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Therapeutic drug monitoring of biologics in inflammatory bowel disease: unmet needs and future perspectives

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Summary

Therapeutic drug monitoring (TDM) has emerged as a useful tool for optimizing biologics, and in particular anti-tumor necrosis factor (anti-TNF) therapy, in both inflammatory bowel disease (IBD) and other immune-mediated inflammatory diseases such as rheumatoid arthritis and psoriasis. However, there are still some challenges hindering the widespread implementation of TDM in clinical practice. These barriers include identification of the optimal drug concentration to target, the lag time between sampling and results, and the proper interpretation of anti-drug antibody titers among different assays. Solutions to overcome these barriers include the harmonization of TDM assays and the use of point-of-care testing. Other unmet needs include well-designed prospective studies and randomized controlled trials focusing on proactive TDM particularly during induction therapy. Future studies should also investigate the utility of TDM in

biologics other than anti-TNFs in both IBD and other immune-mediated inflammatory diseases and the use of pharmacokinetic dashboards and pharmacogenetics towards individual personalized medicine.

Keywords

inflammatory bowel disease; Crohn's disease; ulcerative colitis; therapeutic drug monitoring; infliximab; adalimumab; vedolizumab; ustekinumab; pharmacokinetic dashboards

Introduction

Therapeutic drug monitoring (TDM) has emerged as a useful tool for optimizing biologic therapy, specifically anti-tumor necrosis factor (anti-TNF) therapy, in inflammatory bowel disease (IBD) and other immune-mediated inflammatory diseases (IMID).[1] Reactive TDM is defined as the evaluation of drug concentrations and anti-drug antibodies (ADA) in the setting of primary non-response (PNR) or secondary loss of response (SLR). Proactive TDM is utilizing the regular measurement of drug trough concentrations and ADA with dose adaptation to target appropriate drug concentration. Reactive TDM has rationalized the management of PNR and SLR and has proven more cost-effective than empiric dose optimization of infliximab.[2-4] Moreover, preliminary data suggest that proactive TDM may be associated with better therapeutic outcomes than empiric dose optimization and/or reactive TDM.[5-13] In addition numerous exposure-outcome relationship data both in IBD (Table 1)[14-53] and other IMID including rheumatoid arthritis (RA) and psoriasis (Table 2) not only from retrospective but also prospective studies and post-hoc analyses of randomized controlled trials (RCTs), demonstrate that higher drug concentrations are associated with improved therapeutic outcomes.[54-91] Conversely, lower drug concentrations, with or without ADA, are associated with treatment failure and drug discontinuation.[2,3] Preliminary data also suggest that proactive TDM of infliximab can potentially safely guide treatment de-escalation[92-94] and support the concept of optimized monotherapy in lieu of combination therapy with an immunomodulator (IMM).[95,96]

However, there are still several issues the use of TDM in patients with IBD. These include the identification of the optimal drug concentrations to target taking into account also inter-individual variability, the lag time between testing and TDM results and interpretation of ADA titers among different assays. These issues could efficiently be addressed by the harmonization of assays and the use of rapid, point-of-care, testing. Further unmet needs include well-designed prospective studies and RCTs focused on proactive TDM particularly during induction therapy when the inflammatory burden and drug clearance is greatest. Research should also emphasize the role of TDM of non anti-TNF biologics. Future perspectives towards a more personalized application of TDM ought to embrace pharmacokinetic (PK) modeling and dashboards as well as pharmacogenetics. This would also allow selection of those patients at high risk of accelerated drug clearance who would benefit more from proactive TDM.

This collaborative state-of-the-art review from members of the intErnational Consortium Therapeutic dRUg Monitoring (spECTRUM) aims to present the most recent data from

RCTs, prospective studies and post-hoc analyses of RCTs examining the role of TDM for optimizing biologics in IBD. Moreover, we provide up-to-date information regarding the role of TDM in other IMID. Finally, emphasis is given to the unmet needs and future perspectives for TDM. The spECTRUM consortium is a group that consists of IBD, rheumatology, and dermatology TDM specialists from thirteen countries on five different continents. It is a consortium with global perspectives launched to determine the unmet need, design research to address the issues and expand the utility of TDM with the ultimate aim of improving patient care.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms ‘inflammatory bowel disease’; ‘Crohn’s disease’; ‘ulcerative colitis’; ‘psoriasis’; ‘rheumatoid arthritis’; ‘ankylosing spondylitis’; ‘anti-drug antibodies’; ‘immunogenicity’; ‘therapeutic drug monitoring’; ‘point of care assays’; ‘pharmacokinetics’; ‘pharmacogenetics’; ‘infliximab’; ‘adalimumab’; ‘certolizumab pegol’; ‘golimumab’; ‘vedolizumab’; ‘ustekinumab’; ‘etanercept’; ‘secukinumab’; ‘ixekizumab’; ‘tocilizumab’ from 2000 until March, 2021. Only papers published in English were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this review focusing mainly on the more recent publications.

What is already known regarding the role of TDM of biologics in IBD

Two main types of studies have defined the role of TDM of biologics in IBD; exposure-outcome relationship studies and studies assessing the utility of TDM for optimizing anti-TNF therapy. The latter have compared (1) reactive TDM to empiric treatment optimization and (2) proactive TDM to reactive TDM and/or empiric treatment optimization. Although the majority of these investigations are retrospective that are characterized by inherited limitations and biases there are now several prospective studies, RCTs and post-hoc analyses of RCTs that are presented in relevant sections of this review.

