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Challenges in Therapeutic Drug Monitoring: Optimizing Biological Treatments in Patients With Inflammatory Bowel Disease and Other Immune-Mediated Inflammatory Diseases

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Background: Therapeutic drug monitoring (TDM) is a decision-making tool for optimizing the use of certain therapies. In this article, the authors review the role of proactive TDM of biological agents in patients with inflammatory bowel disease (IBD) and other immune-mediated inflammatory diseases (IMID). They also discuss the future of TDM as a component of personalized medicine from the clinical laboratory perspective.

Methods: This narrative review originated from proceedings of the fifth biannual *Challenges in Therapeutic Drug Monitoring* seminar and was supplemented by additional literature identified at various stages of critical review.

Results: Proactive TDM aims to achieve adequate concentrations of biological drugs, such that patients attain and maintain an optimal treatment response. Proactive TDM may also have a role in de-escalating anti–tumor necrosis factor therapy in patients in clinical remission and in optimizing infliximab monotherapy as an alternative to combination therapy with an immunomodulator. A major proactive TDM application is in pediatric patients with IBD. Achieving mucosal healing in children with IBD requires that infliximab or adalimumab concentrations are monitored early during induction therapy, with dose modifications guided by the timing (week) of measurement. Recent innovations in biological therapy include international standards for infliximab and adalimumab for the global harmonization of bioactivity and monotest devices with an accuracy equivalent to that of conventional enzyme-linked immunosorbent assays and quicker turnaround times.

Conclusions: Despite several knowledge gaps regarding proactive TDM of anti–tumor necrosis factor therapy in patients with IMID, growing evidence suggests that it is associated with better outcomes than empiric optimization and/or reactive TDM in IBD. Enhanced pharmacokinetic modeling to predict drug exposure and patient genotyping for the precise application of proactive TDM are considered key elements to optimize biological therapy in the future.

Key Words: therapeutic drug monitoring, biologicals, immune-mediated inflammatory diseases, pediatric inflammatory bowel disease, biobetters

(*Ther Drug Monit* 2023;45:579–590)

INTRODUCTION

Therapeutic drug monitoring (TDM) is a clinical decision-making tool that aims to optimize the use of biological therapies and provide personalized medicine to patients with inflammatory bowel disease (IBD) and other chronic immune-mediated inflammatory diseases (IMID). TDM of biological drugs is paramount given the high interindividual and intraindividual variability in serum concentrations at both the patient and population levels.[1]

Reactive TDM is defined as the measurement of biological drug concentrations and antidrug antibody levels in the setting of primary nonresponse (lack of response since the start of therapy), secondary loss of response (disease flare after initial response), or an infusion reaction.[2] Proactive TDM is defined as the scheduled measurement of drug

Received for publication November 17, 2022; accepted February 23, 2023.

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Conflicts of Interest: Konstantinos Papamichael has received lecturer/speaker fees from Grifols and Physicians Education Resource LLC, scientific advisory board fees from ProciseDx Inc and Scipher Medicine Corporation, and is a consultant for Prometheus Laboratories Inc. Gabriele Stocco has received lecturer fees from Grifols. Ainhoa Ruiz del Agua is a full-time employee of Progenika Biopharma Grifols.

Author contributions: Conceptualization, K.P., G.S., and A.R.A.; methodology, K.P., G.S., and A.R.A.; software, K.P., G.S., and A.R.A.; validation, K.P., G.S., and A.R.A.; formal analysis, K.P., G.S., and A.R.A.; investigation, K.P., G.S., and A.R.A.; resources, K.P., G.S., and A.R.A.; data curation, K.P., G.S., and A.R.A.; writing—original draft preparation, K.P., G.S., and A.R.A.; writing—review and editing, K.P., G.S., and A.R.A.; visualization, K.P., G.S., and A.R.A.; supervision, K.P., G.S., and A.R.A.; project administration, K.P., G.S., and A.R.A.; and funding acquisition, K.P. and G.S. All authors have read and agreed to the published version of the manuscript.

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concentrations and antidrug antibody levels to achieve an adequate concentration threshold such that patients attain and maintain an optimal response to the biological treatment.[2]

Although reactive TDM has become the standard of care for optimizing biological therapies in IBD, recent data demonstrate the benefits and important role of proactive TDM in patient management.[3] Maintaining the concentration of biological agents within a therapeutic window according to the timing of measurement aims to prevent relapse and reduce the risk of complications.[4]

This narrative review originated from proceedings of the fifth biannual *Challenges in Therapeutic Drug Monitoring* seminar in which recent evidence regarding the role of proactive TDM of biological agents in patients with Crohn's disease (CD), ulcerative colitis (UC), and other IMID was presented and interpreted. Special focus was placed on the application of proactive TDM in pediatric IBD. Also explored was the future of TDM as a major component of personalized medicine from the perspective of the clinical laboratory. Throughout the development of this manuscript, the source material selected by the authors was supplemented with additional literature known to the authors or identified by critical reviewers.

