBD-related hospitalization, IBD-related surgery and risk for antibodies to infliximab and serious infusion reactions in comparison to reactive TDM.⁶⁰ Additionally, proactive TDM was proven beneficial even when applied after reactive TDM as it was related with less treatment failure and IBD-related hospitalization compared to reactive TDM alone.⁶² Finally, proactive TDM rather than only clinical-based de-escalation was found to better guide infliximab de-escalation in patients in clinical remission and a trough drug concentration higher than 7 $\mu\text{g/mL}$ as patients with proactive infliximab monitoring had less risk of relapse (OR: 0.45; 95%CI: 0.22-0.90; $p=0.024$).⁶³ A recent large multi-center retrospective study showed that at least one proactive TDM vs. no any proactive TDM of adalimumab was independently associated with a reduced risk for treatment failure (hazard ratio [HR]: 0.4; 95%CI: 0.2-0.9; $p=0.022$).⁶⁵

The Future of Therapeutic Drug Monitoring

Point of care testing

Point of care (POC) assays are analytical devices that provide clinically relevant information without the need for a core clinical laboratory. While traditional assays require sample transport to a clinical laboratory and sample preparation, POC tests can be performed on-site by clinical staff without laboratory training and ideally without the need for sample preparation, thereby decreasing the turnaround time (TAT).

POC assays show great promise in improving TDM. More particularly, they allow optimization of the drug dosage based on real-time PK information, and not based on information from weeks or months back. This is particularly valuable in settings with high *intra*-patient PK variability, like acute settings such as severe UC.⁶⁶

The idea that clinical decision-making needs to be based on the most appropriate (most recent) information is the key driver for the development of POC tests. In 2013, Corstjens *et al.* were the first to report on a rapid lateral flow (LF)-based assay for on-site monitoring of infliximab serum concentrations.⁶⁷ Today, CE-marked POC LF immunoassays are available to quantify infliximab, anti-infliximab antibodies and adalimumab in patients' serum.⁶⁸⁻⁷³ However, the need to apply serum instead of full blood requires sample preparation and thus hinders a widespread on-site use of these POC assays.

The expedited workflow is the main reason why these assays may improve the delivery of care. The currently available POC tests allow a reduction of the analysis time to 15-20 minutes.^{68,73} Although the decreased TAT of POC tests can potentially improve patient care and cost-effectiveness, the evidence is still awaited. Bossuyt *et al.* recently confirmed feasibility and effectiveness (i.e., reduced CRP levels) of 'ultra-proactive' TDM of infliximab in a pilot study involving patients with IBD using a commercially available POC test.⁷⁴

To date, the application of POC devices in TDM of biologicals remains very limited. Hurdles of cost, connectivity to the laboratory information system, quality control, and external

quality assurance procedures, still exist. As for the classical clinical laboratory tests, assay interchangeability requires harmonization of the capture, detection and calibrator antibodies in the immunoassays.^{75,76}

Model-informed precision dosing

Fixed dosing and weight-based dosing of biologicals following the standard induction and maintenance treatment regimens may be convenient but has been shown to leave numerous patients deprived from their optimal dose.⁷⁷ TDM algorithms like the TAXIT⁵⁸ and TAILORIX⁵⁸ algorithms have been proposed to optimize dosing based on drug concentration measurements. These algorithms are analogous flowcharts and have the advantage of being relatively simple tools for guiding clinical decision-making. However, the enormous, unpredictable PK variability of therapeutic monoclonal antibodies makes it extremely difficult to hit the exposure target fast and precise, thereby undermining the potential benefits of TDM.

Model-informed TDM or model-informed precision dosing (MIPD) has been suggested as a strategy to overcome this hurdle. A population PK model is the basis of MIPD and serves as a Bayesian *prior*. To make this population model suitable to inform precision dosing, it can be ‘updated’ to a *posterior* model of an individual patient by considering this patient’s covariates/characteristics that explain variability in PK parameters (probabilistic dosing or *a priori* prediction) and/or by considering previous drug concentrations measurements in that patient (Bayesian forecasting or *a posteriori* prediction). Based on patient characteristics and drug concentration measurements, the individual PK parameters can be estimated (empirical Bayes estimates, EBEs) and subsequently be used to predict the next dose that is required for that patient to achieve a predefined exposure target.

As opposed to analogous TDM algorithms, MIPD tools are computationally intensive systems. It was only in recent years that MIPD gained renewed attention as evidenced by the development of several MIPD software tools.^{78,79}

There is plenty of potential for implementing MIPD of biologicals in clinical IBD practice, as evidenced by a number of retrospective studies^{80,81}, but prospective evidence for its cost-effectiveness is only just emerging. In the PRECISION trial (NCT02453776), Strik *et al.* compared the efficacy of model-based dose optimization of infliximab to a 3.0 µg/L TC during maintenance as compared to a control group that continued infliximab dosing without dose adaptation.⁸² The authors concluded a significantly higher proportion of patients maintaining clinical remission when on model-based TDM as compared to the control group. Dubinsky *et al.* employed a PK dashboard to proactively dose infliximab during both induction and maintenance. By targeting a pre-dose concentration of ≥ 25 µg/L at infusion 2, ≥ 17 µg/L at infusion 3 and ≥ 10 for infusion 4 and throughout maintenance, 78% of patients were guided to receive a dose and/or interval that would be considered off-label already by the third or fourth infusion.⁸⁵

The pharmaceutical industry is increasingly using population modelling techniques in a model-informed drug design and development (MID3) framework.⁸⁴ Up to today, there seems however a persistent reluctance to develop drugs requiring MIPD. However, since December 2017 the situation has been changing, as evidenced by United States Food and Drug Administration (US FDA) approval of a commercial application of a companion MIPD tool for personalized dosing of octocog alfa, a recombinant coagulation factor VIII, to prevent bleeding in patients with hemophilia A. In the end, joining forces between pharmaceutical industry, academia and regulatory agencies will be needed to achieve

adoption of model-informed dosing of biological therapies at the point of care and to prevent further undertreatment of patients with IBD.

Conclusion

TDM is a key component of managing IBD patients treated with biologics. Both society guidelines and common practice support the role of reactive based dose optimization at the time of loss of response. This strategy however does not maximize the benefits of TDM as we are now beginning to see with well powered proactive TDM studies. Moreover model based proactive dosing combined with point of care testing has the potential to maximize the durability of biologics and improve the outcomes of IBD patients.

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Table 1. Prospective studies associating serum biologic drug concentration with therapeutic outcomes in inflammatory bowel disease during both induction and maintenance therapy.

Drug	IBD type	Time point	Threshold ($\mu\text{g/mL}$)	Therapeutic outcome (time point)	Ref.
IFX	CD ^a	w14	≥ 7	Clinical remission (w14 & w54)	18
	CD	w10	≥ 9.1	Drug retention (w52)	19
	CD	w2	≥ 26.7	Clinical response (w14)	20
	CD	w6	≥ 15.9	Clinical response (w14)	20
	UC	w6	> 6.6	Endoscopic response (w8)	21

	CD/UC	w14	>4.8	Clinical response (w14)	22
CT-P13	CD	w2	>20.4	Clinical remission (w14)	23
	UC	w14	>3.2	Mucosal healing (w14)	24
	UC	w2	>15.3	Clinical remission (w14)	23
ADM	CD ^b	w14	>6.7	Clinical remission (w14)	25
	CD ^b	w14	>3.7	CRP normalization (w14)	25
	CD	w4	>12	CRP≤5mg/L (w12)	26
	CD ^a	w14	≥12	Clinical remission (w14 & w54)	18
	CD	w12	>7.3	Clinical remission (w12)	27
	CD/UC	w4	>3.5	Clinical response (w4)	22
VDZ	CD	w22	>10	Endoscopic remission (w26)	28
	CD/UC	w6	>18	Mucosal healing (within w54)	29
UST	CD	w4	>15.9	50% decrease in <i>f</i> Cal (w8)	30
	CD	w8	>4.2	50% decrease in <i>f</i> Cal (w8)	30
	CD	w8	>7.2	Biological remission (w8)	30
	CD	w16	>2.3	Endoscopic response (w24)	30
	CD	w24	>1.9	Endoscopic response (w24)	30
	CD	w4	>13	HBI≤4, CRP<5mg/L & <i>f</i> Cal <250mg/g (w16)	31
	CD	w8	>2	HBI≤4, CRP<5mg/L & <i>f</i> Cal <250mg/g (w16)	31
	CD	w16	>1.4	HBI≤4, CRP<5mg/L & <i>f</i> Cal <250mg/g (w16)	31

^aPANTS study; ^bPOETIC study. IFX: infliximab; ADM: adalimumab; CTZ: certolizumab pegol; GOL: golimumab; VDZ: vedolizumab; UST: ustekinumab; IBD: inflammatory bowel disease; Ref.: reference; CD: Crohn's disease; UC: ulcerative colitis; w: week; CRP: C-reactive protein, *f*Cal: fecal calprotectin; HBI: Harvey Bradshaw index.

Table 2. *Post-hoc* analyses of randomized controlled trials associating serum biologic drug concentration with therapeutic outcomes in inflammatory bowel disease during both induction and maintenance therapy.

Drug	IBD type	RCT	Time point	Threshold (µg/mL)	Therapeutic outcome	Ref.
IFX	CD	TAILORIX	w2	>23.1	Endoscopic remission (w12)	32
	CD	TAILORIX	w6	>10	Endoscopic remission (w12)	32
	CD	SONIC	w30	≥3	Mucosal healing (w26)	33
	CD	ACCENT 1	w14	>3.5	Clinical response (w54)	34
	CD	JAPIC	w2	>21.3	Clinical remission (w14)	35
	UC	ACT1-2	w2	≥18.6	MES<2 (w8)	36
	UC	ACT1-2	w6	≥10.6	MES<2 (w8)	36
	UC	ACT1-2	w6	>22	Clinical response (w8)	37
	UC	ACT1-2	w14	>5.1	Clinical response (w30)	37
	UC	ACT1-2	w30	>2.4	Clinical response (w54)	37
ADM	CD	DIAMOND	w26	>5	Clinical remission (w52)	38
CTZ	CD	MUSIC	w8	>23.3	Endoscopic remission (w10)	39
	CD	9 RCTs	w6	>31.9	CRP≤5mg/L (w6)	40
	CD	9 RCTs	w6	>32.7	fCal <250mg/g (w6)	40
	CD	9 RCTs	w6	>34.5	fCal<250mg/g & CDAI≤150 (w6)	40
	CD	9 RCTs	w6	>36.1	fCal<250mg/g & CDAI≤150 (w26)	40
	CD	9 RCTs	w12	>13.8	fCal <250mg/g (w26)	40
	CD	9 RCTs	w12	>14.8	fCal<250mg/g & CDAI ≤150 (w26)	40
GOL	UC	PURSUIT	w2	>8.9	Clinical response (w6)	41
	UC	PURSUIT	w4	>7.4	Clinical response (w6)	41
	UC	PURSUIT	w6	>2.5	Clinical response (w6)	41
	UC	PURSUIT	w28	>0.9	Clinical remission (w30 and 54)	41
	UC	PURSUIT	w44	>1.4	Clinical remission (w30 and 54)	41

VDZ	UC	GEMINI 1	w6	> 37.1	Clinical response (w14)	42
	UC	GEMINI 1	w14	>18.4	Clinical response (w14)	42
UST	CD	UNITI 1-2	w8	>3.3	Clinical remission (w8)	43
	CD	UNITI 1-2	w24 ^a	>0.8	Clinical remission (w24)	43
	CD	UNITI 1-2	w40 ^b	>1.4	Clinical remission (w44)	43

^aCombined q8w and q12w; ^bq8w only. IFX: infliximab; ADM: adalimumab; CTZ: certolizumab pegol; GOL: golimumab; VDZ: vedolizumab; UST: ustekinumab; IBD: inflammatory bowel disease; Ref.: reference; RCT: randomized controlled trial; CD: Crohn's disease; UC: ulcerative colitis; w: week; MES: Mayo endoscopic score; CRP: C-reactive protein, fCal: fecal calprotectin; CDAI: Crohn's disease activity index.

Table 3: Infliximab and adalimumab concentration to target for achieving favourable therapeutic outcomes in IBD.

Drug	Time point	Drug concentrations (µg/ml)*
Infliximab	Induction (week 2)	≥20-25
	Induction (week 6)	≥10-15
	Post-induction (week 14)	≥3-7
	Maintenance	≥3-7
Adalimumab	Post-induction (week 4)	≥5-7
	Maintenance	≥5-8

Figure 1. Proposed clinical algorithm in case of reactive drug monitoring.

Drug	Anti-drug Antibodies	Suggested intervention
High	Not clinically relevant to measure	Objectify loss of response If confirmed, mechanistic failure is presumed and switch out of class preferred
Adequate	Not clinically relevant to measure	Objectify loss of response If confirmed, treatment intensification (for a limited period of time) as the individual patients may require higher concentrations If response not regained, switch out of class
Low	Intermediate or absent	Check compliance Increase drug concentrations (decrease interval, increase dose or possibly add an immunomodulator)
Absent	Intermediate or absent	Check compliance Increase drug concentrations (decrease interval, increase dose or add an immunomodulator) or consider re-induction
Absent	High	Switch within class (or out of class)