Randomized controlled trials

There are currently five RCTs[9,10,97-99] that have investigated the role of TDM for anti-TNF therapy in IBD patients with inconsistent results probably also due to differences in study design and population, primary end-points and TDM-based algorithms (Table 3).[100] Four studies examined infliximab. Steenholdt et al.[97]examined the cost-effectiveness and clinical efficacy of reactive TDM compared to empiric treatment optimization in patients with CD and SLR to infliximab, whereas TAXIT (Trough Concentration Adapted Infliximab Treatment)[9] and TAILORIX (A Study investigating Tailored Treatment With Infliximab for Active Crohn’s Disease)[98] RCTs examined the role of proactive TDM. The fourth study, the PRECISION (Precision Dosing of Infliximab Versus Conventional Dosing of Infliximab) RCT[99] was designed to investigate the efficacy of dashboard-driven infliximab dosing compared to standard dosing. For Adalimumab, the PAILOT (Pediatric Crohn’s Disease Adalimumab Level-based Optimization Treatment) RCT[10] specifically investigated the role of proactive TDM in pediatric CD.

In the RCT by Steenholdt et al.[97], although reactive TDM proved to be more cost-effective than routine dose intensification in patients with SLR, it did not improve clinical efficacy. The TAXIT[9] and the TAILORIX[98] RCTs did not also meet their primary endpoint. However, the TAXIT RCT showed that during the optimization phase in patients with CD with low drug concentrations, proactive TDM-based dose optimization led to higher rates of clinical remission (88% vs. 65%; p=0.020) and improvement in C-reactive protein (CRP) (3.2 vs. 4.3 mg/L; p<0.001) compared to before dose escalation. Moreover, some of the secondary endpoints of TAXIT favored the proactive TDM over the clinical-based dosing arm including disease relapse over time and the rate of undetectable drug trough concentrations. The PAILOT RCT[10] assessed a pediatric population with CD naïve to biological therapy who had responded to adalimumab induction therapy and showed that the rate of sustained corticosteroid-free clinical remission was significantly higher in the proactive arm compared to the reactive TDM arm (82% vs. 48%; p=0.002) achieving its primary endpoint. Several secondary outcomes also favored proactive over reactive TDM, the most important being the composite outcome of sustained corticosteroid-free remission, normal CRP and normal FC (42% vs. 12%; p=0.003). The PRECISION[99] was the first RCT to investigate the efficacy of PK-dashboard-driven infliximab dosing compared to standard dosing in patients with IBD in clinical remission. Meeting its primary endpoint the study showed that more patients in the PK model arm were in sustained clinical remission compared to the control group (88% vs. 64%; p=0.017). Furthermore, a composite outcome of combined clinical remission and normal fecal calprotectin levels was higher in the PK model arm compared to the clinical arm (95% vs. 68.2%; p=0.027).

The major limitations of these RCTs are described in Table 3. We would like to point out that there are two main issues common to all of them. The first is the use of a rather low targeted drug concentration. Numerous recent reports suggest that higher drug concentrations are associated with more stringent therapeutic outcomes such as endoscopic and histologic remission[101] The other concern is that patients had to wait until the next dose before treatment changes were implemented. Future RCTs should address these issues with the hope of better defining the role of TDM.

Prospective studies and post-hoc analyses of RCTs

Multiple prospective exposure-outcome relationship studies in both adult and pediatric IBD and post-hoc analyses of RCTs have demonstrated a positive correlation between biologic drug concentrations and favorable therapeutic outcomes (Table 1).[102,103] Studies demonstrated similar results during induction and maintenance therapy. In the largest prospective study, PANTS (The personalised anti-TNF therapy in Crohn's disease study), infliximab concentrations of > 7 μg/mL and adalimumab concentration of > 12 μg/ml at week 14 were associated with clinical remission at both week 14 and 54. Low drug concentrations at week 14 were independently associated with immunogenicity, PNR and non-remission at week 54.[28] A recent post-hoc analysis of the ACCENT-II [A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNFa Chimeric Monoclonal Antibody (Infliximab; REMICADE Janssen Biotech, Inc, Malvern, PA) in the Long-term Treatment of Patients with Fistulizing Crohn’s Disease] RCT showed that higher infliximab concentrations at week 14 were independently associated with composite remission at week

14 [odds ratio (OR): 2.32; 95% confidence interval (CI): 1.55–3.49; p<0.001) and week 54 (OR: 2.05; 95% CI: 1.10–3.82; p=0.023). Based on receiver operating characteristic curve analysis, infliximab concentration thresholds of ≥20.2 μg/mL at week 2, ≥15 μg/mL at week 6, and ≥7.2 μg/mL at week 14 were associated with composite remission at week 14.[24] Preliminary data from prospective studies and post-hoc analyses of RCTs have also examined anti-TNF drug concentrations in relation to perioperative complications[104] and post-operative recurrence in patients with CD undergoing ileocolic resection (Table 4).[105-108]

A major limitation of prospective exposure-outcome relationship studies and post-hoc analyses of RCTs is that these studies only show an association and not causation as higher serum drug concentrations may just reflect lower disease activity related to lower drug clearance. Furthermore, the association of drug concentrations with outcomes typically is less clear for maintenance than induction therapy. This finding is probably because a significant portion of patients withdraws during the course of the study. This dropout eventually decreases the power to detect differences in drug concentrations of patients achieving the investigated outcome at latter time points. Another limitation is that the great majority of these studies investigate infliximab and adalimumab. Consequently, drug concentrations threshold to target for other biologics are not clearly defined. This is important as these studies often provide a starting point to define values when designing prospective studies of TDM.

