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A comprehensive literature review and expert consensus statement on therapeutic drug monitoring of biologics in inflammatory bowel disease

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Abstract

Therapeutic drug monitoring (TDM) of biologics is a rapidly evolving field. We aimed to provide a consensus statement regarding the clinical utility of TDM for biologics in inflammatory bowel disease (IBD).

A modified Delphi method was applied to develop consensus statements. A comprehensive literature review was performed regarding TDM of biologic therapies in IBD and 45 statements were subsequently formulated on the potential application of TDM in IBD. The statements, along with literature, were then presented to a panel of 10 gastroenterologists with expertise in IBD and TDM who anonymously rated them on a scale of 1 to 10 (1=strongly disagree and 10=strongly agree). An expert consensus development meeting was held virtually to review, discuss, refine and reformulate statements that did not meet criteria for agreement, or that were ambiguous. During the meeting, additional statements were proposed. Panellists then confidentially re-voted, and statements rated ≥7 by 80% or more of the participants were accepted.

During the virtual meeting, 8 statements were reworded; 7 new statements were proposed; and 19 statements were rerated. Consensus was finally reached in 48/49 statements. The panel agreed that reactive TDM should be utilized for all biologics for both primary non-response and secondary loss of response. It was recommended that treatment discontinuation should not be considered for infliximab or adalimumab until a drug concentration of at least 10-15μg/ml was achieved. Consensus was also achieved regarding the utility of proactive TDM for anti-tumor necrosis factor (anti-TNF) therapy. It was recommended to perform proactive TDM post-induction and at least once during maintenance.

Consensus was achieved in most cases regarding the utility of TDM of biologics in IBD, specifically for reactive and proactive TDM of anti-TNFs.

Keywords

consensus statement; Crohn’s disease; ulcerative colitis; immunogenicity; anti-TNF; vedolizumab; ustekinumab

INTRODUCTION

Although biologics are effective for treating inflammatory bowel diseases (IBD)[1], up to 30% of patients do not respond (primary non-responders) and another 50% lose response over time [secondary loss of response (SLR)].[2, 3] Sub-therapeutic drug concentrations with or without the development of anti-drug antibodies (ADA) can explain a substantial portion of these outcomes.[4]

Therapeutic drug monitoring (TDM), defined as the measurement of drug concentrations and ADA, has surfaced as an important tool for optimizing biologic therapy.[5] Reactive TDM is the evaluation of drug concentration and ADA in the setting of treatment failure and can help facilitate decision-making in both primary non-response (PNR) and SLR.[6-10] Preliminary data suggests that proactive TDM, defined as the systematic

measurement of drug trough concentrations and ADA with dose adaptation to a target drug concentration, can also improve the efficacy of anti-tumor necrosis factor (anti-TNF) therapy.[11-19] Proactive TDM may also be utilized to decrease the dose of infliximab in patients in remission with greater than adequate infliximab concentrations[20-23] or for optimizing infliximab monotherapy as a potential alternative to combination therapy with an immunomodulator (IMM) in select patients.[24, 25] However, there is debate on when and how to perform TDM in clinical practice.

We aimed to reach a consensus on the role of TDM of biologics in IBD and sought to identify clinically relevant drug concentrations and ADA thresholds to guide physicians on how to better apply TDM in clinical practice.

METHODS

We applied a modified Delphi method to establish consensus, as previously described.[5, 26] A comprehensive literature review was performed regarding TDM of biologic therapies in IBD using PubMed and Medline databases. We utilized the search terms: ‘inflammatory bowel disease’; ‘Crohn’s disease’; ‘ulcerative colitis’; ‘anti-drug antibodies’; ‘immunogenicity’; ‘therapeutic drug monitoring’; ‘point of care assays’; ‘pharmacokinetics’ AND ‘infliximab’ OR ‘adalimumab’ OR ‘certolizumab pegol’ OR ‘golimumab’ OR ‘vedolizumab’ OR ‘ustekinumab’. Forty-five statements were subsequently formulated (K.P., A.S.C) on the potential application of TDM in IBD. These statements were grouped into 5 domains: reactive TDM; proactive TDM; general statements regarding TDM; immunogenicity; and drug concentrations to target. The statements, along with literature, were then presented to a panel of 10 gastroenterologists with expertise in IBD and TDM who anonymously rated them on a scale of 1 to 10 (1=strongly disagree and 10=strongly agree). An Expert Consensus Development Meeting was held virtually on October 30, 2020, to review, discuss, refine and reformulate statements that did not meet criteria for agreement or that were ambiguous. During the meeting, additional statements were proposed. Panellists then confidentially re-voted, and statements rated ≥7 by 80% or more of the participants were accepted.

RESULTS

During the virtual Expert Consensus Development Meeting, 8 statements were reworded; 7 new statements were proposed; and 19 statements were rerated. Consensus was finally reached in 48 of 49 statements (Tables 1-5 and Table 1, Supplemental Digital Content #1).

Reactive TDM

Statements that reached consensus regarding the role of reactive TDM are presented in Table 1. Supportive text for these statements (1-9) is provided in Supplemental Digital Content #2.[27-44]

Proactive TDM

Statements that reached consensus regarding the role of proactive TDM are presented in Table 2. Supportive text for these statements is provided below.

Numerous exposure-outcome relationship data from prospective studies and post-hoc analyses of randomized controlled trials (RCTs) have shown that higher induction, post-induction and maintenance anti-TNF drug concentrations are associated with more favorable therapeutic outcomes suggesting a role for proactive TDM for optimizing anti-TNF therapy.[3-5] Furthermore, the TAXIT (Trough Concentration Adapted Infliximab Treatment) (RCT), although didn't reached its the primary endpoint, showed that proactive TDM compared to clinically-based dosing was associated with lower frequency of undetectable infliximab concentrations and lower risk of relapse.[15] Additionally, in patients with CD and subtherapeutic drug concentrations, a one-time dose optimization increased clinical remission rates and decreased C-reactive protein (CRP).[15] The PAILOT (Pediatric Crohn's Disease Adalimumab Level-based Optimization Treatment) RCT demonstrated that proactive dose adjustment of adalimumab when treating pediatric CD was associated with a higher rate of corticosteroid-free clinical remission at all visits from weeks 8 to 72 when compared to reactive TDM. A proactive TDM approach was also associated with a higher rate of composite sustained corticosteroid-free clinical remission, normal CRP and normal fecal calprotectin at all time-points.[16] Furthermore, several retrospective studies for infliximab and one for adalimumab have demonstrated that proactive TDM compared to empiric dose optimization and/or reactive TDM was associated with better therapeutic outcomes, such as greater treatment persistence, less need for IBD-related surgery or hospitalization, and lower risk of ADA.[11-13, 17, 18] A recent retrospective multi-center study showed that in patients with a SLR to infliximab who underwent reactive TDM, subsequent proactive TDM following the initial reactive TDM was associated with greater infliximab treatment persistence and fewer IBD-related hospitalizations than reactive TDM alone.[19]

Proactive TDM is probably most important in more severely active patients and in those who have higher drug clearance, such as patients during induction therapy and patients with acute severe UC and more severe CD. These patients have a high inflammatory burden, an increased drug clearance, and therefore a greater risk of inadequate drug exposure, immunogenicity and treatment failure.[45-48] Another IBD population with a high drug clearance is the pediatric population.[49, 50]

Proactive TDM can also have an important role when de-escalating therapy.[20-23] A prospective study by Amiot *et al.*[20] suggested that in patients with IBD in clinical remission de-escalation of infliximab therapy should be done based on TDM rather than symptoms and CRP. A recent retrospective study of 96 patients with IBD in remission showed that TDM-based compared to clinically based de-escalation was associated with a decreased risk of relapse.[21] Furthermore, it is clinically reasonable to confirm that the trough concentration is still adequate after dose de-escalation. A study from Peticolloin *et al.* of 91 patients with IBD in deep remission showed that TDM is also useful for following patients after de-escalation.[22] Similarly, proactive TDM should be considered after removal of an immunosuppressive therapy (i.e. azathioprine or methotrexate).[51] A study by Drobne et al. including patients with CD treated with infliximab combination therapy with an IMM showed that a detectable trough infliximab concentration at the time of IMM withdrawal is associated with long-term response.[52] Of note, drug trough concentrations >5 μg/mL at the time of IMM withdrawal had a positive predictive value of 100% for not losing response to infliximab.[52]

Another possible use of proactive TDM could be to optimize monotherapy in a select group of patients as an alternative to combination therapy with an IMM. In a post-hoc analysis of the SONIC (Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease) RCT stratification of infliximab concentrations displayed comparable outcomes within each concentration quartile irrespective of concomitant azathioprine suggesting that combination therapy with infliximab and azathioprine may not be required if adequate drug concentrations of infliximab are attained using proactive TDM.[51] Furthermore, two recent retrospective studies showed that drug persistence was similar between patients on optimized infliximab monotherapy based on proactive TDM and patients receiving combination therapy.[24, 25] Lega *et al.* also showed that in patients undergoing proactive TDM for optimizing infliximab monotherapy compared to those receiving unoptimized infliximab monotherapy, infliximab drug concentrations during maintenance therapy were higher and treatment discontinuation was lower. Moreover, no patient undergoing proactive TDM had antibodies to infliximab (ATI) at first TDM compared to 41% of patients receiving unoptimized infliximab monotherapy (p=0.002).[24] However, currently there are no data from RCTs supporting the concept of optimized infliximab monotherapy based on proactive TDM as an alternative to combination therapy with an IMM.

It should be clear that we are not recommending anti-TNF monotherapy over combination therapy with an IMM, as unoptimized monotherapy without early and aggressive proactive TDM is not as effective as combination therapy with an IMM and should not be considered. However, proactive TDM-based optimized anti-TNF monotherapy could be considered in a select group of adherent patients based on several factors such as risk of adverse events and patient preference.[53-56] Examples include situations where there is concern for increased risk of serious infection or malignancy[54] or when there is no genetic predisposition for immunogenicity.[55, 56] Proactive TDM for optimizing anti-TNF monotherapy is better than unoptimized anti-TNF monotherapy.

Regarding biologics other than anti-TNF therapies the only data supporting the role of proactive TDM currently derives exclusively from exposure-response relationship studies showing that higher vedolizumab and ustekinumab concentrations are associated with better therapeutic outcomes.[30-44]

General considerations regarding TDM

General statements regarding TDM that reached consensus are presented in Table 3. