Gut Guide

10 Years of Mistakes in…

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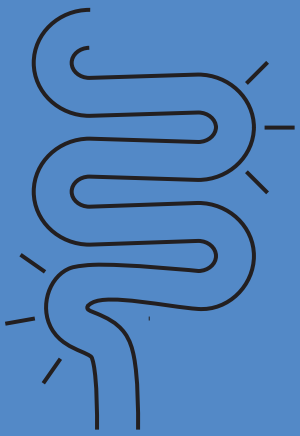
Chapter 6
Inflammatory Bowel Disease



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Mistakes in …

Therapeutic drug monitoring of biologics in IBD

… and how to avoid them

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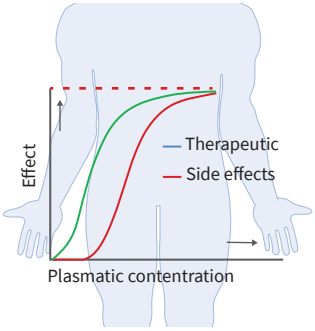

Biological therapy has revolutionised the treatment of moderate to severe inflammatory bowel disease (IBD), namely Crohn's disease (CD) and ulcerative colitis (UC). However, up to one-third of patients with IBD are primary non-responders, and up to half can lose response over time.[1] These unwanted outcomes can be explained by either pharmacodynamic (mechanistic failure) or pharmacokinetic (PK) issues with or without the development of anti-drug antibodies (ADA), so-called immunogenicity.[1] Reactive therapeutic drug monitoring (TDM), defined as the measurement of drug concentrations and anti-drug antibody (ADA) levels in the setting of primary non-response (PNR) or secondary loss of response (SLR), can help to explain better and manage these unwanted outcomes. However, it would make sense to try to prevent PNR and SLR by routinely measuring drug concentrations and ADA to achieve and maintain a targeted therapeutic drug concentration, the so-called proactive TDM.

Here we discuss some common mistakes and significant errors to avoid when utilising TDM of biologics in patients with IBD. The discussion is based on evidence, whenever possible, and our clinical experience and perception of the field.

Mistake: Only doing empiric dose escalation and not performing reactive TDM in patients with a non-primary non-response or secondary loss of response to biological therapy

Reactive TDM has rationalised the management of PNR or SLR by identifying the underlying mechanisms of these unfavourable outcomes. Reactive TDM can help tailor and individualise treatment; for example, increasing the drug dose in patients with sub-therapeutic drug concentrations and undetectable or low-titer ADA. Testing for drug concentrations and ADA also would avoid giving more drug to a patient with a mechanistic failure and adequate drug concentration. The latter would necessitate a switch in drug class.[2,3] Reactive TDM increases endoscopic remission rates and lessens hospitalisations compared to empiric treatment optimisation.[4] In addition, reactive TDM is more cost-effective than empiric drug optimisation based only on clinical symptoms.[5] Of note, the active disease should always be confirmed with objective measures of inflammation, including biomarkers, such as C-reactive protein (CRP) and faecal calprotectin, as well as endoscopy with histological evaluation.

Mistake: Failing to adequately optimise a previous biologic before changing to a new one

When utilising reactive TDM, a common mistake is abandoning treatment before optimising it. This is important as subsequent biologic therapies typically show less efficacy. It is most important when using anti-tumour necrosis factor (anti-TNF) therapy, specifically infliximab, as there are limited pharmacological options for some specific IBD phenotypes, such as

perianal fistulising CD and acute severe ulcerative colitis. Of note, giving up on one anti-TNF due to adequate drug concentration suggests a mechanistic failure not just to that agent but all anti- TNFs. Thus, it is recommended that treatment discontinuation should not be considered until an infliximab or adalimumab concentration of at least 10-15 µg/mL is achieved.[6] However, there may be occasions where these drug concentrations may not be attainable for various reasons, including very high drug clearance and insurance issues limiting dose intensification.

