Best Practice for Therapeutic Drug Monitoring of Infliximab: Position Statement from the International Association of Therapeutic Drug Monitoring and Clinical Toxicology

Dahham Alsoud, MD, Dirk Jan A. R. Moes, PharmD, PhD,† Zhigang Wang, PharmD,‡ Rani Soenen, PhD,§¶ Zohra Layegh, MD,‖ Murray Barclay, FRACP, MD,** Tomoyuki Mizuno, PhD,†††‡ Iris K. Minichmayr, PhD,§§ Ron J. Keizer, PharmD, PhD,¶¶ Sebastian G. Wicha, PhD,‖‖ Gertjan Wolbink, MD, PhD,***††† Jo Lambert, MD, PhD,§¶ Séverine Vermeire, MD, PhD,*‡‡‡ Annick de Vries, PhD,§§§ Konstantinos Papamichael, MD, PhD,¶¶¶ Núria Padullés-Zamora, PharmD, PhD,‖‖‖**** and Erwin Dreesen, PharmD, PhD‡*

Background: Infliximab, an anti–tumor necrosis factor monoclonal antibody, has revolutionized the pharmacological management of immune-mediated inflammatory diseases (IMIDs). This position statement critically reviews and examines existing data on therapeutic drug monitoring (TDM) of infliximab in patients with IMIDs. It provides a practical guide on implementing TDM in current clinical practices and outlines priority areas for future research.

Methods: The endorsing *TDM of Biologics* and *Pharmacometrics* Committees of the International Association of TDM and Clinical Toxicology collaborated to create this position statement.

Results: Accumulating data support the evidence for TDM of infliximab in the treatment of inflammatory bowel diseases, with limited investigation in other IMIDs. A universal approach to TDM may not fully realize the benefits of improving therapeutic outcomes. Patients at risk for increased infliximab clearance, particularly with a proactive strategy, stand to gain the most from TDM. Personalized exposure targets based on therapeutic goals, patient phenotype, and infliximab administration route are recommended. Rapid assays and home sampling strategies offer flexibility for point-of-care TDM. Ongoing studies on model-informed precision dosing in inflammatory bowel disease will help assess the additional value of precision dosing software tools. Patient education and empowerment, and electronic health record–integrated TDM solutions will facilitate routine TDM implementation. Although optimization of therapeutic effectiveness is a primary focus, the cost-reducing potential of TDM also merits consideration.

Conclusions: Successful implementation of TDM for infliximab necessitates interdisciplinary collaboration among clinicians, hospital pharmacists, and (quantitative) clinical pharmacologists to ensure an efficient research trajectory.

Key Words: infliximab, therapeutic drug monitoring, model-informed precision dosing, immune-mediated inflammatory diseases, inflammatory bowel disease

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INTRODUCTION

Crohn disease (CD) marked the initial indication for the commercial development of infliximab, a chimeric monoclonal antibody targeting tumor necrosis factor. Conditional approval was granted based on data from 4 clinical studies.[1–4] These studies collectively assessed single intravenous (IV) doses ranging from 1 to 20 mg/kg. Notably, the 1 mg/kg dose exhibited a more transient response, whereas higher doses showed no dose–response relationship concerning both the duration and the magnitude of clinical response, consequently supporting the use of a 5 mg/kg dose. The doses of 5 and 10 mg/kg were advanced for every eight weeks (Q8W) maintenance dosing in the phase 3 ACCENT I trial for luminal CD. This trial confirmed the absence of a dose–response relationship.[5] The phase 3 ACCENT II trial for fistulizing CD focused solely on testing a 5 mg/kg Q8W maintenance dose. Still, it allowed a crossover to 10 mg/kg for patients experiencing loss of response (LOR), successfully reestablishing the response.[6] The infliximab ulcerative colitis (UC) program adopted a direct-to-phase 3 approach based on efficacy in CD,[7] again demonstrating no dose–response relationship when comparing 5 and 10 mg/kg induction and maintenance dosing.

Authorization of infliximab for the treatment of other chronic immune-mediated inflammatory diseases (IMIDs) followed, making infliximab a blockbuster drug that revolutionized the treatment of patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis. Furthermore, infliximab has also gained approval for the treatment of pediatric CD and UC.[8,9]

The clinical development of infliximab not only investigated dose–response relationships but also explored exposure–response relationships. During this exploration, even at the plateau of the dose–response relationship, no flat exposure–response relationship was found. At the 5 mg/kg and, surprisingly, at the 10 mg/kg dose level, patients without a sustained response exhibited lower infliximab trough concentrations than those with sustained responses.[10] This

observation spurred research into concentration-guided infliximab dose optimization, assuming a causal link between trough concentrations and therapeutic response.

Despite decades of research on the infliximab exposure–response relationship and therapeutic drug monitoring (TDM) practices, especially in patients with inflammatory bowel diseases (IBDs), consistent evidence is still lacking, and TDM is not widely implemented in clinical practice. Clinical challenges persist with patients not responding adequately to infliximab therapy (primary nonresponse [PNR]) and experiencing a decline in efficacy over time (LOR). Consequently, some clinicians have turned to combination therapies, predictors of response, or simply switching between drugs in the expanding therapeutic armamentarium.[11,12] Nevertheless, we assert that TDM continues to hold promise in ensuring more patients benefit from infliximab, necessitating a comprehensive analysis and discussion. This includes critical evaluations of clinical settings, sampling designs, exposure targets, dose optimization practices, and health care resources.

This position statement reviews and discusses available data on TDM approaches for infliximab in patients with IMIDs. It also provides an evidence-based practical guide on how TDM can be applied in today's routine clinical practice to enhance therapeutic outcomes in patients with IMIDs. Finally, priority areas for future TDM research are highlighted, aiming to devise efficient and precise TDM strategies to improve infliximab therapy for patients with IMIDs.

METHODS

Position Paper Expert Panel

This position statement was developed through an initiative led by members of the IATDMCT. The expert

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From the *Translational Research in Gastrointestinal Disorders, Department of Chronic Diseases and Metabolism, KU Leuven, Leuven, Belgium; †Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center, Leiden, the Netherlands; ‡Clinical Pharmacology and Pharmacotherapy Unit, Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, Leuven, Belgium; §Dermatology Research Unit, Ghent University, Ghent, Belgium; ¶Department of Dermatology, Ghent University Hospital, Ghent, Belgium; ‖Department of Pathology, Amsterdam University Medical Center, Amsterdam, the Netherlands; **Departments of Gastroenterology and Clinical Pharmacology, Christchurch Hospital, Te Whatu Ora Waitaha and University of Otago, Christchurch, New Zealand; ††Division of Translational and Clinical Pharmacology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; ‡‡Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, Ohio; §§Department of Clinical Pharmacology, Medical University Vienna, Vienna, Austria; ¶¶InsightRX, San Francisco, California; ‖‖Department of Clinical Pharmacy, Institute of Pharmacy, University of Hamburg, Hamburg, Germany; ***Department of Rheumatology, Amsterdam Rheumatology and Immunology Center Location Reade, Amsterdam, Netherlands; †††Sanquin Research and Landsteiner Laboratory, Department of Immunopathology, Amsterdam UMC, Amsterdam, Netherlands; ‡‡‡Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium; §§§Sanquin Diagnostic Services, Pharma & Biotech Services, Amsterdam, the Netherlands; ¶¶¶Center for Inflammatory Bowel Diseases, Division of Gastroenterology, Beth-Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts; ‖‖‖Department of Pharmacy, Bellvitge University Hospital, Bellvitge Biomedical Research Institute (IDIBELL), Hospitalet de Llobregat, Barcelona, Spain; and ****School of Pharmacy, University of Barcelona, Barcelona, Spain.

Conceptualization: Ideas; formulation or evolution of overarching research goals and aims: D. Alsoud, D. J. A. R. Moes, Z. Wang, S. G. Wicha, G. Wolbink, A. de Vries, K. Papamichael, and E. Dreesen. Writing—Original Draft: Preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation): D. Alsoud, D.J. A. R. Moes, Z. Wang, R. Soenen, Z. Layegh, K. Papamichael, N. Padullés-Zamora, and E. Dreesen. Writing—Review & Editing: Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision—including pre-or post-publication stages: D. Alsoud, D. J. A. R. Moes, Z. Wang, R. Soenen, Z. Layegh, M. Barclay, T. Mizuno, I. K. Minichmayr, R. J. Keizer, S. G. Wicha, G. Wolbink, J. Lambert, S. Vermeire, A. de Vries, K. Papamichael, N. Padullés-Zamora, and E. Dreesen. Visualization: Preparation, creation and/or presentation of the published work, specifically visualization/ data presentation; E. Dreesen. Supervision: Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team: N. Padullés-Zamora, K. Papamichael and E. Dreesen. Project administration: Management and coordination responsibility for the research activity planning and execution. E. Dreesen. Funding acquisition: Acquisition of the financial support for the project leading to this publication; NA.

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D. Alsoud, D. J. A. R. Moes, and Z. Wang share first authorship.

K. Papamichael, N. Padullés, and E. Dreesen share senior authorship.

Correspondence: Erwin Dreesen, PharmD, PhD, ON2 Herestraat 49, Box 521, 3000 Leuven, KU Leuven, Leuven, Belgium (e-mail: erwin.dreesen@kuleuven.be).

panel contributing to this position statement was selected by the endorsing IATDMCT *TDM of Biologics* and *Pharmacometrics* committees.

Process Overview

A combination of face-to-face and virtual focus group discussions was used to structure and outline the content of the position paper, ensuring efficient consensus among expert panel members. The members were categorized into 3 teams based on their expertise: clinical, clinical pharmacology, and precision dosing/pharmacometrics. Each expert team, led by a primary author (K.P., N.P.-Z., and E.D.), collaborated with coauthors.

Literature Review and Evaluation

Expert teams conducted comprehensive literature reviews and assessed available data. Extensive searches on PubMed and Embase, with no starting date restriction until September 2023, were performed. The teams compiled their findings into a draft document covering all aspects of the TDM process related to (1) identifying patients suitable for TDM, (2) determining therapeutic targets, (3) specifying specimens and accompanying clinical data, (4) translating (laboratory) data into dosing recommendations, and (5) implementing infliximab dosing recommendations for patients with CD, UC, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and hidradenitis suppurativa. The document highlighted recommendations for clinical practice and identified areas for future research.

Panel Consensus

The full draft document underwent review by all expert panel members. Opinions were sought, and any discrepancies were thoroughly discussed until a consensus was achieved.

CONFLICTING EVIDENCE ON THE ROLE OF TDM

The established exposure–response relationship of IV infliximab, particularly the link between higher infliximab trough concentrations in serum and favorable therapeutic outcomes, has long been recognized in patients with IBD.[10,13] Extending beyond gastroenterology, studies in rheumatology and dermatology have also indicated positive associations between infliximab concentrations and therapeutic outcomes in patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.[14] These relationships have formed the basis for conducting TDM both reactively, to address patients experiencing LOR, and proactively, to prevent PNR and LOR.[14–16] In addition to enhancing therapeutic outcomes, TDM also aids in avoiding unnecessary dosing optimizations in patients already attaining supratherapeutic concentrations for their condition, potentially leading to cost savings and minimizing the inconvenience of frequent administrations.[14]

A pivotal randomized controlled trial (RCT) by Steenholdt et al[17] compared reactive TDM with unguided dose escalation in patients with CD. Although no difference in disease control at 12 weeks was observed, reactive TDM was found to be more cost-effective than "blind" dose escalation. Subsequently, the Trough Concentration Adapted Infliximab Treatment (TAXIT) trial (CD and UC) and the Tailored Treatment With Infliximab for Active CD (TAILORIX) trial (CD) investigated proactive TDM to prevent LOR during maintenance therapy. However, both RCTs failed to meet their primary endpoints.[18,19] The conflicting results from these RCTs regarding the benefit of TDM in IBD have hindered the widespread adoption of TDM in clinical guidelines (see **Tables**, **Supplemental Digital Content 1**, http://links.lww.com/TDM/A735 and http://links.lww.com/TDM/A736).[20–37] The American Gastroenterological Association conditionally recommended reactive TDM based on very low-quality evidence.[21] The European Crohn's and Colitis Organization guidelines recommend neither proactive nor reactive TDM.[24] Similarly, neither proactive nor reactive TDM was recommended in any rheumatology and dermatology guidelines because of insufficient evidence.[38] Therefore, in clinical practice, lack and LOR are generally addressed through empirical adjustments in doses and intervals according to clinical parameters instead of TDM.

More recently, the Norwegian Drug Monitoring (NORDRUM) study part B investigated the effectiveness of proactive TDM in patients with IMIDs, including CD, UC, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis, receiving maintenance therapy with infliximab. The study demonstrated that proactive TDM was more effective than standard treatment in sustaining disease control without worsening.[39] Guidelines are currently being updated, cautiously incorporating TDM.[40] By contrast, NORDRUM part A, assessing the role of proactive TDM during infliximab induction therapy, concluded no significant improvement in clinical remission rates over the first 30 weeks of treatment compared with standard therapy.[41]

Several methodological flaws have contributed to the lack of benefit of TDM in the aforementioned RCTs, including, but not limited to, suboptimal patient selection criteria (cf. Whom to monitor), subtherapeutic targeted trough concentrations (cf. Defining the therapeutic target), long turnaround times of TDM sample analysis (cf. Obtaining appropriate monitoring data), imprecise dosing algorithms, overly simple infusion schemes restricted to 4-, 6-, or 8-week intervals and 5, 7.5, or 10 mg/kg doses (cf. Translating laboratory data into dosing recommendations), and mistakes because of a high impact on the clinical workload (cf. Implementing dose recommendations into patient care; Fig. 1).

WHOM TO MONITOR

Is TDM Beneficial for Every Patient?

Some patients are likely to have non–TNF-driven disease, and thus, are unresponsive to infliximab despite high serum concentrations.[42] In addition, many patients with TNF-driven disease can achieve adequate drug exposure and attain/regain favorable outcomes with dosing adjustments based on clinical symptoms and inflammatory markers such as C-reactive protein (CRP) and fecal calprotectin (FC), or even without the need for dose adjustments whatsoever.[43] The

inclusion of these patients in RCTs may confound the results and obscure the benefits of TDM. Instead, RCTs investigating the outcomes of TDM should be designed to enrich for patients who may benefit most from it, being those at increased risk of underexposure, for instance, because of augmented drug clearance or other reasons covered in the following paragraphs.[44]

Patients With Specific Disease Phenotypes

High IBD disease activity damages the intestinal barrier function, resulting in protein-losing enteropathy. Consequently, this increases infliximab clearance, leading to lower drug exposure, which, in turn, leaves disease activity uncontrolled.[45] A retrospective study showed that a baseline infliximab clearance threshold of 0.63 L/d identified hospitalized patients with acute severe UC (ASUC) who required colectomy.[46] Another multicenter prospective study showed that an estimated infliximab clearance above 0.48 L/h on day 3 of therapy was associated with colectomy (hazard ratio 58.2; 95% confidence interval 6.0–568.6; $P < 0.001$).[47] In such patients with accelerated infliximab clearance related to disease activity, TDM can guide dose escalations to overcome high infliximab clearance and help attain adequate exposure.[48] This can break the vicious circle between impaired infliximab exposure and high disease activity, increasing the odds of therapy success. The Induction For Acute UC (TITRATE) trial (NCT03937609) is currently investigating the role of TDM during infliximab induction therapy in patients with ASUC.

Similar to patients with ASUC, patients with fistulizing perianal CD and hidradenitis suppurativa seem also to require higher infliximab exposure to achieve healing, which can be reached through TDM-guided dosing.[49–52] Dose reduction in the Precision Dosing of Infliximab versus Conventional Dosing of Infliximab (PRECISION) trial targeting an infliximab TC of 3 mg/L led to the reopening of perianal fistulas in 3 patients with CD.[53] The Prospective Randomized Controlled Trial of Adults With Perianal Fistulizing CD And Optimized Therapeutic Infliximab Levels (PROACTIVE; ACTRN12621000023853) is investigating the role of proactive TDM in patients with perianal fistulizing CD compared with standard dosing.[54]

Patients With Genetic Susceptibility for Accelerated Clearance

Specific variant alleles significantly impact infliximab pharmacokinetics (PK) and treatment outcomes. For instance, the presence of the HLA-DQA105 allele is linked to an increased risk of immunogenicity and LOR.[55,56] Furthermore, a polymorphism in the FCGR3A gene, responsible for encoding the Fc gamma receptor III, is associated with a higher likelihood of immunogenicity, heightened infliximab clearance, lower infliximab levels, diminished clinical response, and an elevated risk of relapse after infliximab discontinuation.[57–59] Similarly, a polymorphism in the neonatal Fc-receptor gene was associated with reduced infliximab exposure.[60] Proactive TDM can guide dose escalations in patients carrying these genetic variants, ensuring adequate drug exposure and enhancing therapeutic outcomes. Notably, a recent systematic review and meta-analysis demonstrated that the routine implementation of proactive TDM in patients with IMIDs treated with anti-TNF therapy reduces the risk of immunogenicity on LOR and secondary LOR in patients with HLA-DQA1*05 variants.[61] In addition, the concomitant use of methotrexate and azathioprine can suppress the formation of antibodies towards infliximab (ATI).[62–67] Patients with ankylosing spondylitis less frequently receive methotrexate treatment, potentially putting them at a higher risk of immunogenicity and emphasizing the role of TDM.[68]

Pediatric Patients

Proactive TDM proves beneficial in the pediatric IBD population, particularly in younger children (below 10 years), who exhibit higher infliximab clearance relative to body weight and require more frequent dose optimization.[69] In a cohort of children with CD, low infliximab clearance early upon the start of treatment emerged as the sole significant and consistent predictor of remission.[70] Similarly, a recent study involving children with IBD receiving standard infliximab induction dosing revealed that infliximab clearance at weeks 6 and 12 was predictive of deep remission.[71] An RCT from South Korea, encompassing 112 biologic-naive children with CD who responded to induction treatment with infliximab, demonstrated the superiority of proactive TDM over clinically based dosing in sustained corticosteroid-free clinical remission and endoscopic healing.[72] A retrospective single-center study assessing outcomes in pediatric patients receiving either infliximab or adalimumab before (pre-TDM; 72.2% received infliximab) and after the implementation of institutional guidelines for proactive TDM (post-TDM; 65.5% received infliximab) found that proactive TDM improved key clinical outcomes, including sustained clinical remission, the incidence of high ATI titer, and anti-TNF cessation related to ATI.[73] The prospective Precise Infliximab Exposure and Pharmacodynamic Control (REMODEL-CD) study is investigating the safety and effectiveness of personalized dosing of infliximab with specific PK and pharmacodynamic (PD) targets from the start of therapy using a "PK dashboard" for children and young adults with CD (NCT05660746; cf. Translating laboratory data into dosing recommendations).[74,75]

Treatment De-escalation

Preliminary data indicate that proactive TDM could be valuable for guiding infliximab therapy de-escalation in patients with IBD and other IMIDs.[40] A French study demonstrated that de-escalation based on proactive TDM in patients with clinical remission and drug concentrations above 7 mg/L was associated with fewer relapses compared with de-escalation based solely on clinical symptoms (hazard ratio 0.45; $P = 0.024$).[76] The same group reported a higher likelihood of sustained remission in patients with infliximab trough concentrations ≥2.4 mg/L at the time of de-escalation compared with those with drug concentrations below 2.4 mg/L.[77] Proactive TDM may also guide the withdrawal of an immunomodulator in IBD patients in remission receiving

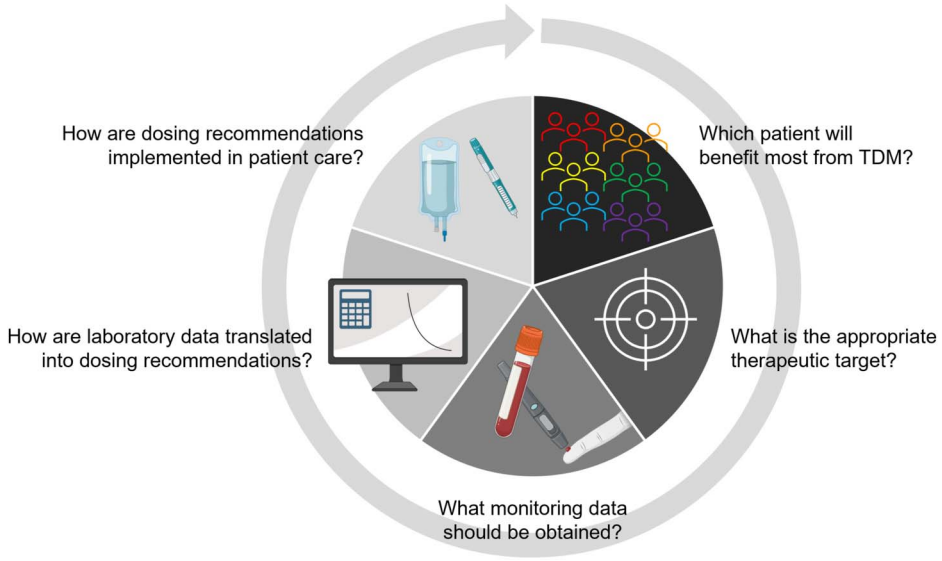

FIGURE 1. Five key aspects of TDM and research priority areas to enhance infliximab therapy for patients with IMIDs. TDM, therapeutic drug monitoring.

infliximab combination therapy. A retrospective study revealed that detectable infliximab trough concentrations (particularly >5 mg/L) at the time of immunomodulator withdrawal are associated with a long-term response.[78] The Model-informed Dose De-escalation of Infliximab in Patients With Inflammatory Bowel Diseases (MODIFI) trial is investigating the benefit of TDM during infliximab de-escalation (NCT04982172).

Restarting Infliximab after a Drug Holiday

Preliminary data suggest that applying TDM early after the reinduction of infliximab after a drug holiday may help predict the response and the likelihood of an infusion reaction. A large retrospective study assessing patients with IBD restarting infliximab after a drug holiday indicated that the lack of ATI in an early sample was associated with better efficacy and safety after re-initiation of therapy.[79] A recent prospective study in adult patients with clinically and objectively active luminal CD in whom infliximab was discontinued because of secondary LOR or drug intolerance showed that ATI at week 4 after reintroduction of infliximab was associated with drug failure or infusion reaction at week 26.[80]

Clinical Recommendations

A one-size-fits-all implementation of TDM in patients with IMIDs treated with infliximab is unlikely to reveal the benefits of TDM in improving therapeutic outcomes. Clinicians should ideally assess the need for TDM on an individual basis, considering patient and disease characteristics. Those with a higher risk for increased infliximab clearance could benefit the most from TDM, especially from a proactive strategy (Fig. 2). We recommend infliximab monitoring in patients with a more acute, severe disease presentation, fistulizing manifestations, younger age, or with genetic susceptibility for accelerated clearance to ensure sufficient drug exposure.

Area(s) for Future Research

Further research is needed to precisely identify patient populations in which TDM could maximize infliximab therapy outcomes. First, the discovery of robust PD biomarkers will help avoid the inconvenience and costs of monitoring and dosing adjustments, which would be futile in patients with non–TNF-driven disease.[81] Second, the practicality and benefits of pharmacogenomics in guiding precision dosing still need to be investigated in prospective studies. Third, extensive profiling of infliximab clearance and exposure should be conducted in groups with distinct patient and disease characteristics, such as children, elderly patients, those with extensive disease involvement, longstanding disease, and especially patients with reported lower response rates to infliximab. This would help characterize any alterations in infliximab PK and understand how drug monitoring in these patients could improve outcomes.

DEFINING THE THERAPEUTIC TARGET

Different TC windows and targets have been prospectively targeted, and a plethora of therapeutic concentration windows and targets—both at trough and at intermediate time points—have been proposed for IV infliximab therapy. These were typically derived from exposure–response studies and receiver operating characteristic analyses using data from retrospective and prospective studies and post hoc analyses of RCTs. Most data were generated for IBD, rheumatoid arthritis, and plaque psoriasis. In general, infliximab target concentrations can depend on the desired therapeutic outcome, time after drug initiation, phenotype, and disease activity. For this reason, there is a growing tendency to consider individualized TDM targets.

Noteworthy, infliximab target concentrations also differ between routes of administration. A subcutaneous (SC) formulation of infliximab was recently approved. The SC formulation provides higher trough concentrations and lower peak concentrations as compared with IV infliximab, yet comparable total exposure (8-week averaged area under the

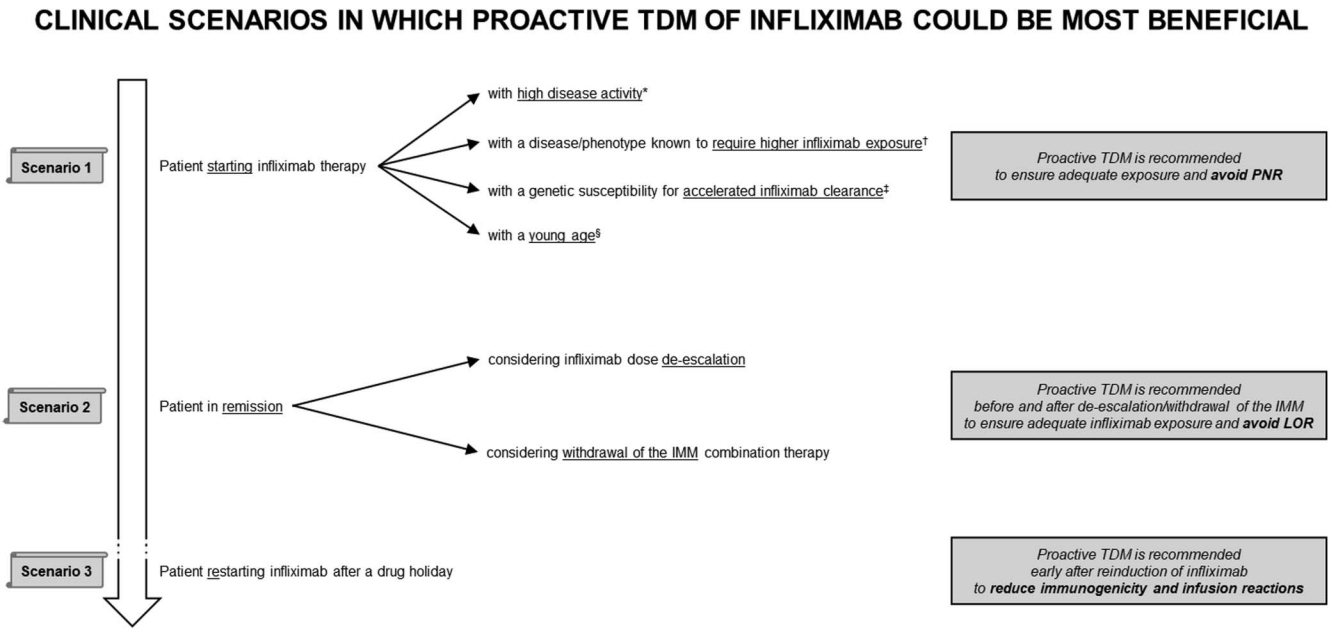

FIGURE 2. Clinical scenarios where proactive TDM of infliximab could be particularly advantageous. *Including patients with acute severe UC, experiencing protein-losing enteropathy because of extensive colon inflammation; †including patients with fistulizing perianal CD and hidradenitis suppurativa; ‡Carriage of the HLA-DQA1*05 allele or specific polymorphisms in the FCGR3A or the neonatal Fc-receptor genes; §Below the age of 10 years. IMM, immunomodulator; LOR, loss of response; PNR, primary nonresponse.

concentration–time curve; AUC_{8w}).[82] Target concentrations for SC infliximab are expected to be roughly 1.2 times higher than IV infliximab targets, yet prospective confirmation is awaited.

Because higher infliximab concentrations are not associated with increased risks of infection, cardiovascular complications, malignancy, and other adverse events, the upper limit of the therapeutic window should be considered as a saving measure to control financial toxicity rather than a safety measure to avoid adverse drug reactions.[83]

IBD

In the Danish RCT by Steenhold et al,[17,84] a therapeutic infliximab threshold of 0.5 mg/L was used to guide dose intensifications for patients with CD who lost response. However, this threshold is generally considered too low today. The TAXIT, TAILORIX, and NOR-DRUM studies relied on therapeutic windows of 3–7, 3–10, and 3–10 mg/L, respectively, for optimizing infliximab therapy in IBD and beyond, implying dose escalations only if infliximab concentrations were below 3 mg/L.[18,19,85] In the PRECISION trial, infliximab trough concentrations of patients with IBD were targeted at 3 mg/L.[53] In addition, higher TC targets have been identified for more stringent IBD outcomes such as endoscopic and histological remission or fistula healing and for phenotypes characterized by a higher inflammatory burden such as ASUC and penetrating or perianal fistulizing CD.[48,49]

Table 1 provides an overview of infliximab target concentrations identified from prospective studies and post hoc analysis of RCTs during both induction and maintenance therapy.[10,13,86–102] Post hoc analysis of the pivotal ACCENT I and ACCENT II trials in CD showed that infliximab trough concentrations ≥3.5 and ≥7.2 mg/L at week 14 were predictive of clinical response at week 54 and combined fistula response and CRP normalization (composite remission) at week 14, respectively.[10,86] Also, infliximab trough concentrations ≥20.2 mg/L at week 2 and ≥15 mg/L at week 6 were associated with composite complete remission at week 14. A post hoc subgroup analysis of the ACCENT II study demonstrated that infliximab trough concentrations above 13.9 mg/L at week 6 and above 4.8 mg/L at week 14 were correlated with a complete fistula response at week 14.[86] Post hoc analysis of the landmark Active Ulcerative Colitis (ACT) 1 and 2 trials identified similar infliximab TC targets for clinical remission of patients with UC.[13] Post hoc analysis of the TAILORIX data identified infliximab TC targets at weeks 2 and 6 of induction therapy for targeting CD endoscopic remission at week 12.[91] Many more exposure–response analyses have been performed for adult and pediatric CD, UC, and mixed CD/UC populations, all identifying infliximab trough and intermediate concentrations during induction and maintenance therapy. A wide variety of therapeutic responses, including clinical response or remission, endoscopic healing, mucosal healing, fistula response, normalization of CRP and/or FC, radiological remission, and drug retention, have been investigated.[50,51,88,103–105]

Rheumatoid Arthritis

An association between infliximab concentrations and clinical response has also been demonstrated in patients with

TABLE 1. Infliximab Concentration Targets in IBD From Prospective Studies and Post Hoc Analysis of RCTs