What is already known regarding the role of TDM of biologics in other IMID

Evidence is growing regarding the role of TDM in other IMID. Similar to IBD, numerous exposure-outcome relationship studies demonstrate that higher biologic drug concentrations are associated with higher rates of favorable clinical outcomes, especially in RA and psoriasis (Table 2). [54-91] Studies have shown that TDM can help to identify possible causes of poor outcomes such as mechanistic failure or insufficient drug exposure due to PK issues or non-adherence.[109-120] TDM has been demonstrated to efficiently guide treatment de-escalation for adalimumab[121,122] and etanercept[123] in patients with RA. Although, TDM-based therapeutic algorithms have already been described, such as in psoriasis,[124] a recent survey showed that most dermatologists still perform dose adaptations empirically.[125] Routine use of TDM in clinical practice is not widely applied outside of IBD.[126,127]
The NOR-DRUM (NORwegian DRUg Monitoring study) RCT included 398 adults with spondyloarthritis (n=117), rheumatoid arthritis (n=80), psoriatic arthritis (n=42), psoriasis (n=22) or IBD (n=137, 80 with UC and 57 with CD) who received their randomized intervention, either proactive TDM based on a predefined algorithm or standard infliximab therapy with treatment adjustments based on clinical assessment. The primary outcome of clinical remission at week 30 was comparable between the two groups (100/198, 50.5% for the standard therapy vs. 106/200, 53% for the TDM group; p=0.78).[128] However, it is difficult to draw firm conclusions for IBD or other IMID as the trial did not have the statistical power to test hypotheses within each disease subgroup. Moreover, the therapeutic range for defining adequate infliximab concentrations for the TDM group was rather low based on recent data.[1,101,129]

Unmet needs regarding the role of TDM of biologics in IBD

There are several unmet needs regarding the role of TDM of biologics in IBD that are described in detail below.

Optimal drug concentrations to target

One of the most important unmet need is the identification of the optimal drug concentrations to target as these can be therapeutic outcome-, assay-, time- and IBD phenotype-dependent.[129] Exposure-outcome relationship studies show that typically higher drug concentrations are needed to achieve more stringent outcomes such as endoscopic and histologic remission or fistula healing.[101] Moreover, recent data show that there may be quantitative and qualitative discrepancies among assays concerning both drug concentrations and ADA titers.[130-133] Regarding IBD phenotypes, preliminary data suggest that patients with perianal fistulising CD may require higher infliximab concentrations to achieve fistula closure.[134,135]

Proper interpretation of anti-drug antibody titers

Another difficulty is the correct interpretation of ADA titers across different assays, such as the commonly used enzyme-linked immunosorbent assay (ELISA), the homogeneous mobility shift assay (HMSA) and the electrochemiluminescence immunoassay (ECLIA). ADA titers are often expressed in arbitrary units and cannot be compared directly between different assays.[133,136] This is important as physicians may inadequately stop a biologic due to hypothetical high titer ADAs. For example, Imbrechts et al.[133] showed that a cut-off of 8 μg/ml measured with the first generation ELISA had a similar impact as the cut-off of 374 ng/ml with the second generation ELISA and a cut-off of 119 ng/ml in the ready-to-use ELISA kit. This is quite significant as different ADA titer thresholds may be associated with diverse clinical outcomes and guide management. A recent 3-year study of patients receiving infliximab who developed ADA >8 μg/ml evaluated by a drug-tolerant ELISA showed that ADA cut-off values of 16, 19, 37 and 45 μg/ml were associated with treatment failure, steroid use, development of infusion reactions and switch to another biologic, respectively.[137]

Other unmet needs regarding the role of TDM of biologics in IBD

A very important point to consider is that the current techniques used to measure drug concentrations and ADA, require significant incubation times and may have long turnaround times. Furthermore, dose-escalation may require a pre-authorization from payers that can add even more time to the process of dose optimization. These factors do not allow physicians to dose adjust promptly at the time of infusion or injection.[136] Further investigation is also needed to determine the role of peak[48] or intermediate concentrations[22,95] as well as total drug exposure[138] and the role of drug concentrations measured in tissue[139,140] or stool samples.[141] Beyond these issues, there is the need for high quality data demonstrating that strategic use of TDM changes clinically meaningful outcomes in IBD. As mentioned above, two of the large RCTs examining the role of proactive TDM-dose adjustment likely missed their primary endpoint due to methodological issues. Alternative trial designs are needed to address this deficit.

Furthermore, the role of TDM in biologics other than anti-TNFs such as vedolizumab and ustekinumab, needs greater clarification, especially as data from exposure-outcome relationship studies are only available and as these drugs exhibit low immunogenicity.[142] A post-hoc analysis of the UNITI (A Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease) RCT identified a ustekinumab concentration of 0.8 μg/ml at week 24 and 1.4 μg/ml at week 40 for clinical remission at weeks 24 and 44, respectively.[51] Another prospective study identified a ustekinumab concentration cut-off of 2.3 μg/ml at week 16 and 1.9 μg/ml at week 24 to be associated with endoscopic response at week 24.[49] Löwenberg et al. demonstrated that drug concentrations >10 mg/L at week 22 were associated with endoscopic remission at week 26 in patients with IBD.[47] A recent multi-center observational study assessed the outcome of vedolizumab dose-increase and pre-escalation drug concentrations. It demonstrated that pre-intensification vedolizumab trough concentrations were comparable or higher among patients who subsequently attained post-optimization clinical, biomarker and endoscopic remission, compared with non-remitting patients. This was true during induction and maintenance therapy. Moreover, the same study demonstrated that integrin-receptors on M1- and M2-macrophages were saturated by low concentrations of vedolizumab. Based on these data PK issues may not be the main mechanism for loss of response to vedolizumab and higher pre-escalation drug concentrations may indicate lower clearance due to a less severe disease and a higher likelihood of subsequent re-gaining of response regardless of therapy escalation.[143] It is fortunate that the pharmaceutical industry has realized the importance of incorporating TDM into more recent drug trials. Some ongoing registration trials currently incorporate TDM arms, such as risankizumab for UC (https://www.clinicaltrials.gov/ct2/show/NCT03398135). If shown to be effective, this should allow for early adoption of TDM into clinical practice for these novel medications.

Future perspectives regarding the role of TDM of biologics in IBD

Potential investigations, addressing some of the unmet needs described above, should examine the harmonization of assays, the use of rapid point-of-care assays, the incorporation of PK modelling dashboards and pharmacogenomics as well as the application of telemedicine and home TDM testing (Figure 1).