Mistake: Only doing reactive TDM and not utilising proactive TDM to optimise anti-TNF therapy

Cumulative evidence suggests that proactive TDM of anti-TNF therapy is associated with better outcomes than empiric treatment optimisation and/or reactive TDM. A recent meta-analysis, including retrospective studies and randomised controlled trials (RCTs), found that proactive TDM of anti-TNF therapy was associated with lower treatment failure rates than standard of care or reactive TDM. Moreover, proactive was associated with higher endoscopic remission rates than standard care.[7] Other clinical scenarios that proactive TDM could efficiently guide clinical decisions are anti-TNF therapy de-escalation or even discontinuation and optimising infliximab monotherapy when combination therapy with an immunomodulator (IMM) is not an option due to patient preference or high risk of serious adverse events. Proactive TDM is also recommended after starting infliximab following a drug holiday (Figure 1).

Growing data suggest that proactive TDM can efficiently guide clinical decisions when anti-TNF therapy de-escalation is considered in patients with IBD due to clinical remission, including lengthening the dosing intervals, decreasing the dose, and stopping the IMM in case of combination therapy. The TAXIT RCT showed that dose reduction in patients with IBD and infliximab trough concentrations higher than 7 µg/mL was safe (no flares or increase of inflammatory markers) and cost-effective.[30] A study from Drobne and colleagues found that infliximab concentrations ≥5 µg/mL at the time of IMM withdrawal are related to long-term response in patients with CD after discontinuation of IMMs.[31] Regarding adalimumab, concentrations higher than 12.2 µg/mL were associated with successful de-escalation in patients with IBD.[32] We would like to point out that the 'one-size-fits-all' also should not apply when proactive TDM is used for treatment de-escalation. Higher drug concentration thresholds may be required for patients with a more complicated IBD phenotype, such as perianal fistulising CD. For this IBD population, supra-therapeutic infliximab concentrations are probably higher than 15-20 µg/mL.[33]

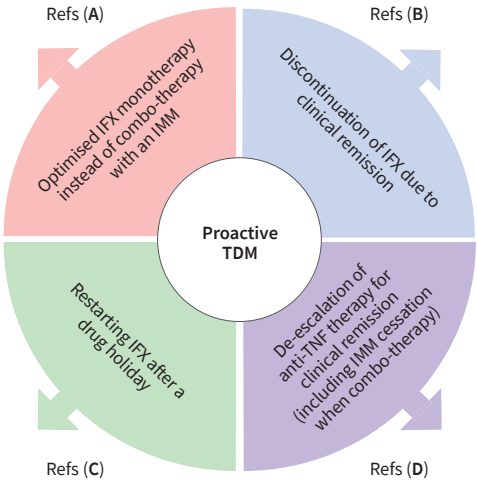

Figure 1 | Other potential applications of proactive therapeutic drug monitoring in clinical practice. TDM: therapeutic drug monitoring; IFX: infliximab; TNF: tumor necrosis factor; IMM: immunomodulators. Refs (**A**) 8,9 and 10-12, Refs (**B**) 13-17, Refs (**C**) 18-21 and Refs (**D**) 22-29.

Mistake: Using the same biologic drug concentration threshold for all patients

Optimal biologic drug concentrations to target can vary based on treatment phase, IBD phenotype, TDM assay used, targeted therapeutic outcome and route of drug administration (Figure 2). Most studies suggest that higher drug concentrations are needed to achieve more stringent therapeutic outcomes, including endoscopic and histologic healing. Recent data suggest that subcutaneous, compared to intravenous, administration of infliximab and vedolizumab produce multiple-fold higher serum drug concentrations due to PK differences.[34,35] Additionally, there may be discrepancies when measuring biologic drug concentrations among various assays, such as the enzyme-linked immunosorbent assay (ELISA), the homogenous mobility shift assay (HMSA) and point-of-care assays.[36-39] Importantly, higher drug concentrations are needed during the induction phase compared to the maintenance phase. Finally, higher drug concentrations are probably needed for patients with a more complicated phenotype, such as perianal fistulising CD.[33] Consequently, applying the "one-size-fits-all" concept when performing TDM for optimising biologics is a mistake. A more personalised approach is needed.

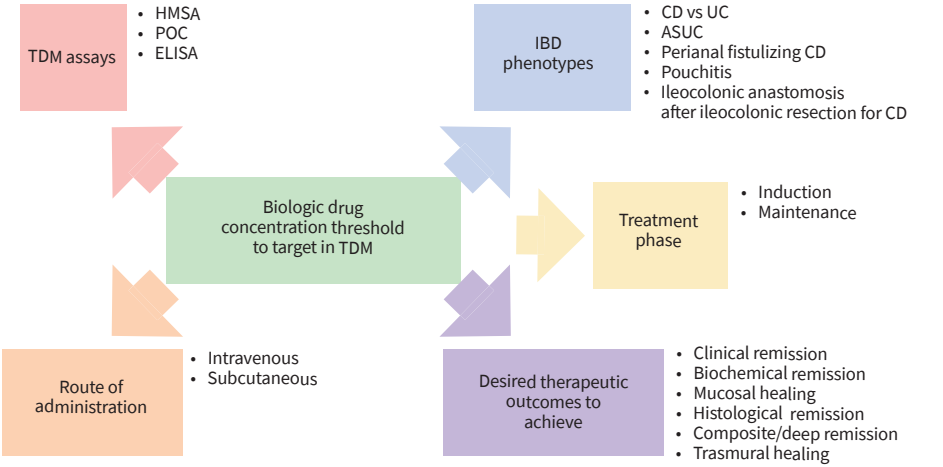

Figure 2 | Factors associated with biologic drug concentrations threshold to target in therapeutic drug monitoring. TDM, therapeutic drug monitoring; HMSA, homogenous mobility shift assay; POC, point-of-care; ELISA, enzyme-linked immunosorbent assay; IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; ASUC, acute severe ulcerative colitis.

Preliminary data suggest that there may be quantitative and qualitative inconsistencies among different assays when evaluating drug concentrations.[39] This may also be the case for different commercial kits using the same quantification method. For example, significant differences were found among different ELISA commercial kits for both infliximab[40] and golimumab.[36] Even most importantly, ADAs are not easy to correctly interpret as titers are often expressed in different units across different assays, such as the enzyme-linked immunosorbent assay (ELISA), the homogenous mobility shift assay (HMSA) and the electrochemiluminescence immunoassay (ECLIA) (Table 1). Consequently, ADA levels cannot be directly compared among assays and thresholds for low and high titers cannot be adequately defined. Discrepancies among assays could lead to inappropriate clinical decisions as these often rely on drug concentration

thresholds to target and ADA titer cut-offs that can be overcome. It would make sense to use the same assay for each patient, at least until harmonisation of assays and units of measurement is feasible.[41] We recommend that physicians be very comfortable interpreting ADA in their chosen assay.

TDM assay	ATI units	Assay type	ATI titer	Therapeutic outcome	Refs
ELISA	ng/mL	RIDASCREEN (r-biopharm)	<282	Higher success rate of treatment optimization	42
			>222	Unable to overcome immunogenicity	43
		LISA-TRACKER (Theradiag)	>200	Lack of response to treatment optimization	44
	U/mL	IDKMonitor (Immundiagnostik)	<10	Recapture clinical remission	45
			>30	Non-response to dose intensification	46
	µg/mL	Prometheus Laboratories	>8	Shorter clinical response	47
		Janssen (in house)	>4.9	SLR	48
		Anti-human lambda chain antibody (in house)	≥4	Treatment discontinuation	49
			>9	Longer duration of response when anti-TNF agents are switched than when dosage is increased for SLR	50
			>4.3[a]	PNR at week 14	51
			>2.5[b]		
HMSA	U/mL	Anser IFX (Prometheus Laboratories)	<3.1	Biochemical remission (CRP ≤5 mg/L)	52
			≥10	Immunogenicity to adalimumab	53
			<8.8	Drug retention	54
			>9.1	Failure of dose intensification after SLR	55
			>12	Higher risk for surgery	56
			<3.3	Post-adjustment endoscopic remission	57
			>9.1	Drug discontinuation / infusion reactions	9
			≤8.5	Drug concertation ≥5µg/mL and no ATI	58
			>10	Not able to overcome	59
ECLIA	ng/mL	DoseASSURE IFX (Esoterix-Labcorp)	<197	ATI reversal	60
			>23	Increased drug clearance	

[a]at week 2; [b]at week 6. TDM: therapeutic drug monitoring; ATI: antibodies to infliximab; ELISA: enzyme-linked immunosorbent assay; HMSA: homogeneous mobility shift assay; IMM: immunomodulator; CRP: C-reactive protein; SLR: secondary loss of response; PNR: primary non-response.

Table 1 | Association of antibody to infliximab titers evaluated with different assays with therapeutic outcomes in patients with IBD.