NEW INSIGHTS FOR PROACTIVE TDM OF BIOLOGICALS

Proactive TDM for Optimizing Biologicals in IBD and Other IMID

Numerous exposure–outcome relationship studies have shown that higher concentrations of anti–tumor necrosis factor (anti-TNF) biological agents are associated with higher rates of favorable therapeutic outcomes in IBD[5] and other IMID,[6] most of which refer to infliximab and adalimumab. In parallel, there is cumulative evidence to indicate that proactive TDM of anti-TNF therapy is associated with better outcomes than reactive TDM or empirical dose optimization in patients with IBD.[7–23] A recent systematic review and meta-analysis showed that proactive TDM of anti-TNF therapy compared with standard of care was associated with reduced treatment failure and surgical rates as well as improved endoscopic remission and response.[9] The same meta-analysis demonstrated that proactive compared with reactive TDM of anti-TNF therapy was related to less hospitalization and treatment failure.[9]

Currently, there are 6 published randomized controlled trials (RCTs) of proactive TDM of infliximab[17–19] or adalimumab[20–22] in IBD, although the SERENE (Study of a Novel Approach to Induction and Maintenance Dosing with Adalimumab) trials in CD[21] and UC[22] were not powered to confirm the role of proactive TDM of adalimumab in IBD. Two of the RCTs met their primary outcome.[19,20] Pharmacokinetic (PK)-driven dashboard dosing of infliximab was associated with a higher proportion of patients with IBD in sustained clinical remission after 1 year compared with standard dosing.[19] Proactive TDM of adalimumab was associated with a higher proportion of pediatric patients with IBD with sustained corticosteroid-free clinical remission rate at all visits (week 8 through week 72) compared with reactive TDM.[20] A major limitation of all 6 RCTs was the relatively low targeted trough concentrations of anti-TNF therapy (3 μg/mL for infliximab; 5 μg/mL for adalimumab).[5] Notwithstanding, in 3 of the studies, proactive TDM provided a significant benefit over standard dosing for secondary outcomes including stringent composite end points.[17,19,20]

The Norwegian Drug Monitoring (NOR-DRUM) RCT enrolled patients with a range of IMIDs (CD, UC, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and psoriasis) who were starting treatment (part A) or receiving maintenance therapy (part B) with infliximab.[23] In both parts A and B, patients were randomized 1:1 to receive either proactive TDM with dose and interval adjustments based on scheduled monitoring of serum drug levels and antidrug antibodies (TDM group) or standard infliximab therapy without drug and antibody level monitoring (standard therapy group). In part A (infliximab induction therapy), no statistically significant difference in 30-week remission rates was observed between proactive TDM and standard therapy, possibly (as suggested by the investigators) because the benefits of TDM were diminished by high drug exposure during induction therapy.[24] Nonetheless, it is suggested that patients at high risk of developing antidrug antibodies may benefit from proactive TDM during induction therapy.[25] Timing may also have influenced the results; because infliximab dose adjustments were not permitted before week 14 of induction therapy, there was limited time (16 weeks) in which to detect a difference in remission rates between proactive TDM and standard therapy.[26] In part B of the NOR-DRUM study (infliximab maintenance therapy), patients receiving proactive TDM had a lower probability of disease worsening at 52 weeks compared with the standard therapy group (hazard ratio [HR] 2.1; 95% confidence interval [CI] 1.5−2.9; Fig. 1).[27]

Several medical societies and TDM expert groups recommend proactive TDM of anti-TNF therapy in IBD,[28–33] although the American Gastroenterology Association and the European Crohn's and Colitis Organisation regard existing RCT evidence as insufficient to support the routine use of proactive TDM in clinical practice (Table 1).[34,35] Two RCTs of proactive TDM are currently in progress. The OPTIMIZE (Proactive infliximab optimization using a pharmacokinetic dashboard versus standard of care in patients with Crohn's disease) study is comparing proactive TDM combined PK dashboard-driven infliximab dosing with standard-of-care dosing in patients with CD.[36,37] The PROACTIVE (Prospective randomized controlled trial of adults with perianal fistulizing Crohn's disease and optimized therapeutic infliximab levels) study is investigating whether optimizing infliximab dosing to higher trough levels using proactive TDM will improve outcomes compared with standard therapy in patients with perianal fistulizing CD.[38] In both RCTs, proactive TDM is initiated early during induction therapy.

Proactive TDM algorithms are available to guide management strategies for patients with IBD during infliximab maintenance therapy. According to a suggested algorithm adapted from Papamichael and Cheifetz,[39] patients with supratherapeutic infliximab concentrations (>10−15 μg/mL)

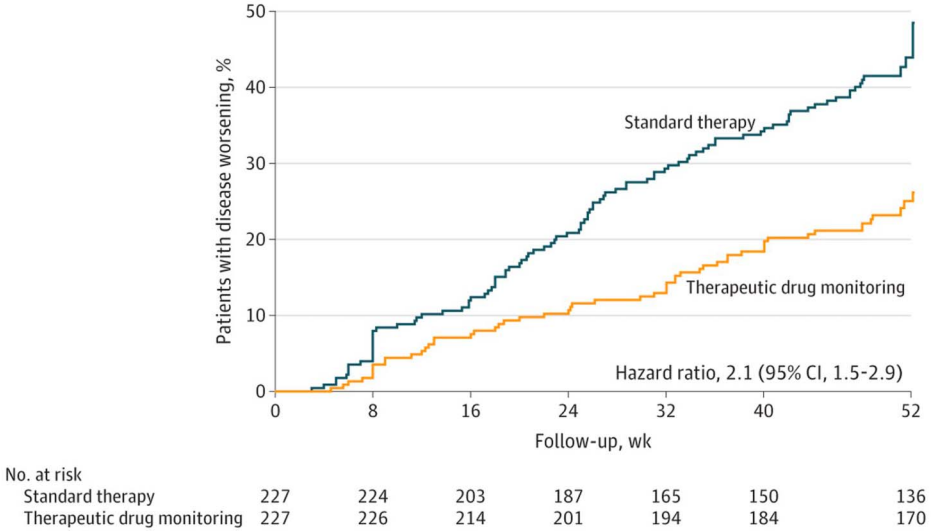

FIGURE 1. Time to disease worsening in the standard therapy group and therapeutic drug monitoring group of the NOR-DRUM B study. Reproduced with permission from Syversen et al.[27]