Harmonization of TDM assays

Many academic groups and diagnostics companies have developed assays for the quantification of biologic drug concentration. Although drug concentrations correlate well between different assays, their agreement may not always be good; if possible, it may be best to use the same assay over time for individual patient follow-up.[130-132,136] Efforts are ongoing to standardize assays for measuring drug concentrations by producing reference standards. Implementation of universal calibrators for quantifying ADA has also been proposed to facilitate inter-laboratory harmonization of ADA measurements.[144,145] Since assays for determining ADA are still not harmonized worldwide, it is almost impossible to set ADA cut-off levels that would preclude successful dose escalation and overcoming of ADA. Consequently, generation of robust immunogenicity data for inclusion in product

labels and TDM-based therapeutic algorithms to support clinical practice continues to be a challenge.

Point-of-care assays

Point-of-care assays are medical diagnostic tests applied at the time and place of patient care. When referring to TDM of biologics, this could be done either in the infusion unit, the clinic or even at home. Such assays allow clinicians to get results within minutes and therefore more timely adjust drug dosage, although the timely availability of the assay result may still not be able to be immediately implemented due to restrictions by payers and insurers on increased drug dosing.[146] Point-of-care assays have been clinically validated for quantifying both infliximab and adalimumab in serum. [32,146] However, as the number of such tests increases, it is important that their quality is carefully assessed and their accuracy is compared with the commonly used laboratory measurements of drug concentrations and ADA as there may be discrepancies.[147-149]

Pharmacokinetic modelling and dashboards

Performing TDM is a smart way to evaluate variability in drug PK between patients and within a patient over time. Population PK modelling has been used to create algorithms which also include a variety of parameters that may affect drug concentrations. For biologics, common factors that have been shown to impact drug clearance include gender, body weight, serum albumin, inflammatory burden, immunogenicity, concomitant immunomodulation and polymorphisms in the neonatal Fc receptor.[150,151] By applying population PK models, one can utilize previous and concurrent drug concentration measurements to predict the timing and/or magnitude of future doses required to reach a pre-specified drug concentration. Such methods are referred to as ‘dashboards’. Dashboards integrate individual clinical and PK data to generate dosing recommendations to achieve pre-specified target trough concentrations using adaptive Bayesian forecasting towards precision medicine.[152-154] Clinical intuition alone does not accurately predict the need for dose escalation highlighting the importance of a more robust method of selecting the right dose at the right time for the individual patient.[155] As detailed above the clinical efficacy of a PK-dashboard was recently demonstrated by the PRECISION RCT showing that PK-dashboard-driven infliximab dosing was superior than standard dosing in patients with IBD in terms of clinical remission.[99] However, as an absolute value may be less informative at an individual level, TDM could be combined with pharmacodynamic measures, such as clinical disease activity, biomarkers and/or imaging for better guiding treatment optimization.

There is also the potential for a population PK model to be used prior to initiation of therapy, to calculate drug clearance at baseline in an individual. Drug clearance has been shown to correlate with endoscopic remission in patients with moderately to severely active UC starting infliximab. More specifically there was a linear relationship between baseline infliximab clearance and Mayo endoscopic scores (MES) at week 8 and a threshold of <0.397 L/d was associated with week 8 MES ≤1.[156] Furthermore, it was found that in patients with acute severe UC, higher values of baseline infliximab clearance were associated with higher rates of treatment failure and colectomy.[157,158] Using the data from the ACT (Active Ulcerative Colitis Trials)-1/2 phase 3 clinical trials of infliximab in patients

with UC, a decision support tool was developed and validated to calculate at baseline the likelihood that a subject would achieve endoscopic remission at week 8 or week 30 following initiation of infliximab.[159] Such a model could now be tested to stratify patients and identify those patients who are at risk of accelerated drug clearance and who may benefit from proactive TDM and optimized dosing. Model-informed precision dosing guided by real-world PK may also be available at the bedside in real-time as these decision-support PK dashboards can be embedded within the electronic health record allowing individual personalised TDM.[160]

Pharmacogenomics

Preliminary data suggest that patients with IBD carrying specific gene alleles are at high risk of low infliximab or adalimumab concentrations or developing immunogenicity to either of these drugs.[161-166] A genome-wide analysis of the PANTS prospective study identified the HLA-DQA1*05 allele to increase the risk of immunogenicity to both infliximab and adalimumab in patients with CD.[161] Another study showed that the same allele was associated with a high risk of antibodies to infliximab in addition to loss of response and infliximab discontinuation in patients with IBD.[162] These high-risk patients could be treated with combination therapy with either thiopurines or methotrexate to help prevent immunogenicity and/or to undergo proactive TDM starting early during induction therapy.[6,167] Pharmacogenomics is one more step towards personalized medicine and identifying patients that would benefit more from proactive TDM and combination therapy.

Telemedicine and home testing related to TDM

Even before COVID-19, there was growing evidence to support virtual healthcare and a clear desire from patients.[168] However, the COVID-19 pandemic acted as a key driver for widespread adoption of virtual health and telemedicine.[169] Additionally, electronic health smartphone applications are an adjunct to virtual healthcare, but in many cases have become synonymous with the delivery of telemedicine.[170] Virtual healthcare and use of electronic health applications have been associated with reduced outpatient visits[171,172] and hospital admissions[172] as well as reduced costs to healthcare providers[173] and patients.[174] New easier sampling methods, such as home-sampled dried blood spots, may allow for “home TDM.”[175,176] A prospective observational cohort study showed that the use of a web-based, mobile infliximab dosing calculator for therapy optimization is feasible and potentially effective, facilitating both standardization and individualization of therapy in clinical care.[177]

Conclusion

Reactive TDM is emerging as the new standard of care for optimizing biologic therapy in IBD. There is still a debate regarding the role of proactive TDM in clinical practice and there are still limited data from well-designed prospective studies and RCTs for both IBD and other IMID. Several areas of TDM that still need to be defined include the potential use of point-of-care assays, PK dashboard models and pharmacogenetics. Prospective studies of proactive TDM starting from the induction phase which is characterised by increased disease

activity and consequently higher drug clearance are needed to better define its role in the management of IBD and other IMID.

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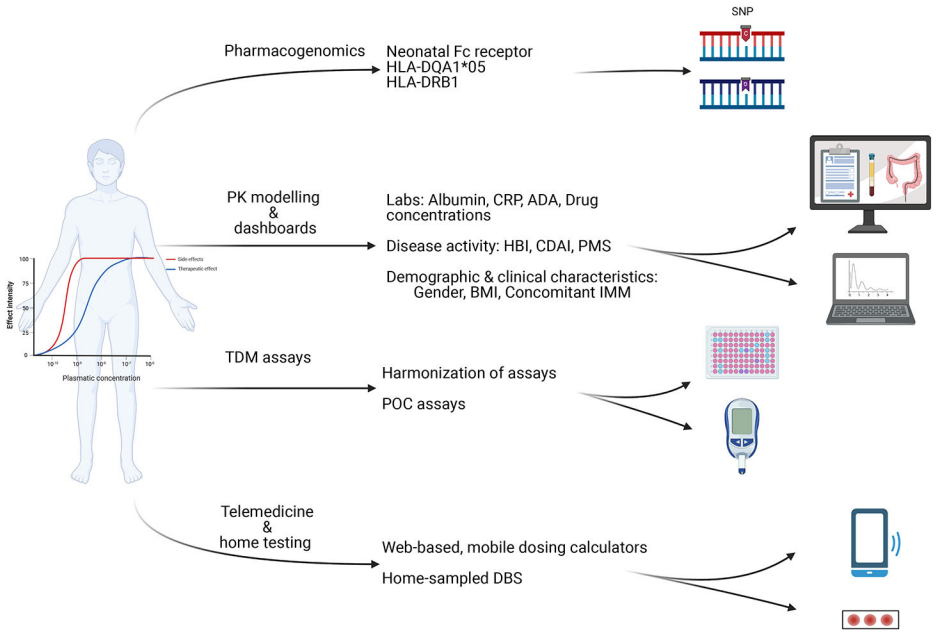

Figure 1: Future perspectives of therapeutic drug monitoring of biologics in IBD.

PK: pharmacokinetic; TDM: therapeutic drug monitoring; HLA: human leukocyte antigen; SNP: Single nucleotide polymorphisms; CRP: C-reactive protein; ADA: anti-drug antibodies; HBI: Harvey-Bradshaw index; CDAI: clinical disease activity index; PMS: partial Mayo score; BMI: body mass index; IMM: immunomodulator; POC: point of care; DBS: dried blood spots.

Table 1.

Biologic drug exposure-outcome relationship data in IBD from prospective studies and post-hoc analysis of RCTs.

TDM time point	Study type / acronym	IBD type	Drug concentration threshold (μg/mL)	Therapeutic outcome (time point)	Assay type	Ref.
Infliximab						
Week 2	TAILORIX *	CD	>23.1	Endoscopic remission (w12)	ELISA	14
Week 2	JAPIC *	UC	>21.3	Clinical remission (w14)	ELISA	15
Week 2	ACT 1 & 2 *	UC	≥18.6	MES<2 (w8)	ELISA	16
Week 2	Prospective **	CD	≥26.7	Clinical response (w14)	ELISA	17
Week 2	Prospective ***	CD	>20.4	Clinical remission (w14)	ELISA	18
Week 2	Prospective ***	UC	>15.3	Clinical remission (w14)	ELISA	18
Week 2	Prospective	CD/UC	>22.9	Clinical response (w14)	ELISA	19
Week 6	Prospective	CD/UC	>11.8	Clinical response (w14)	ELISA	19
Week 6	TAILORIX *	CD	>10	Endoscopic remission (w12)	ELISA	14
Week 6	Prospective **	CD	≥15.9	Clinical response (w14)	ELISA	17
Week 6	Prospective	UC	>6.6	Endoscopic response (w8)	ELISA	20
Week 6	ACT 1 & 2 *	UC	≥10.6	MES<2 (w8)	ELISA	16
Week 6	ACT 1 & 2 *	UC	>22	Clinical response (w8)	ELISA	21
Week 8	ACT 1 & 2 *	UC	>41.1	Clinical response (w8)	ELISA	21
Week 8	ACT 1 & 2 *	UC	≥34.9	MES<2 (w8)	ELISA	16
Week 10	Prospective **	CD	≥9.1	Drug retention (w52)	ELISA	22
Week 14	TAILORIX *	CD	>7.8	Radiological remission (w54)	ELISA	23
Week 14	ACCENT II *	CD	≥7.2	Complete fistula response & CRP normalization (w14)	ELISA	24
Week 14	ACCENT I *	CD	>3.5	Clinical response (w54)	ELISA	25
Week 14	ACT 1 & 2 *	UC	>5.1	Clinical response (w30)	ELISA	21
Week 14	ACT 1 & 2 *	UC	≥5.1	MES<2 (w30)	ELISA	16
Week 14	ACT 1 & 2 *	UC	≥6.7	MES=0 (w30)	ELISA	16
Week 14	Prospective	CD/UC	>4.8	Clinical response (w14)	ELISA	26
Week 14	Prospective ***	UC	>3.2	Mucosal healing (w14)	ELISA	27
Week 14	Prospective [a]	CD	≥7	Clinical remission (w14/54)	ELISA	28
Week 14	Prospective **	CD	>11.5	FC<100μg/g (w14)	ELISA	29
Week 30	SONIC *	CD	≥3	Mucosal healing (w26)	ELISA	30
Week 30	ACT 1 & 2 *	UC	>2.4	Clinical response (w54)	ELISA	21
Week 30	ACT 1 & 2 *	UC	≥2.3	MES<2 (w30)	ELISA	16

TDM time point	Study type / acronym	IBD type	Drug concentration threshold (μg/mL)	Therapeutic outcome (time point)	Assay type	Ref.
Week 30	ACT 1 & 2 *	UC	≥3.8	MES=0 (w30)	ELISA	16
Adalimumab						
Week 2	Prospective *b*	CD	>6.7	Clinical remission (w14)	ELISA	31
Week 4	Prospective	CD	>12	CRP≤5mg/L (w12)	ELISA	32
Week 4	Prospective	CD/UC	>3.5	Clinical response (w4)	ELISA	26
Week 4	Prospective **	CD	>22.5	PCDAI<10, CRP≤5mg/L & FC<250μg/g (w24)	ELISA	33
Week 8	Prospective **	CD	>12.5	PCDAI<10, CRP≤5mg/L & FC<250μg/g (w24)	ELISA	33
Week 12	Prospective	CD	>7.3	HBI<5 (w12)	ELISA	34
Week 14	Prospective *b*	CD	>3.7	CRP normalization (w14)	ELISA	31
Week 14	Prospective *a*	CD	≥12	Clinical remission (w14/54)	ELISA	28
Week 16	Prospective **	CD	>8.8	SES-CD=0 (w16)	ELISA	35
Week 26	DIAMOND *	CD	>5	Clinical remission (w52)	ELISA	36
Certolizumab pegol						
Week 6	9 RCTs *	CD	>31.9	CRP≤5mg/L (w6)	ELISA	37
Week 6	9 RCTs *	CD	>36.1	FC<250μg/g & CDAI≤150 (w26)	ELISA	37
Week 8	MUSIC *	CD	>23.3	Endoscopic remission (w10)	ELISA	38
Week 12	9 RCTs *	CD	>14.8	FC<250μg/g & CDAI≤150 (w26)	ELISA	37
Golimumab						
Week 2	PURSUIT *	UC	>8.9	Clinical response (w6)	ECLIA	39
Week 4	PURSUIT *	UC	>7.4	Clinical response (w6)	ECLIA	39
Week 6	PURSUIT *	UC	>2.5	Clinical response (w6)	ECLIA	39
Week 6	Prospective	UC	>10.7	MES ≤1 (w52)	ELISA	40
Week 6	Prospective *c*	UC	>3.8	SCCAI<3 & FC<250μg/g (w6)	ELISA	41
Week 28	PURSUIT *	UC	>0.9	Clinical remission (w30/54)	ECLIA	39
Week 44	PURSUIT *	UC	>1.4	Clinical remission (w30/54)	ECLIA	39
Vedolizumab						
Week 2	Prospective	CD/UC	≥23.2	Steroid-free endoscopic remission (w52)	HMSA	42
Week 6	Prospective	CD/UC	≥19.8	Steroid-free endoscopic remission (w52)	HMSA	42
Week 6	Prospective	CD/UC	>18	Mucosal healing (w52)	ELISA	44
Week 6	Prospective	CD/UC	>22	Endoscopic & clinical remission (w46)	ELISA	45
Week 6	Prospective	CD/UC	>29.9	Clinical remission (w14)	ELISA	46
Week 6	GEMINI 1 *	UC	> 37.1	Clinical response (w14)	ELISA	43
Week 14	GEMINI 1 *	UC	> 18.4	Clinical response (w14)	ELISA	43
Week 14	Prospective	CD/UC	>16.6	Drug persistence (w52)	ELISA	46

TDM time point	Study type / acronym	IBD type	Drug concentration threshold (μg/mL)	Therapeutic outcome (time point)	Assay type	Ref.
Week 22	Prospective	CD/UC	>8	Endoscopic & clinical remission (w46)	ELISA	45
Week 22	Prospective[d]	CD	>10	Endoscopic remission (w26)	ELISA	47
Ustekinumab						
Week 2	Prospective	CD	>24.7	FC<100μg/g (w8/16)	ELISA	48
Week 4	Prospective	CD	>15.9	50% decrease in FC (w8)	ELISA	49
Week 4	Prospective	CD	>13	HBI<5, CRP<5mg/L, FC<250μg/g (w16)	ELISA	50
Week 4	Prospective	CD	>23.7	SES-CD<4 without ulceration (w24)	ELISA	48
Week 8	Prospective	CD	>4.2	50% decrease in FC (w8)	ELISA	49
Week 8	Prospective	CD	>7.2	CRP≤5mg/L (w8)	ELISA	49
Week 8	Prospective	CD	>2	HBI<5, CRP<5mg/L, FC<250μg/g (w16)	ELISA	50
Week 8	Prospective	CD	>11.1	SES-CD<4 without ulceration (w24)	ELISA	48
Week 8	UNITI 1&2*	CD	>3.3	Clinical remission (w8)	ECLIA	51
Week 8	UNIFI*	UC	>3.7	Histologic improvement (w8)	ECLIA	52
Week 12	Prospective	CD	>1.1	Biological response (w26)	ELISA	53
Week 16	Prospective	CD	>2.3	Endoscopic response (w24)	ELISA	49
Week 16	Prospective	CD	>1.4	HBI<5, CRP<5mg/L, FC<250μg/g (w16)	ELISA	50
Week 24	Prospective	CD	>1.9	Endoscopic response (w24)	ELISA	49
Week 24[e]	UNITI 1&2*	CD	>0.8	Clinical remission (w24)	ECLIA	51
Week 40[f]	UNITI 1&2*	CD	>1.4	Clinical remission (w44)	ECLIA	51

*Post-hoc analysis of RCT

**Pediatric

***CT-P13

[a]PANTS: The personalised anti-TNF therapy in Crohn's disease study

[b]POETIC: Prospective Observational Evaluation of Time-Dependency of Adalimumab Immunogenicity and Drug Concentrations

[c]GO-LEVEL: Study of the Golimumab Exposure-Response Relationship Using Serum Trough Levels

[d]LOVE-CD: A Study to Evaluate Efficacy, of Early Versus Late Use of Vedolizumab in Crohn's Disease

[e]Combined q8w and q12w

[f]q8w only.

TAILORIX: A Study investigating Tailored Treatment With Infliximab for Active Crohn’s Disease; JAPIC: Clinical study to assess the efficacy and safety of TA-650 in patients with active ulcerative colitis; ACT: Active Ulcerative Colitis Trials; ACCENT-I: A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNFa Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long-term Treatment of Patients With Moderately to Severely Active Crohn’s Disease; ACCENT-II: A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNFa Chimeric Monoclonal Antibody (Infliximab; REMICADE Janssen Biotech, Inc, Malvern, PA) in the Long-term Treatment of Patients with Fistulizing Crohn’s Disease; SONIC: The Study of Biologic and Immunomodulator Naïve Patients in Crohn’s Disease; DIAMOND: Comparison of Adalimumab Monotherapy and a Combination With Azathioprine for Patients With Crohn’s Disease: A Prospective, Multicenter, Open-Labeled Clinical Trial; MUSIC: Endoscopic Mucosal Improvement in Patients with Active Crohn’s Disease Treated with Certolizumab Pegol; PURSUIT: A study to Evaluate the Safety and Efficacy of Golimumab Maintenance Therapy, Administered Subcutaneously, in Subjects With Moderately

to Severely Active Ulcerative Colitis; GEMINI: A Study of Vedolizumab (MLN0002) in Patients With Moderate to Severe Ulcerative Colitis; UNITI: A Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Crohn's Disease; UNIFI: A Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects With Moderately to Severely Active Ulcerative Colitis; IBD: inflammatory bowel disease; TDM: therapeutic drug monitoring; RCT: randomized controlled trial; CD: Crohn's disease; UC: ulcerative colitis; MES: Mayo endoscopic score; CRP: C-reactive protein, FC: fecal calprotectin; CDAI: Crohn's disease activity index; HBI: Harvey Bradshaw index; PCDAI: Pediatric Crohn's disease activity index; SES-CD: Simple Endoscopic Score-CD; SCCAI: simple clinical colitis activity index. ECLIA: electrochemiluminescent immunoassay; ELISA: enzyme-linked immunosorbent assay; HMSA: homogenous mobility shift assay; w: week; ref.: reference.

Table 2.

Association of biologic drug concentrations and clinical outcomes in other IMID.

IMID type	Study type	Threshold, μg/mL (time point)	Clinical outcome (time point)	Ref.
Infliximab				
RA	Prospective	>2.5 (week 6)	Good EULAR response (week 26)	54
RA	Retrospective	<4.4 (week 6)	Drug discontinuation (week 52)	55
RA	Retrospective	>1	DAS28≤3.2 (week 42)	56
RA	Post-hoc analysis of RCT[a]	Higher drug concentrations were associated with higher rates of clinical response and a greater reduction of CRP		57
RA	Prospective	Patients who did not respond after 14 weeks of treatment had significantly lower drug concentrations compared with responders and CRP levels were negatively correlated with drug concentrations		58
Psoriasis	Prospective	>1 (week 48)	PASI75 (week 48)	59
Psoriasis	Prospective	PASI score and PASI 90/100 response were significantly associated with trough drug concentrations		60
AS	Retrospective	Higher drug concentrations were associated with lower ASDAS-ESR/CRP scores		61
AS	RCT	No association of drug concentrations with treatment failure		62
Adalimumab				
RA	Prospective	>1.3	Good EULAR response (week 26)	63
RA	Prospective	>6.4	Persistent remission after dose-halving (week 24)	64
RA	Prospective	>5	EULAR response (week 28)	65
RA	Prospective	<5 (week 12)	No EULAR response (week 52)	66
AS	Retrospective	>6.4 >7.7 >4.6	BASDAI<4 ASDAS-ESR< 2.1 ASDAS-CRP< 2.1	67
AS	Retrospective	<3.4 (week 2) <4.3 (week 4)	Primary non-response	68
AS	Prospective	Association of drug concentrations with ASDAS		69
Psoriasis	Prospective	>7.8 (week 48)	PASI75 (week 48)	59
Psoriasis	Prospective	>3.2	PASI75	70
Psoriasis	Prospective	>3.51	ΔPASI75-100	71
Psoriasis	Retrospective	Drug concentrations at weeks 4, 12 and 24 were higher in responders than non-responders who failed to t achieve PASI50		72
Psoriasis	Prospective	There was a correlation between drug serum levels and PASI scores		73
PsA	Prospective	Patients with detectable ADA compared with patients without had lower drug concentrations and a poorer clinical outcome		74
PsA	Prospective	ADA were associated with lower drug concentrations and reduced clinical response		75
Peripheral SpA	RCT	No clear association between drug concentrations or ADA with clinical response or with relapse upon treatment discontinuation		76
Certolizumab pegol				
RA	Prospective	Higher drug concentrations were associated with better EULAR response (12 months)		77
RA, Axial SpA, PsA	RCT[b]	≥20	Treatment response (3 and 6 months)	78

IMID type	Study type	Threshold, μg/mL (time point)	Clinical outcome (time point)	Ref.
Golimumab				
RA	Prospective	EULAR responders compared with non-responders were found to have higher golimumab concentrations at week 52.		79
Ustekinumab				
Psoriasis	Retrospective	>3.6 (w4)	PASI≤2 (w4)	80
Psoriasis	Prospective	Inverse correlation between drug concentrations at week 6 and absolute PASI score		81
Psoriasis	Prospective	Early drug concentration (1-12 weeks after starting treatment) were associated with PASI75 response (6 months)		82
Etanercept				
RA	Prospective	>1.2	Good EULAR response (week 26)	63
RA	Prospective	EULAR good responders compared with EULAR moderate and non-responders had higher drug concentrations		83
AS	Prospective	Drug concentrations were higher in patients with ASDAS<2.1 compared to those with ASDAS≥ 2.1		84
Psoriasis	Retrospective	Positive correlation between drug concentration and decrease in the PASI scale with respect to the baseline value		85
Psoriasis	Prospective	Inverse correlation between drug concentration and PASI in patients <50 years old		86
Secukinumab				
PsA	RCT	>33.2	PASI≤2	87
PsA	RCT	Patients with low drug concentrations were at higher risk of radiographic progression		88
Ixekizumab				
Psoriasis	RCT	Steady-state drug trough concentrations were associated with high clinical responses at week 12		89
Psoriasis	Post-hoc analysis of 3 RCTs	Higher drug concentrations were associated with higher response levels based on static physician global assessment and PASI		90
Tocilizumab				
RA	Prospective	Association between drug concentrations and ΔDAS28		91

[a] ATTRACT: Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy

[b] NOR-DMARD: Norwegian-biologic disease-modifying antirheumatic drug.

IMID: immune mediated inflammatory diseases; RA: rheumatoid arthritis; EULAR: European league against rheumatism; PsA: psoriatic arthritis; AS: Ankylosing Spondylitis; RCT: randomized controlled trial; Δ: delta; PASI: Psoriasis area and severity index; DAS: disease activity score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; ASDAS: Ankylosing Spondylitis Disease Activity Score- ESR Erythrocyte Sedimentation Rate; CRP: C-reactive protein; SpA: spondyloarthritis; ADA: anti-drug antibodies; Ref.: reference.

Table 3.

Randomized controlled trials regarding the role of therapeutic drug monitoring in IBD.

RCT acronym	IBD type	Study arms	Primary end point	Major limitations
Infliximab				
N/A[97]	CD	Reactive TDM *vs.* empiric dose optimization	Cost-effectiveness and CDAI response after 12 weeks	- IFX TC to target of 0.5 μg/mL
TAXIT[9]	CD / UC	Proactive TDM *vs.* clinically based dose optimization	Clinical and biochemical remission at one year after optimization phase	- All patients were optimized based on IFX TC, prior to randomization that may eliminated the opportunity for proactive TDM to prove its benefit - IFX TC to target 3-7 μg/mL - Only one year follow up
TAILORIX[98]	CD	Dose optimization based on clinical symptoms and biomarkers and/or proactive TDM *vs.* dose optimization based on clinical symptoms alone	Sustained CS-free clinical remission from weeks 22 to 54 with no ulcers at week 54	- IFX TC to target of 3 μg/mL - IFX dose in the 'TDM' arms could be escalated based also on symptoms and biomarkers - IFX dose in the 'control' group could be escalated based only on clinical symptoms and as a result a high number of dose optimizations were driven by nonspecific symptoms as demonstrated by normal drug and biomarker levels in these patients - IFX concentrations were similar in all 3 groups which likely accounted for the similar efficacy outcomes - Sustained IFX TC of >3μg/mL in <50% in the 'TDM' arms
PRECISION[99]	CD / UC	Proactive TDM based on PK dashboard driven dosing *vs.* standard dosing	Sustained clinical remission after 1 year	- IFX TC to target ≥ 3 μg/mL - No dosing adaptations were allowed in the control group - Lack of endoscopic outcomes
Adalimumab				
PAILOT[10]	CD*	Proactive *vs.* reactive TDM	Sustained CS-free clinical remission from weeks 8 to 72	- ADM TC to target ≥ 5 μg/mL - Lack of endoscopic endpoints - Rather small sample size

*Pediatric.

TAXIT: Trough Concentration Adapted Infliximab Treatment; TAILORIX: A Study investigating Tailored Treatment With Infliximab for Active Crohn's Disease; PRECISION: Precision Dosing of Infliximab Versus Conventional Dosing of Infliximab; PAILOT: Pediatric Crohn's Disease Adalimumab Level-based Optimization Treatment; RCT: randomized controlled trial; IBD: inflammatory bowel disease; N/A: not applicable; CD: Crohn's disease; UC: ulcerative colitis; CS: corticosteroids; TDM: therapeutic drug monitoring; TC: trough concentration; PK: pharmacokinetic; CDAI: Crohn's disease activity index; IFX: infliximab; ADM: adalimumab.

Table 4.

Association of anti-TNF drug concentrations with post-operative recurrence in patients undergoing an ileocolonic resection for CD.

Biologic drug	Study type	Association of anti-TNF drug concentrations with POR in patients undergoing an ileocolonic resection for CD	Ref.
IFX / ADM	Prospective	- Drug TC > 1μg/mL and > 3 μg/mL were not associated to increased rates of early (30-day) postoperative complications.	104
IFX	RCT[a]	- Inverse correlation between IFX concentrations at week 72 and POR rates at week 76.	105
ADM	Prospective	- Lower ADM concentration in patients with normal mucosa (Rutgeerts' score ≤i1) compared to those with endoscopic POR (Rutgeerts' score ≥i2) (7.95 μg/mL vs. 3.25μg/mL; p=0.048). - ADM concentration was inversely correlated to the Rutgeerts' score. - Patients with ADM concentrations <4.2 μg/mL compared to those with concentrations ≥4.2 μg/mL had higher POR (86% vs. 15%; p=0.025).	106
ADM	Post-hoc analysis of RCT[b]	- ADM concentration did not statistically significant differ between patients in endoscopic remission vs. endoscopic POR defined as a Rutgeert's score ≥i2.	107
ADM	Post-hoc analysis of RCT	- In patients with clinical or endoscopic POR ADM TC were lower than in those who maintained remission both at baseline (9.5 vs. 14.4 μg/mL; p<0.01) and during follow-up (7.5 vs. 13.9 μg/mL; p<0.01).	108

[a]PREVENT: Prospective, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial Comparing REMICADE® [infliximab] and Placebo in the Prevention of Recurrence in Crohn's Disease Patients Undergoing Surgical Resection Who Are at an Increased Risk of Recurrence

[b]POCER: Postoperative Crohn's Endoscopic Recurrence.

IBD: inflammatory bowel disease; Ref.: reference; CD: Crohn's disease; UC: ulcerative colitis; CRP: C-reactive protein, FC: fecal calprotectin; HBI: Harvey Bradshaw index; TC: trough concentrations; IFX: infliximab; ADM: adalimumab; POR: post-operative recurrence; RCT: randomized controlled trial.