Study Type (Acronym)	IBD Type	Infliximab Concentration Target, mg/L (Time Point)	Therapeutic Outcome (Time Point)	References
RCT (ACCENT I)	CD	>3.5 (w14)	Clinical response (w54)	Cornillie et al[10]
RCT (ACCENT II)	CD	≥7.2 (w14)	Complete fistula response and C-reactive protein normalization (w14)	Papamichael et al.[86]
RCT (ACT 1/2)	UC	≥18.6 (w2)	Mayo endoscopic score <2 (w8)	Vande Casteele et al[87]
		≥10.6 (w6)	Mayo endoscopic score <2 (w8)	
		≥34.9 (w8)	Mayo endoscopic score <2 (w8)	
		≥5.1 (w14)	Mayo endoscopic score <2 (w30)	
		≥6.7 (w14)	Mayo endoscopic score = 0 (w30)	
		≥2.3 (w30)	Mayo endoscopic score <2 (w30)	
		≥3.8 (w30)	Mayo endoscopic score = 0 (w30)	
		>22.0 (w6)	Clinical response (w8)	Adedokun et al.[13]
		>41.1 (w8)	Clinical response (w8)	
		>5.1 (w14)	Clinical response (w30)	
		>2.4 (w30)	Clinical response (w54)	
RCT (SONIC)	CD	≥3.0 (w30)	Mucosal healing (w26)	Reinisch et al.[88]
RCT (PREVENT)	CD	Inverse correlation between drug concentrations at w72 and postoperative recurrence rates at w76		Regueiro et al.[89]
RCT (JAPIC)	UC	>21.3 (w2)	Clinical remission (w14)	Kobayashi et al.[90]
RCT (TAILORIX)	CD	>23.1 (w2)	Endoscopic remission (w12)	Dreesen et al.[91]
		>10.0 (w6)		
		>7.8 (w14)	Radiological remission (w54)	Bossuyt et al.[92]
RCT (REACH)*	CD	≥7.1 (w10)	Clinical remission (w10)	Cheifetz et al 2023
		≥6.5 (w10)	Long-term clinical response (w30)	
RCT	CD/UC	>4.0 (w14)	Clinical remission (w30 and 54)	Park et al.[93]
Prospective*	CD	≥9.1 (w10)	Drug retention (w52)	Stein et al.[94]
Prospective	UC	>3.2 (w14)	Mucosal healing (w14)	Farkas et al 2016
Prospective	UC	>6.6 (w6)	Endoscopic response (w8)	Brandse et al.[96]
Prospective	CD	>20.4 (w2)	Clinical remission (w14)	Gonczi et al.[97]
	UC	>15.3 (w2)		
Prospective	CD/UC	>4.8 (w14)	Clinical response (w14)	Tighe et al.[98]
Prospective*	CD	≥26.7 (w2)	Clinical response (w14)	Clarkston et al.[99]
		≥15.9 (w6)		
Prospective (PANTS)	CD	≥7.0 (14)	Clinical remission (w14/54)	Kennedy et al.[100]
Prospective	CD/UC	>22.9 (w2)	Clinical response (w14)	Buhl et al.[101]
		>11.8 (w6)		
Prospective*	CD	>11.5 (w14)	Fecal calprotectin <100 mg/kg (w14)	Colman et al.[102]

*Pediatric. ACCENT I, A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNF 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-TNF Chimeric Monoclonal Antibody (Infliximab, Remicade) in the Long-term Treatment of Patients With Fistulizing Crohn's Disease; ACT, Active Ulcerative Colitis Trials; JAPIC, clinical study to assess the efficacy and safety of TA-650 in patients with active UC; PANTS, the personalized anti-TNF therapy in CD study; PREVENT, prospective, multicenter, randomized, double-blind, placebo-controlled trial comparing REMICADE [infliximab] and placebo in the prevention of recurrence in CD patients undergoing surgical resection who are at an increased risk of recurrence; SONIC, The Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease; TAILORIX, a study investigating tailored treatment with infliximab for active CD; w, week.

rheumatic diseases (Table 2).[62,106–119] Multiple factors exert influence on the clearance of infliximab, encompassing dosage, concomitant methotrexate use, and ATI. Prior research indicates that patients who are initiated on a high starting dose exhibit reduced ATI formation, referred to as "high dose tolerance."[64] The incorporation of immunosuppressive medications such as methotrexate can also modulate the immune response towards infliximab, which is mainly important in the beginning of the treatment.

Analysis of treatment outcomes from the landmark Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT) in patients with rheumatoid arthritis found a trend toward higher response rates, a greater reduction in serum CRP concentrations, and less radiographic progression of joint damage with increasing infliximab trough concentrations at week 54, especially when the infliximab TC was >1 mg/L.[108] These results coincide with findings of the Clinical Study to Assess the Efficacy and Safety of Increased Dose of TA-650 (Infliximab) in Patients With Rheumatoid Arthritis (RISING), where an infliximab TC >1 mg/L was suggested for clinical response.[110] Other authors have found an association between clinical response and infliximab trough concentrations at week 14 (3.6 mg/L [1.4–8.2] versus 0.5 mg/L [0.2–2.2]) and week 42 (3.26

TABLE 2. Infliximab Concentration Targets in IMIDs Other Than IBD

Study Type (Acronym)	Infliximab Concentration Target, mg/L (Time Point)	Therapeutic Outcome (Time Point)	References
Rheumatoid arthritis			
Prospective	>2.5 (w6)	Good EULAR response (w26)	Van Den Bemt et al[106]
Retrospective	>4.4 (w6)	DAS28 < 3.2 (w54)	Jurado et al.[107]
Post hoc analysis of an RCT (ATTRACT)	Higher drug concentrations were associated with higher rates of clinical response and a greater reduction of C-reactive protein		St Clair et al[108]
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		Wolbink et al.[62]
Prospective	Infliximab concentrations was predictive of DAS28 <3.2 (w42). Patients with low disease had significantly higher concentrations than in those with persistent active disease		Mulleman et al.[109]
RCT (RISING)	There was a negative correlation between progression of joint damage and trough serum concentration		Takeuchi et al.[110]
Spondyloarthritis			
Retrospective	Higher drug concentrations were associated with lower ASDAS-ESR/C-reactive protein scores		Patil et al.[111]
Retrospective	>6.0	Improvement in BASDAI	Meríc et al.[112]
Retrospective	>6.5	Longer maintenance therapy	Ducourau et al.[113]
Prospective	<6.7 (w12)	Long-term clinical failure (w52)	Martínez-Feito et al.[114]
RCT	No association of drug concentrations with treatment failure		Krzysiek et al.[115]
Retrospective	High drug concentrations correlated with a good clinical response (ASAS-20)		De Vries et al[116]
Psoriasis			
Prospective	>0.92 (w48)	PASI75 (w48)	Takahashi et al.[117]
Prospective	PASI score and PASI 90/100 response were significantly associated with drug trough concentrations		Colls-Gonzalez et al[118]
Retrospective	A therapeutic range of 2–10 mg/L significantly improved the sensitivity of predicting patients with PASI75		Dodero-Anillo et al[119]

ASAS, Assessment in Ankylosing Spondylitis; ASDAS-ESR, Ankylosing Spondylitis Disease Activity Score-Erythrocyte Sedimentation Rate; ATTRACT, Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; DAS28, Disease Activity Score-28; EULAR, European Alliance of Associations for Rheumatology; RISING, Efficacy and Safety of Increased Dose of TA-650 (Infliximab) in Patients With Rheumatoid Arthritis; w, week.

versus 0.16 mg/L), with significantly higher concentrations in responders than nonresponders.[62,109] In another study, infliximab trough concentrations at week 14 were higher in responders compared with nonresponders. The combination of either a Disease Activity Score-28 (DAS28) ≥4.2 and/or an infliximab TC ≤2.5 mg/L at week 6 was a fair predictor of not achieving low disease activity.[106] In line with these results, Jurado et al[107] found that a week 6 infliximab TC >4 mg/L was predictive of lower DAS28 scores at week 54.

Spondyloarthritis

For patients with ankylosing spondylitis and psoriatic arthritis, a tendency toward higher infliximab concentrations in responding patients has been observed.[116] In one study, patients with ankylosing spondylitis with infliximab trough concentrations >6.0 mg/L experienced an improvement in their Bath Ankylosing Spondylitis Disease Activity Index.[112] In another cohort of 81 patients with ankylosing spondylitis, a low infliximab TC at week 12 was associated with long-term clinical failure.[114] The authors suggested an infliximab TC ≥6.7 mg/L at week 12 to discriminate between responders and nonresponders and to predict long-term drug retention. Recently, Pedersen et al[120] identified an infliximab TC threshold of 2.8 mg/L for discriminating between treatment failure and remission/low disease activity in rheumatic diseases and proposed a therapeutic range of 3–7 mg/L. Trough concentrations of 1–2 mg/L of infliximab might be enough to block tumor necrosis factor. However, it is not known if that is the case for all the IMIDs. We expect different infliximab PK/PD in patients with spondyloarthritis because these patients often receive no concomitant methotrexate, and infliximab is dosed more frequently (Q6W) than in other IMIDs (Q8W).

Plaque Psoriasis

In the last decade, data supporting TDM of infliximab in plaque psoriasis has accumulated (Table 2). Several studies have demonstrated that the presence of ATI is associated with lower serum infliximab concentrations and poorer clinical outcomes.[117,118,121–127] Associations between serum concentrations and therapeutic response have been identified in various studies.[117–119,128] Takahashi et al[117] reported that a TC ≥0.92 mg/L was required to achieve at least 75% improvement in Psoriasis Area and Severity Index (PASI) from baseline (PASI 75). In addition, Reich et al[128] found a greater proportion of patients achieving PASI 75 on continuous therapy compared with those on intermittent therapy at week 52 (80% versus 47%) and fewer serious infusion-related reactions (<1% versus 4%). Colls et al[118] found a probability

of achieving a PASI 90 response with infliximab trough concentrations ≥2.5 mg/L of >75% in normal-weight patients and approximately 50% in overweight and obese patients. When the infliximab TC was ≥5 mg/L, these probabilities increased to >85% in normal-weight patients and approximately 70% in overweight and obese patients. In line with these results, Rodero-Anillo et al proposed a therapeutic range of 2–10 mg/L.[119] In the NOR-DRUM trial, a maintenance serum infliximab concentration of 3 mg/L was targeted.[39]

Hidradenitis Suppurativa

Only 1 case series study of TDM for infliximab in hidradenitis suppurativa has been published.[129] In this study, 5 of 21 patients who did not respond to infliximab were found to have subtherapeutic infliximab concentrations and 3 of the 5 patients had detectable ATI. In another study including 52 patients with hidradenitis suppurativa, 1 patient stopped treatment because of immunogenicity.[130] The 2015 European guideline for the treatment of hidradenitis suppurativa proposed that the addition of low-dose methotrexate could reduce the formation of ATI.[131] In addition, Wang et al demonstrated the role of low-dose methotrexate as a rescue treatment in patients who develop ATI.[132]

Abdalla et al[52] proposed an algorithm for TDM of infliximab in patients with hidradenitis suppurativa having a suboptimal response. They suggested a TC target above 5 mg/L based on IBD data. Hidradenitis suppurativa and CD share predisposing factors, inflammatory pathways, and histological features (granulomatous infiltration, suppuration and fistula, and sinus tracks formation). Because of these similarities between perianal hidradenitis suppurativa and CD, some authors expressed doubt about using a target regardless of the location of hidradenitis suppurativa lesions and wondered if higher infliximab concentrations would be necessary in fistulizing perianal hidradenitis suppurativa.[133]

Clinical Recommendations

Because of the unique exposure–response relationships of each IMID, it is necessary to establish disease-specific exposure targets (Table 3). Moreover, a personalized approach should be considered because target concentrations can depend on the desired outcome, time of assessment, patient phenotype, and disease activity.

Currently, induction therapy targets of 20–25 mg/L at week 2 and 15–20 mg/L at week 6 and a maintenance therapy target of 5–10 mg/L (7–10 mg/L at week 14) are suggested to achieve favorable outcomes in patients with IBD.[10,13,86,87,91] Higher concentrations are required for more aggressive phenotypes such as perianal fistulizing CD and ASUC.[48,49] A TC >5 mg/L may be necessary in hidradenitis suppurativa.[52] However, because of similarities between perianal fistulizing CD and perianal hidradenitis suppurativa, higher infliximab concentrations will probably be necessary in fistulizing perianal hidradenitis suppurativa. Maintenance therapy targets of 3–7 mg/L, ≥6–7 mg/L, and 2–5 mg/L are suggested in rheumatoid arthritis, ankylosing spondylitis, and plaque psoriasis, respectively.[62,107–109,111,112,114,117,118,120,133,134]

Area(s) of Future Research

An SC formulation of infliximab has recently become available, altering the PK profile of infliximab in patients. This necessitates a reevaluation of target concentrations for this specific formulation because trough concentrations are higher during standard SC therapy compared with IV therapy.[82] Larger studies are needed to determine the target concentrations in plaque psoriasis, hidradenitis suppurativa, and rheumatic patients treated with IV infliximab.

OBTAINING APPROPRIATE MONITORING DATA

Sample Collection

In general, trough concentrations (concentrations measured in samples taken right before or up to 24 hours before IV infliximab infusion) obtained during maintenance treatment are commonly used because most reference values are available for this target measure.[134,135] Serum is the ideal sampling matrix, although ethylenediaminetetraacetic acid plasma, heparin, or citrate plasma samples may also be used.[136] Serum tubes with clot activator and gel separator are recommended, and most published assays are validated in both serum and plasma matrices.[137] Reference values are expressed as mg/L or mcg/mL in serum or plasma.[138]

Capillary blood, collected through a finger prick, is a suitable source for infliximab concentration measurement, allowing patients to collect their own samples through a finger prick, and subsequent analysis can be conducted in the laboratory.[139] Both dried blood spot and capillary wet sampling methods have been validated, with dried blood spot

TABLE 3. Executive Summary for Infliximab Target Concentrations

Disease	Induction	Maintenance	Specific Situations
IBD	20–25 mg/L at w2	7–10 mg/L at w14	>10 mg/L maintenance in perianal fistulizing CD and ASUC
	15–20 mg/L at w6	5–10 mg/L after w14	
Rheumatoid arthritis	No recommendation	3–7 mg/L	—
Spondyloarthritis	No recommendation	≥6–7 mg/L	—
Plaque psoriasis	No recommendation	>2–5 mg/L	—
Hidradenitis suppurativa	No recommendation	No recommendation	—

Further research is required to define target concentrations where there are no recommendations as above and when infliximab is administered subcutaneously.
w, week.

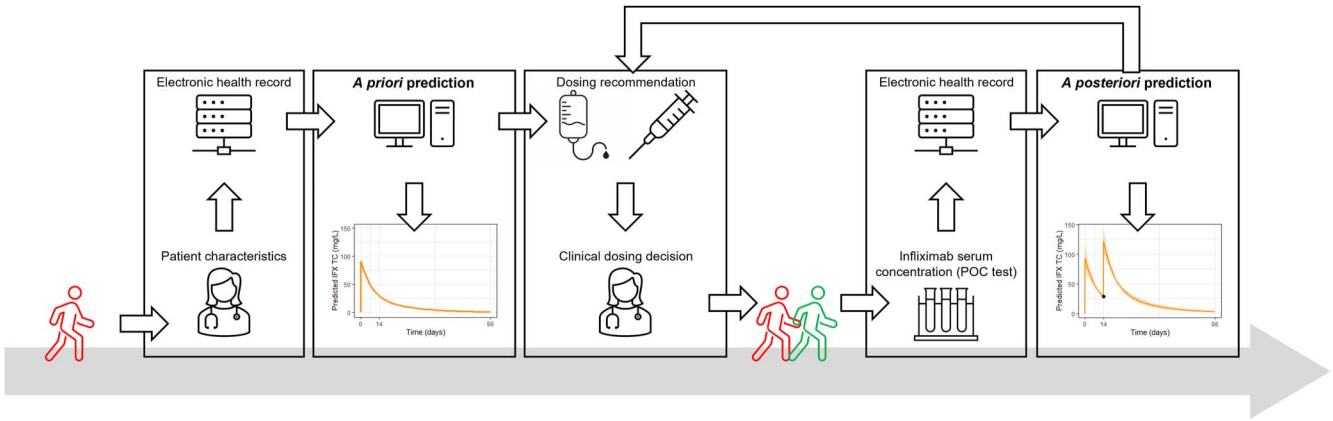

FIGURE 3. The proposed workflow for MIPD of infliximab in clinical practice with an illustration in a virtual patient. Conc, concentration; IFX, infliximab.

requiring a conversion factor to translate whole blood values into serum or plasma reference values.[139–141]

Sample Transport and Storage

Stability studies indicate that serum and plasma samples remain stable for infliximab when frozen,[142] with stability at 4°C confirmed for up to 14 days. Samples are also stable at room temperature for at least 7 days in both serum and whole blood, enabling direct posting from clinics and research centers to the analyzing laboratory.[143,144] To prevent hemolysis, it is recommended to remove serum from the clot as soon as possible (within 4 hours). Infliximab maintains stability after 4 freeze–thaw cycles.[143] Transportation to the analyzing laboratory can be done at room temperature or cooled if a long shipment duration is expected.

Quantification of Infliximab

An essential requirement for TDM is access to a validated and standardized bioanalytical assay. Various techniques are available for measuring infliximab, including enzyme-linked immunosorbent assay (ELISA), electrochemiluminescence immunoassay (ECLIA), radioimmunoassay (RIA), reporter-gene assay, enzyme immunoassay, and homogeneous mobility shift assay. ELISA and ECLIA are the most commonly used techniques. Infliximab concentration can be determined using commercially available ELISA kits or analyzers.[145,146] Advances in proteomics research have demonstrated that liquid chromatography–tandem mass spectrometry methods are also capable of analyzing peptides and proteins in biological matrices with high selectivity and specificity.[143,147,148] The lower limit of quantification varies between assays but is generally well below the therapeutic threshold, making it suitable for TDM applications, with reported LLOQs ranging from 0.001 to 0.06 mg/L.

Centralized diagnostic TDM services can be cost-effective for clinical sites with a lower volume of infliximab samples. Alternatively, point-of-care (POC) testing can be considered. Although traditional assays necessitate sample transport to a clinical laboratory and preparation, POC tests can be conducted on-site by clinical staff without laboratory training, reducing turnaround time. Despite some reported acceptable agreement between ELISAs and POC tests, not all tests exhibit the same recovery of international standards, affecting result comparability and uniform target concentrations.[149–151] Adequate training of nonlaboratory personnel is crucial for using these devices.[152] Furthermore, implementing international standards and universal calibrators, along with participation in proficiency testing rounds, is essential for continuous accuracy and precision of POC testing. At present, CE-marked POC tests require a specialized analyzer, affecting budget and resource allocation for quality measures.[153–155] In addition, this still necessitates patients to visit a clinic. Hospitals often use external services for specialized measurements with fast turnaround times for commonly used biologics, and it is relatively straightforward to determine infliximab in hospitals' qualified laboratories.

The determination of infliximab concentration through ELISA and other immunoassays reflects the presence of bioactive infliximab. It is crucial to note that the presence of ATIs can impact the measured serum or plasma concentration, potentially leading to underestimation, especially when analyzers measure total infliximab.[138,156]

Measuring ATIs involves various assay formats, such as solid-phase ELISAs and fluid-phase formats like RIA and homogeneous mobility shift assay. Most ATI assays are drug-sensitive because the binding of infliximab to ATIs may compromise the bivalency required for signal generation by bridging the capture and detection antibodies.[157] Consequently, these tests are suitable only for samples with undetectable or very low concentrations of infliximab. Monoclonal ATIs are often used as calibrators, with ATI titers expressed in relative units (eg, nanogram per milliliter equivalents of the calibrator antibody). Direct comparison of ATI titers between different assays is not feasible,[156] leading to vague categorizations as low, intermediate, and high ATIs to facilitate assay independence in dose optimization algorithms. Proposals for universal calibrators aim to enhance interlaboratory harmonization of ATI measurements.[158,159]

Clinical Information

Interpretation of infliximab concentration data should be done in conjunction with relevant clinical findings and

assessments. Considerations include body composition measures (eg, body weight), disease activity measures (eg, CRP, serum albumin, erythrocyte sedimentation rate, and FC), and pharmacology data, including concomitant immunomodulators and/or previous use of (other) biologics.

Clinical Recommendations

Clear clinical protocols detailing the time of sampling, sampling material, and transport conditions are essential. Laboratories measuring infliximab concentrations and ATIs should be certified and participate in proficiency testing programs to ensure the quality and interchangeability of analysis results.

Area(s) for Future Research

Investigating the feasibility of POC testing is crucial, along with determining effective ways to educate clinical staff without formal laboratory training in specimen collection and handling. In addition, exploring optimal strategies for global implementation of at-home monitoring through microsampling is essential. This includes addressing patient training, efficient sample logistics, and secure data transfer, ensuring seamless communication back to the clinician.

TRANSLATING LABORATORY DATA INTO DOSING RECOMMENDATIONS

Limited prospective evidence supporting the benefits of TDM of infliximab currently exists. With results from major prospective RCTs, such as NOR-DRUM B trial,[39] failing to demonstrate a clear advantage for TDM in achieving improved clinical outcomes,[17–19,41] there is a need for more precise and efficient TDM algorithms. Analog flowcharts or decision trees used in these trials may contribute to the imprecision of TDM, leading to a trial-and-error approach in dose optimization and potentially underestimating the potential of TDM.[160]

To enhance precision and accuracy in individualized dosing, model-informed precision dosing (MIPD), also known as dashboard-driven dosing, can be used.[160,161] MIPD uses population PK models, patient-specific monitoring data, and custom MIPD software tools to predict the optimal dose or dosing interval for achieving a desired drug concentration in a patient. Numerous commercially and freely available MIPD software tools are now accessible for clinical practice,[162] using typical PK estimates in a population PK model as prior information. With patient covariate measurements like body weight and serum albumin, the model provides rough estimates of individual PK parameters (a priori prediction). Incorporating drug concentration measurements alongside covariate values enables the model to "update" to a personalized PK model, facilitating patient-specific simulations for predicting the next dose needed to achieve a predefined concentration target (a posteriori prediction or Bayesian forecasting). Although validated in in silico simulations and retrospective studies,[163,164] the prospective RCT PRECISION trial was the first to evaluate the benefits of MIPD in infliximab dosing for patients with IBD.[53]

Results from the PRECISION trial demonstrated the superiority of MIPD over standard dosing for maintaining remission during maintenance therapy. Moreover, MIPD of infliximab displayed advantages in reducing immunogenicity and enhancing drug durability during induction, along with improved short-term efficacy in adults with IBD.[165,166] In pediatric patients with IBD, MIPD exhibited benefits in achieving targeted infliximab concentrations and minimizing immunogenicity.[75] Ongoing trials like TITRATE, MODIFI, REMODEL-CD, and OPTIMIZE are expected to provide further insights into the advantages of MIPD for infliximab. However, whether MIPD offers better outcomes compared with TDM, whether reactive or proactive, remains to be determined.[167,168]

There are ongoing efforts to enhance the predictive performance of MIPD and provide more evidence supporting its implementation in clinical practice. The predictive accuracy of MIPD is significantly influenced by the type of patient information considered. Among the published population PK models of infliximab, ATI status, serum albumin, and body weight were the most frequently identified covariates on infliximab clearance, with body weight being the most commonly identified covariate on volumes of distribution.[169] However, the clinical relevance of these statistically significant covariates to therapeutic target attainment remains undetermined. MIPD of infliximab based solely on covariates (a priori prediction) has been shown to be biased and imprecise.[169,170] By incorporating 1 or more measured drug concentrations, the precision and accuracy of MIPD can be significantly improved.[169–171] This improvement is expected because covariates generally explain only a small part of the total interindividual variability (IIV, up to 6% for clearance), whereas Bayesian forecasting based on drug concentrations can identify the remaining, often high, "unexplained" IIV (median of 32.7%, interquartile range 28.0%–36.0% on clearance).[172,173]

Second, there are significant efforts underway to enhance the methodological components of MIPD, focusing on methods for model selection[171,174,175] and the estimation of PK parameters.[176–178] Dozens of infliximab models have been developed to offer quantitative insights into the PK of specific populations. The predictive performance of infliximab population PK models was previously externally evaluated in patients with inflammatory diseases.[179–181] However, the selection and validation of the model with the best forecasting performance in often heterogeneous real-world populations remain challenging and costly.

To address this challenge, Uster et al[171] assessed multimodel approaches, such as a model averaging algorithm (MAA) and model selection algorithm (MSA), using vancomycin as a case study. The findings demonstrated more reliable Bayesian forecasting compared with using a single-model approach. In a recent retrospective study by Kantasiripitak et al,[169] the predictive performance of MIPD of infliximab based on the MAA/MSA algorithm was evaluated in adult patients with IBD undergoing infliximab dose de-escalation. The results indicated that an MAA resulted in the most accurate and precise a posteriori prediction compared with the MSA and a single-model approach.

Moreover, the predictive performance of both single- and multi-model approaches remained robust even in the absence of covariate data, as long as a single most recent TC (preferably at the point of care) of infliximab was provided. Kantasiripitak et al[71] also expanded their work to pediatric patients with IBD.

In addition to multimodel approaches, novel methods such as a continuous learning approach for MIPD,[174,175] Bayesian data assimilation,[176,177] and flattened priors models[178] have been suggested, although validation for infliximab is pending. Furthermore, nonpopulation PK approaches like machine learning and artificial intelligence algorithms[182,183] are under development, although their potential benefits over population PK-based approaches for infliximab remain unclear. Finally, the predictive ability of MIPD is typically described by criteria like classification accuracy (eg, the ability to predict the next TC to be higher or lower than a specific threshold) or the difference between predicted and measured values (eg, root mean square error or relative bias).[169,171,175] However, there is a lack of consensus on how to evaluate the success of MIPD, and further investigation into the impact of different evaluation criteria on choosing a suboptimal model is needed.

There are still regulatory concerns surrounding MIPD. The European Union's General Data Protection Regulation allows a citizen to understand the reasons behind a clinical decision produced by machine learning/artificial intelligence and to reject such a decision under the right of "meaningful human review."[184] However, it remains unclear how applicable, enforceable, and beneficial these articles are for MIPD, given that MIPD only provides dose recommendations, potentially checked and authorized by a clinical pharmacist, with the final decision on adjusting the dosing generally left at the discretion of the treating physician.[185] In addition, with the impact of the new European Union Medical Device Regulation, MIPD software is considered a class II medical device and is subject to strict risk compliance.[186]

Clinical Recommendations

To maximize its effectiveness, we recommend combining MIPD with POC testing or home sampling and integrating it with the electronic health record (EHR) system (Fig. 3). First, seamless integration with the EHR system is necessary to automate the extraction of diverse patient data types directly from the EHR, enhancing the clinical utility of MIPD.[74,185] Second, POC testing can be combined with MIPD to reduce the turnaround time of concentration measurement and allow dose recommendations based on "real-time" PK of the patient.

Area(s) for Future Research

In the future, MIPD with a population PK-PD model may be intriguing for simultaneously predicting treatment outcomes associated with the predicted drug exposure. Understanding the relationship between infliximab exposure, PK parameters, and PD biomarkers may facilitate the identification of patients with mechanistic nonresponsiveness, for whom infliximab monitoring and dosing adjustments should be avoided.[81] Although one most recent TC of infliximab sufficed for accurate and precise Bayesian forecasting in a retrospective evaluation,[169] more research is still required to identify optimal sampling regimens resulting in the most accurate Bayesian forecasting. Finally, an SC formulation of infliximab was recently added to the armamentarium for maintenance treatment in patients with chronic inflammatory disease.[187] Although future prospective evidence is still needed, both in silico simulations and real-world evidence support the use of TDM/MIPD in this new clinical setting.[82,188]

IMPLEMENTING DOSE RECOMMENDATIONS INTO PATIENT CARE

Poor awareness of guidelines, a lack of knowledge, absence of insurance coverage, high out-of-pocket costs, the time lag from test to result, and the perception of TDM being time-consuming have been identified as factors limiting the implementation of TDM in routine practice.[189–192] Implementing TDM for infliximab in routine clinical practice is a complex endeavor that surpasses defining the right patients and therapeutic targets, and formulating correct dosing recommendations. For TDM to yield sensible improvements in individual and population health care, several practical aspects and challenges need to be properly addressed.

TDM in Different Health Care Settings

Successful TDM adoption hinges on tailoring its implementation to individual patient needs in various health care contexts with distinctive challenges.[193] Although TDM integration could be easier in large hospitals equipped with specialized units and advanced laboratories, primary care clinics and some secondary care facilities may face resource constraints hampering TDM adoption. Collaborations with specialized tertiary centers for TDM analysis can overcome such challenges. In addition, proper patient education and training for interested physicians can further enhance TDM integration across all health care circles involved in patient care.[194] Moreover, home-based care, using user-friendly POC TDM devices, should be made available to provide a convenient and patient-centric approach for long-term monitoring.[195]

Patient Education and Empowerment for Self-management

Patients may perceive some inconvenience related to frequent dose adjustments upon TDM implementation. Nevertheless, TDM provides an additional opportunity to engage patients in their health care journey, potentially resulting in better medication adherence and improved disease management.[196] To achieve this, treating physicians should provide patients with clear instructions on monitoring schedules and dose adjustments, helping them interpret TDM results to make informed decisions.

Impact on Workloads for Health Care Teams

TDM implementation can have implications on the workload of health care professionals, in both hospitals and primary care clinics.[197] Introducing TDM will require

additional training for staff involved in sample collection, data interpretation, and dosing adjustments. Consequently, health care teams will need to allocate time for TDM-related tasks, impacting the overall workflow.[136,139] However, effective integration of TDM into EHRs and clinical decision support systems can streamline processes, decrease workload, and enhance efficiency.

Ensuring Accessible and Affordable TDM

For TDM to enhance population health and support personalized treatment strategies, it should be accessible to all patients who require it.[198] This goal can be accomplished by minimizing or even eliminating additional financial burdens for patients. There is a crucial need to assess the cost-effectiveness of TDM and compellingly present these data to policy-makers to justify its reimbursement by payers and health care systems.[199] Furthermore, showcasing the long-term benefits of TDM, such as optimized treatment regimens leading to improved drug survival, reduced hospitalizations, and better disease control, will motivate health care facilities to allocate the necessary resources for TDM implementation.

Clinical Recommendations

In the pursuit of a robust implementation of TDM for infliximab in routine clinical practice, the assessment of individual patient circumstances and preferences to comprehensively identify and map all health care entities engaged in patients' care is recommended. Subsequently, a plan should be devised to ensure seamless integration of TDM interventions across these diverse spheres of health care. By fostering collaboration among health care providers, the realization of operational efficiency and cost-effectiveness becomes attainable. Central to this endeavor is the commitment to patient-centricity, where TDM is made conveniently accessible in proximity to the patient, facilitated through home-based care and the utilization of user-friendly POC TDM devices. Empowering patients by providing unambiguous guidelines and information about interpreting TDM results and implementing subsequent dose adjustments will optimize medication adherence. Finally, periodic evaluations of the TDM process within health care facilities are needed to monitor the workload and adjust processes accordingly to ensure a sustainable TDM implementation.

Area(s) for Future Research

There is a pressing need to investigate the best practices to implement TDM in resource-constrained health care settings and optimize workflow efficiency to minimize workload. In addition, further research on the cost-effectiveness of TDM and reimbursement models is crucial to ensure equitable access to TDM. Other important aspects include understanding patient acceptance of TDM and evaluating the efficacy of patient education in facilitating self-management.

DISCUSSION AND CONCLUSIONS

TDM has established a strong presence in gastroenterology research and practice and to a lesser extentin rheumatology and dermatology. Although generic definitions exist, the diverse practices in TDM have given rise to novel terms. Over 2 decades ago, the concept of target concentration intervention emerged,[200] introducing the idea of using PK models and patient exposure and response information for individualized dosing. This approach differs from the traditional therapeutic range–based TDM, emphasizing the optimization of effectiveness and, to a lesser extent for infliximab, safety. The target concentration intervention concept aligns with what is now known as MIPD. Although relatively new,[201] the term MIPD has not yet gained widespread use in gastroenterology, rheumatology, and dermatology literature. Instead, terms like "PK dashboard" and "dashboard-driven dosing" have been introduced to highlight the need for a software tool for MIPD. The introduction of clearance monitoring in the field of IBD[202] holds potential, but its value requires further validation.

Incorporating TDM of infliximab into routine clinical practice necessitates careful consideration of patient phenotype, clinical setting, and therapeutic targets. An interdisciplinary understanding of the roles and processes involved in TDM is crucial, especially with innovations such as remote sampling, POC testing, and MIPD becoming part of clinical practice. A comprehensive understanding of the health care setting is vital for successful TDM, encompassing the clinical laboratory, hospital pharmacy, and clinical pharmacology/pharmacometrics teams.

Although TDM of infliximab has not yet universally permeated routine practice, ongoing investigations explore exposure–response relationships, focusing on metrics beyond TCs and more ambitious treatment outcomes. The establishment of optimal TDM modalities and accumulating evidence for clinical benefits, even in rheumatology and dermatology, are noteworthy developments. Fundamental questions persist, but pivotal clinical trials like TITRATE, REMODEL-CD, MODIFI, and OPTIMIZE are expected to provide answers in the coming years. Furthermore, as TDM has primarily focused on optimizing therapeutic effectiveness in IBD, its potential for cost reduction warrants serious consideration across other IMIDs.[203]

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