are candidates for treatment de-escalation. Patients with therapeutic infliximab concentrations (5−10 μg/mL) can continue with the same regimen. Patients with undetectable or low infliximab concentrations (<5 μg/mL) are further categorized according to their antibodies to infliximab (ATI) level. Those with an undetectable or low ATI titer (<8 μg/mL evaluated by enzyme-linked immunosorbent assay [ELISA] or <10 U/mL evaluated by homogeneous mobility shift assay) should undergo infliximab optimization by adding an immunomodulator (IMM) or by shortening the dosing interval and/or increasing the dose. Those with a high ATI titer should discontinue infliximab and switch within the drug class using either combination therapy with an IMM or monotherapy with proactive TDM or, alternatively, change outside the drug class. This latter approach is supported by recent evidence suggesting that patients with immunogenicity to previous anti-TNF therapy are more prone to developing antidrug antibodies against a subsequent anti-TNF agent.[40,41]

Proactive TDM During and Early After Induction Therapy in IBD

Higher concentrations of biological agents during and early after induction therapy have been shown to be associated with higher rates of favorable therapeutic outcomes in IBD.[42] In addition to improving clinical outcomes and patients' quality of life, proactive TDM during induction therapy may provide a range of pharmacoeconomic and PK benefits (Fig. 2).[42] The utility of early proactive TDM application was shown in a real-world prospective study in which a PK dashboard model was used to guide infliximab dosing during induction therapy in patients with IBD.[43] Adaptive Bayesian dashboard systems incorporate the previously measured drug concentration and several patient-related factors (eg, body weight, C-reactive protein, and albumin) to inform a subsequent dose.[44] Applying this model, the need for accelerated infliximab dosing at the third infusion to achieve a predefined therapeutic threshold (10 μg/mL) at the fourth infusion was forecast in 80% of patients who began treatment at a 5-mg/kg dose and in about 60% of those who began treatment at a 10-mg/kg dose.[43] Adherence to dashboard-driven forecasts for the third, and especially the fourth, infliximab infusion was associated with greater treatment durability and less immunogenicity.[43] Several studies have assessed PK modeling for anti-TNF agents to treat patients with IBD.[45]

Potential Applications of Proactive TDM

The key applications of proactive TDM of anti-TNF therapy in IBD include guiding treatment de-escalation and optimizing infliximab monotherapy.[39]

De-Escalation of ANTI-TNF Therapy

Preliminary data suggest that proactive TDM can efficiently guide anti-TNF therapy de-escalation in patients with IBD. French investigators showed that TDM-based de-escalation in patients with clinical remission and infliximab trough concentrations above 7 μg/mL significantly improved the cumulative probability of being relapse-free compared with de-escalation based on clinical remission alone (HR 0.45; $P = 0.024$).[46] The probability of sustained remission was found to be greater in patients with infliximab trough concentrations ≥2.4 μg/mL (versus <2.4 μg/mL) at the time of de-escalation.[47] The feasibility of de-escalating anti-TNF therapy based on proactive TDM has been demonstrated in several other studies, including RCTs,[8,17,19,20] with de-escalation rates of 13%–50% suggesting potential for lowering treatment costs. Proactive TDM can also guide the withdrawal of an IMM in patients with IBD in remission receiving anti-TNF combination therapy.[48,49]

Optimized Infliximab Monotherapy

Retrospective studies have suggested that optimized infliximab monotherapy using proactive TDM-guided dose escalations is as effective as combination therapy as regards clinical outcomes[50] and treatment durability in adult and pediatric patients with IBD.[50,51] This is relevant clinically because

TABLE 1. Recommendations of Medical Societies and Expert Groups Regarding Proactive TDM of Biological Therapy in IBD

Medical Society or Expert Group	Methodology	Year [Reference]	Recommendations
Australian IBD Group	Modified Delphi	2017 [Mitrev 2017][28]	•In patients in clinical remission after 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.
American Gastroenterological Association	GRADE	2017 [Feuerstein 2017][34]	•In adult patients with quiescent IBD treated with anti-TNF agents, no recommendation is made regarding the use of routine proactive TDM (knowledge gap).
British Society of Gastroenterology	GRADE	2019 [Lamb 2019][29]	•All patients with IBD 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 antidrug antibody concentrations, blood inflammatory markers, fecal biomarkers, or endoscopy (good practice recommendation).
Building Research in IBD Globally (BRIDGe) Group	Modified Delphi	2019 [Papamichael 2019][30]	•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.
European Crohn's and Colitis Organisation	GRADE	2020 [Torres 2020][35]	•In patients with CD 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 with routine care (weak recommendation, moderate quality evidence).
European Crohn's and Colitis Organisation–European Society of Pediatric Gastroenterology, Hepatology, and Nutrition	GRADE	2021 [Van Rheenen 2021][31]	•In patients on anti-TNF agents, early proactive TDM followed by dose optimization is recommended (level of evidence: 2; agreement: 87.5%).
IBD TDM Expert Group	Modified Delphi	2021 [Cheifetz 2021][32]	•Proactive TDM should be performed after induction for patients treated with anti-TNF therapy (agreement: 90%; strength of recommendation: 9). •Proactive TDM should be performed at least once during maintenance therapy for patients treated with anti-TNF therapy (agreement: 90%; strength of recommendation: 8.8). •Proactive TDM should be used after reactive TDM of anti-TNF therapy (agreement: 80%; strength of recommendation: 8.1). •More data are needed to support the use of proactive TDM for biologics other than anti-TNF therapies (agreement: 100%; strength of recommendation: 9.2).
Emirates Society of Gastroenterology and Hepatology	Delphi	2021 [Annese 2021][33]	•TDM should be recommended at the end of induction in responders to predict final outcome (agreement: 100%). •TDM should be performed at least once in responders during maintenance therapy or when the results will alter treatment decisions (agreement: 100%). •Proactive TDM is desirable during maintenance phase to predict loss of response (agreement: 90%).

CD, Crohn's disease; IBD, inflammatory bowel disease; TDM, therapeutic drug monitoring; TNF, tumor necrosis factor.

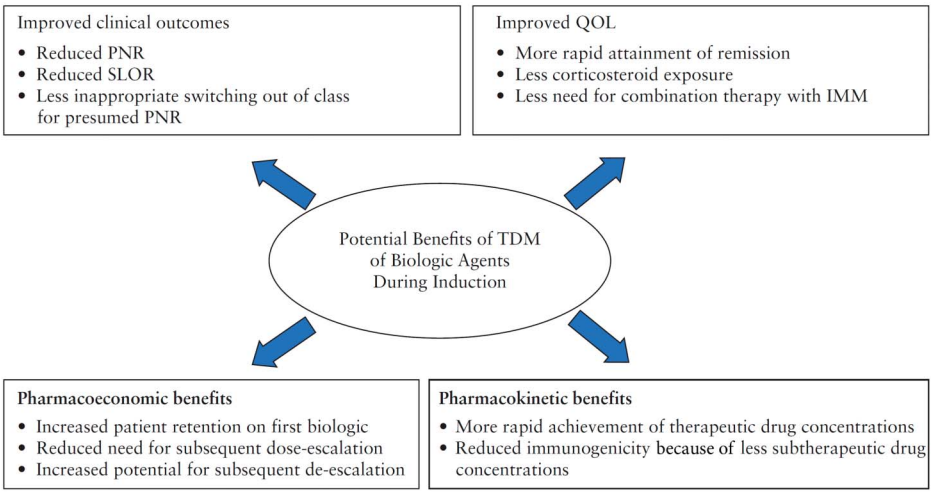

FIGURE 2. Potential benefits of proactive therapeutic drug monitoring (TDM) of anti–tumor necrosis factor (TNF) agents during induction therapy. Reproduced with permission from Sparrow et al.[42] IMM = immunomodulators; PNR = primary nonresponse; QOL = quality of life; SLOR = secondary loss of response.

combination therapy may be associated with an increased risk of infection and malignancy.[52]

A post hoc analysis of the Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) showed that mucosal healing rates at week 26 were comparable between patients receiving infliximab monotherapy or combination therapy (infliximab + azathioprine) within quartiles of infliximab serum concentrations,[53] although this finding must be confirmed in prospective RCTs. The concept of optimized infliximab monotherapy as an alternative to combination therapy was further supported by a large retrospective study showing that thiopurines have a limited impact on ATI formation in the presence of elevated infliximab concentrations (>5 μg/mL).[54]

Recently, it was reported that optimized infliximab monotherapy based on proactive TDM prevented ATI formation and drug discontinuation in patients with IBD regardless of their HLA-DQA1*05 allele carrier status.[55] Again, this is clinically relevant because HLA-DQA1*05 carriage has been associated with lower maintenance-phase infliximab concentrations,[56] as well as the development of ATI and antibodies to adalimumab,[57,58] in patients with IBD.

Cost-Effectiveness of Proactive TDM

Until recently, data on the cost-effectiveness of proactive TDM in IBD were limited and largely inferred based on the putative benefits associated with superior disease control. A Spanish group undertook a systematic review of cost-effectiveness analyses of studies that applied TDM of anti-TNFs in IBD.[59] Of 13 studies identified for inclusion (12 of infliximab), 4 modeling studies,[60–63] 1 prospective observational study,[64] 1 retrospective observational study,[65] 1 nonrandomized clinical trial,[66] and 1 RCT[17] reported economic outcomes for proactive TDM. Overall, the incremental cost-effectiveness ratio for proactive TDM versus an empirical strategy ranged from €57,000 to €3.9 million, indicating cost-effectiveness. However, the analysis was limited by the considerable clinical and methodological heterogeneity among the studies.[59]

Knowledge Gaps Regarding the Utilization of Proactive TDM of Biologicals

Despite growing evidence supporting proactive TDM of biologicals in IMID, several knowledge gaps remain.

Optimal target concentrations of biologicals have yet to be established as these may depend on several aspects of treatment: timing of measurement (induction/maintenance); route of drug administration[67,68]; desired therapeutic outcome[30,69]; type of assay[70,71]; and patient phenotype.[72] Numerous data from prospective studies and post hoc analyses of RCTs suggest a link between higher biological drug concentrations and the achievement of increasingly stringent therapeutic outcomes.[5,30,32] Cheifetz et al[32] have suggested therapeutic windows for biologicals during maintenance therapy of 5−10 μg/mL for infliximab, 8–12 μg/mL for adalimumab, 13–15 μg/mL for certolizumab pegol, 1–3 μg/mL for golimumab, 10–15 μg/mL for vedolizumab, and 1–3 μg/mL for ustekinumab. Although useful as a general guide, until confirmed in prospective RCTs, these concentration ranges should be regarded solely as reference points. As practice varies, it may be necessary for IBD centers to establish their own optimal therapeutic ranges for biologicals based on individual circumstances (eg, cohort population and type of assay).

The role of proactive TDM in guiding treatment with non–anti-TNF biologicals should be better defined. Although higher vedolizumab and ustekinumab concentrations have been associated with higher rates of favorable therapeutic outcomes in IBD,[5] direct comparisons between proactive and reactive TDM, or between proactive TDM and standard of therapy for non–anti-TNF biologicals, are lacking.

Another uncertainty relates to the role of intermediate (between trough) and peak drug concentrations in proactive TDM. Higher infliximab concentrations early in treatment (at 4, 8, and 10 weeks) were associated with higher rates of favorable therapeutic outcomes, including endoscopic remission and drug retention in IBD.[73] An exposure–response relationship was recently reported between higher peak ustekinumab concentrations measured during the first 2 weeks of treatment and the achievement of robust end points including

endoscopic remission at 6 months in patients with CD.[74] However, data are limited, and the concentration thresholds reported in these studies must be verified in prospective RCTs.

By avoiding the time lag associated with conventional clinical laboratory processing of serum samples, point-of-care testing can facilitate prompt ad hoc dose adjustment. However, a recent pragmatic study that compared "ultra-proactive" TDM (center A) with reactive TDM (center B) in patients with IBD receiving maintenance therapy found no differences between cohorts in infliximab failure rates (19% versus 10%; $P = 0.08$) or clinical remission rates (75% versus 83%; $P = 0.17$) after 1 year of follow-up.[75] The apparent lack of benefit of ultraproactive TDM might be explained by certain methodological features of the study. The outcomes were compared between cohorts from 2 different hospitals, introducing a potential bias. Target infliximab trough serum concentrations of 3–7 μg/mL during the optimization and maintenance phases may have been insufficient in some patients. In addition, the 1-year follow-up period may have been insufficient to detect statistical differences between the treatment arms. The potential benefits of ultraproactive TDM merit further study in well-designed comparative RCTs.

TDM OF BIOLOGICAL THERAPY IN PEDIATRIC PATIENTS WITH IBD

An important application of proactive TDM is childhood-onset IBD, which, relative to later-onset IBD, is characterized by more extensive intestinal involvement and rapid clinical progression.[76,77] Early and effective therapy is critical to avoid compromising a child's development, growth, and maturation. Many children with IBD require aggressive anti-TNF therapy on diagnosis.

Proactive TDM in Pediatric IBD

There are several compelling reasons for using proactive TDM in pediatric patients with IBD. Administering an anti-TNF agent at doses insufficient to maintain a minimum therapeutic concentration throughout the dosing interval can result in many days of nonoptimal exposure, increasing the risk of antidrug antibody formation and the consequent loss of response. This is particularly relevant with infliximab maintenance therapy because of the 2-monthly dosing interval.[78] The high interindividual variability in anti-TNF concentrations observed in children is likely due to factors influencing drug clearance, such as demographics, disease variables, and immunogenicity.[79] Young children (<10 years) in particular tend to have rapid infliximab clearance and require intensified treatment regimens to achieve therapeutic concentrations.[80] Although overexposure to anti-TNF agents is not a safety concern, it can waste resources. Proactive TDM can rationalize the use of anti-TNF agents in pediatric IBD and permit treatment de-escalation in suitable patients.[81,82]

In the pediatric Crohn's disease adalimumab level–based optimization treatment (PAILOT) RCT, proactive versus reactive TDM of adalimumab was associated with a significantly higher rate of corticosteroid-free clinical remission (82% versus 48%; $P = 0.002$).[20] Elsewhere, proactive TDM was associated with a significant reduction in the number of children requiring a switch of their primary biological and with superior clinical outcomes including a higher rate of steroid-free clinical remission at 1.5-year follow-up and fewer IBD-related surgeries.[16] The correlation between anti-TNF drug concentrations and therapeutic response in patients with IBD supports the use of proactive TDM for prognostic purposes. In children with IBD, infliximab trough concentrations at week 14 (fourth infusion) were associated with persistent remission status at week 54.[83] Another group showed that infliximab concentrations at week 14 in pediatric patients with IBD predicted efficacy at 1 year, with an association evident as early as 6 weeks (third infusion) of induction therapy.[84] Adalimumab concentrations measured at the end of induction therapy (4 weeks) and during routine clinic visits, not necessarily at the trough level, have also been shown to correlate with long-term response in children with IBD.[85]

To achieve mucosal healing in pediatric luminal CD, the European Crohn's and Colitis Organisation–European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ECCO-ESPGHAN) guidelines recommend that infliximab concentrations be measured before the fourth infusion (14 weeks) and that dose modifications be considered if the concentration is below 5 μg/mL. At-risk patients should have their infliximab concentrations measured at the second or third infusion to target a trough concentration of ≥25 μg/mL at week 2 and ≥15 μg/mL at week 6. Adalimumab concentrations should be measured at weeks 4 and 8 of therapy aiming for a concentration above ≥7.5 μg/mL (Fig. 3).[31]

TDM Algorithm for Pediatric Patients With Active CD

The ECCO-ESPGHAN consensus paper on personalized therapy includes a TDM algorithm for pediatric patients with active CD despite anti-TNF therapy.[31] According to this treatment plan, if the anti-TNF concentration is in range and the patient is not responding (pharmacodynamic failure), the patient should be switched to an out-of-class biological. If the anti-TNF concentration is low, the recommendation is to check for antidrug antibodies and, if present, measure the titer. High-titer antidrug antibodies indicate the need to switch drug, for example, from infliximab to adalimumab. In the case of low-titer antidrug antibodies, options are to escalate the dose of anti-TNF and/or add an IMM. In the absence of antidrug antibodies (PK failure), drug escalation is recommended. Despite the relatively straightforward nature of these therapeutic pathways, there is a lack of agreement regarding what constitutes a low or high titer of antidrug antibodies, and no World Health Organization (WHO) international standards are available to quantify antidrug antibodies.

Measuring Anti-TNF Drug Concentrations and Antidrug Antibodies in Pediatric IBD

Several assays are available to measure anti-TNF concentrations and antidrug antibodies in pediatric IBD (Fig. 4).[86] The most common is the ELISA, although it is best suited for high-throughput settings owing to its multiwell plates. Lateral flow is a point-of-care assay for single-patient analysis that has shown good agreement with traditional

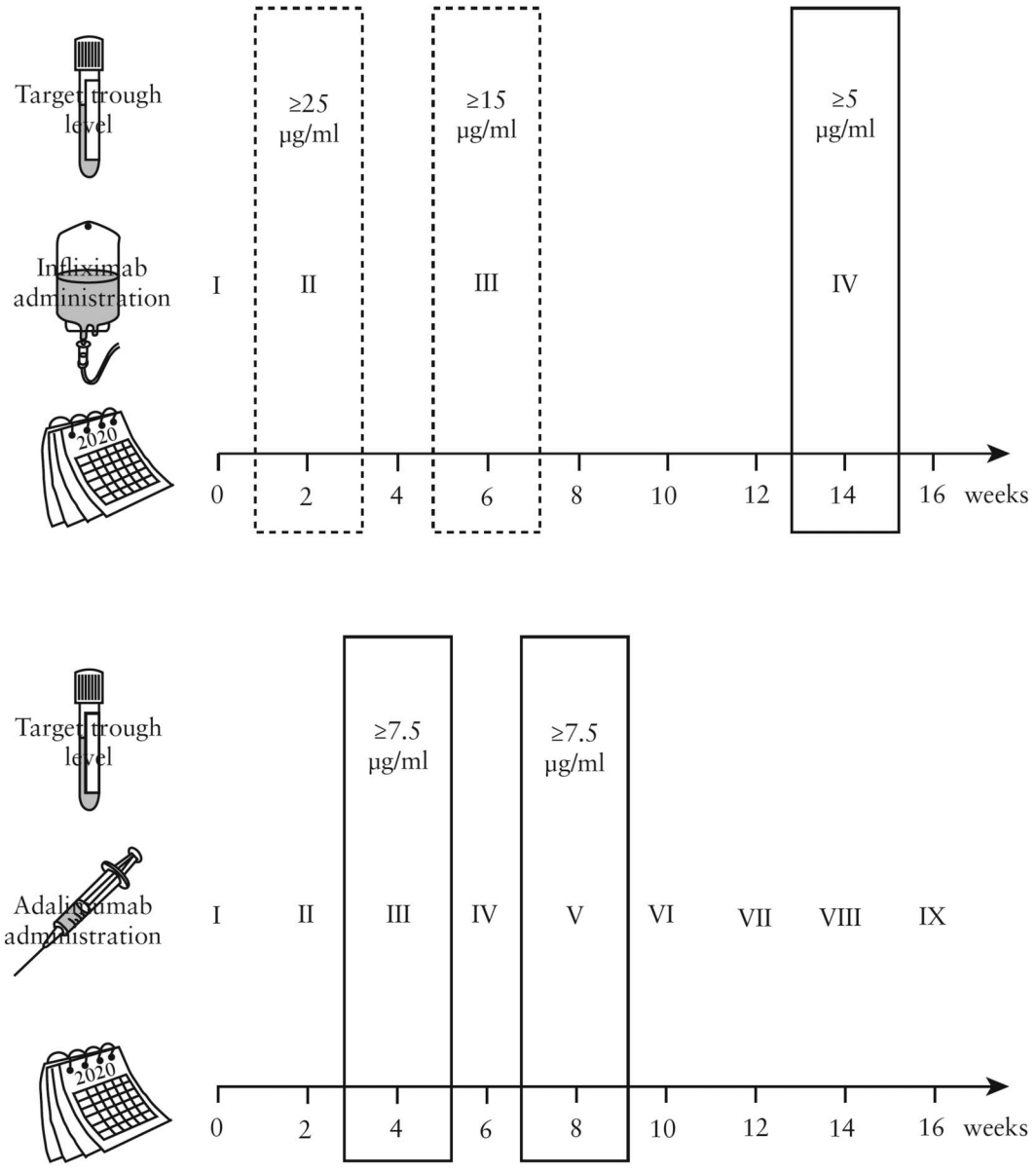

FIGURE 3. Target trough levels of infliximab and adalimumab to achieve mucosal healing in pediatric luminal Crohn's disease. Reproduced with permission from van Rheenen et al.[31]

ELISAs for the quantification of infliximab.[87] Other assays are comparatively labor-intensive and require dedicated instrumentation, which may be difficult for most laboratories to implement. Recently, atomic force microscopy–based nanoassays have been proposed to measure drug concentrations in the serum samples of patients treated with anti-TNF agents. This assay evaluates the variation in the height signal of a nanostructured gold surface covered with a self-assembled monolayer of alkanethiols. DNA conjugated with TNF, which can bind to anti-TNF agents, is embedded inside this monolayer. In a proof-of-concept study, a significant association between height variation and anti-TNF concentration was reported.[88] A potential application of this technique would be to also embed various proteins in the testing surface (eg, infliximab or a portion of the drug) to enable the detection of antidrug antibodies in a single run for a specific sample.

Genetic Variation May Influence Response to Anti-TNF Therapy in Pediatric IBD

The high interpatient variability in response to anti-TNF therapy may have a genetic component. Several studies have investigated gene variants encoding proteins involved in immune processes, inflammation, autophagy, and apoptosis.[89] Confirming an association between genetic variants and treatment response as well as drug PK properties would provide useful markers for genotyping before the start of anti-TNF therapy and enable the identification of patients more likely to respond to treatment.[45]

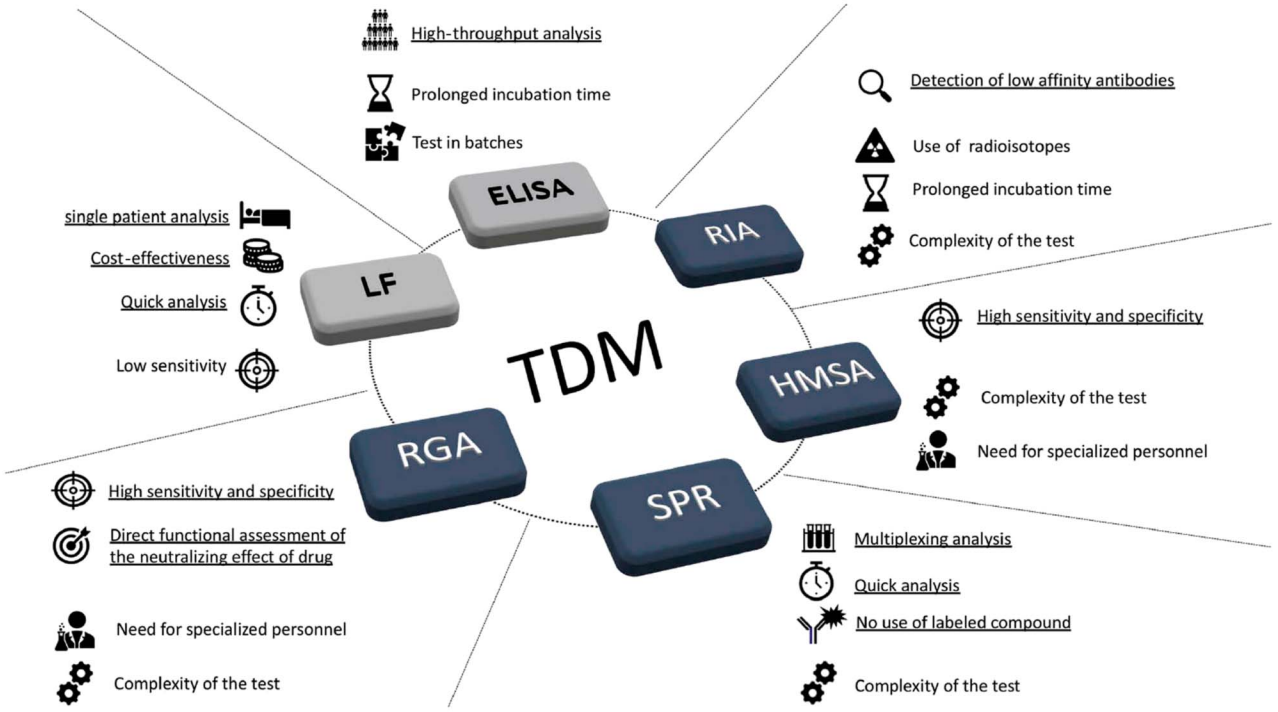

FIGURE 4. Schematic representation of methods used for therapeutic drug monitoring. Reproduced with permission from Franca et al.[86] ELISA = enzyme-linked immunosorbent assay; LF = lateral flow: RGA = reporter gene assay; SPR = surface plasmon resonance; HMSA = homogenous mobility shift assay; RIA = radioimmunoassay; TDM = therapeutic drug monitoring.

A genetic variant of particular interest is the coding nonsynonymous variant rs396991, commonly referred to by its protein alleles Phe158Val,[90] in the *FCGR3A* gene. The *FCGR3A* gene encodes a receptor for the Fc portion of immunoglobulin G and is involved in the removal of antigen–antibody complexes from the circulation, as well as other effects including antibody-dependent cellular-mediated cytotoxicity.[91] In an Italian cohort of 76 pediatric patients with IBD, those with variant *FCGR3A* showed inferior clinical responses at the end of induction, at 22 weeks, and at 52 weeks of infliximab therapy. A significant association between variant *FCGR3A* and lower median infliximab concentrations during maintenance therapy was also observed. Furthermore, patients with the variant allele had a higher production rate of antidrug antibodies.[92]

THE FUTURE OF TDM INVOLVES CONSTANTLY ADAPTING TO IMPROVEMENTS IN BIOLOGICALS

Monoclonal antibodies (mAbs) have advanced considerably since they were first used to treat patients with IBD and other IMID. The evolution from murine to human sequences has lowered their immunogenicity and improved their efficacy and efficiency. Subcutaneous formulations permit at-home use, substantially reducing drug delivery costs and health resource utilization compared with intravenous formulations.[93] Biosimilars have brought further cost savings to health systems and broadened patient access to treatment. The most recent innovation, biobetters, offers improved adaptations of the originator biological, that is, biosimilars with value-added features, such as subcutaneous administration and/or high-concentration citrate-free formulations.

Interchangeability Between Reference Biologicals and Their Biosimilars

The concept of biosimilars refers to the exchange of one medicine with another that is expected to have the same clinical effect. In the case of biologicals, this involves replacing a reference drug with a biosimilar (and vice versa) or a biosimilar with another biosimilar. Initial concerns about interchangeability were resolved by studies showing no differences in clinical outcomes between patients maintained on a reference biological (infliximab or adalimumab) and those transitioned to the respective biosimilars.[94–98] A recent large systematic review (178 studies, >21,000 switched patients) concluded that switching between reference products and biosimilars was not associated with any major efficacy, safety, or immunogenicity issues.[99]

To examine interchangeability at the laboratory level, a study investigated the potential for ATI to cross-react with reference infliximab and 2 approved biosimilars (CT-P13 and SB2).[100] Patients with IBD from the BIOSIM-01 study who had tested positive for ATI during routine analysis of trough sera were consecutively included in the study (23 patients/76 sera samples). Separate bridging ELISAs were constructed using the 3 drugs. ATI titers were compared in patients who had been treated with reference infliximab only or CT-P13 only and in infliximab/CT-P13 switchers. Antibodies raised against reference infliximab cross-reacted fully (100% agreement) with those formed against CT-P13 and SB2. Antibodies raised against CT-P13 cross-reacted fully (100% agreement) in

ELISAs for reference infliximab and SB2. Based on their findings, the authors concluded that "CT-P13 and SB2 are interchangeable and that switching between biosimilars and reference drug will not lead to differences in ATI production."

TRENDS IN TDM FOR CLINICAL LABORATORIES

Clinical laboratories that provide TDM services have a responsibility to keep apprised of developments in biological agents. An example is subcutaneous formulations which, owing to PK differences, produce serum concentrations many-fold higher than those of intravenous formulations from the start of induction therapy.[67,68,101,102] As such, TDM assays must be able to measure a range of drug concentrations sufficiently broad to cover those reported in clinical studies of intravenous and subcutaneous formulations of biologicals.

Clinical laboratories are constantly striving to increase their efficiency and reduce costs. ELISAs are often regarded as the gold standard in assays, but their utility in proactive TDM is hampered by long turnaround times between sampling and results. Point-of-care assays provide results equivalent to those obtained with conventional ELISAs, but within a 30-minute timeframe. Another alternative to ELISAs is a monotest multiparametric immunoassay, which has shown high within-run (repeatability) and within-device (reproducibility) precision in validation testing. Method comparison studies with human clinical samples showed 100% positive and negative agreement and 100% concordance, with a strong Pearson correlation between the Chorus Promonitor (Progenika Biopharma, S.A. Grifols), the monotest multiparametric product, and the Promonitor ELISA (Progenika Biopharma, S.A. Grifols). Evaluation of additional performance parameters showed no statistical differences between the monotest multiparametric immunoassay and ELISA.

Harmonization of TDM Assays

The World Health Organization has developed international reference standards for mAbs in response to the increasing number of biosimilars available or in development. By providing a global benchmark of biological activity, international standards support bioassay performance, calibration, and validation and facilitate the comparability of bioassay data across multiple stakeholders.[103,104] International standards are available commercially for infliximab (NIBSC code 16/170) and adalimumab (NIBSC code 17/236).[103,104] TDM assays for infliximab or adalimumab must be validated against these international standards. Promonitor ELISA assays were used in a collaborative study involving hospitals and clinical laboratories to assess the suitability of the WHO international standards. The accuracy or closeness of agreement between the results provided by Promonitor ELISA and the true value of the analyte was assessed by measuring WHO international standards.

DISCUSSION, GAP ANALYSIS, AND OUTLOOK

Growing evidence suggests that proactive TDM of anti-TNF therapy in patients with IBD and other IMID is associated with better outcomes than empiric optimization and/or reactive TDM. Key applications of proactive TDM in IBD may include de-escalation of anti-TNF therapy in patients in clinical remission and optimizing infliximab monotherapy as an alternative to combination therapy with an IMM. Recently, it was shown that early application of proactive TDM during infliximab induction therapy can facilitate earlier dose optimization, with an associated positive impact on treatment durability and the risk of immunogenicity.

Proactive TDM may be particularly important for achieving better outcomes in pediatric patients with IBD because this population is characterized by high infliximab clearance. Planned studies of proactive TDM in pediatric IBD include a RCT aimed at evaluating the effect of modifying infliximab induction therapy according to drug concentrations at week 6 (before the third infusion). Another planned RCT aims to assess the need for different protocols of personalized therapy in early onset IBD (children under 6 years of age) because these patients are less responsive and have higher rates of azathioprine and infliximab failure and adverse events than older children.[105–107]

Short- to medium-term goals include establishing target drug concentration thresholds for biological agents, defining the role of proactive TDM for non–anti-TNF biologicals, and incorporating PK dashboards to guide dosing decisions. The future of personalized medicine also includes the application of pharmacogenetics/pharmacogenomics (eg, Fc receptor proteins and human leukocyte antigen [HLA] alleles). Genotyping patients before the start of biological therapy and stratifying them according to the probability of nonresponse and inadequate drug exposure may allow for a more precise application of proactive TDM. In addition, refinements to PK modeling and dashboards that consider multiple covariates to predict drug exposure will be key to optimizing treatment with biologicals for IBD and other IMID.

The success of TDM in the future requires adapting to changes and improvements in biological drugs and their biosimilars. Clinical laboratories must ensure that TDM assays cover a broad range of drug concentrations reported for intravenous and subcutaneous biological formulations. TDM assays must be validated against international standards to ensure their reliability and comparability of results with other commercially available assays. To this end, TDM assays should be interchangeable to provide clinical laboratories with more room to maneuver.

ACKNOWLEDGMENTS

Writing assistance for this article was provided by Kerry Dechant, ISMPP CMPP, on behalf of Content Ed Net (Madrid, Spain) with funding from Grifols S.A. (Barcelona, Spain).

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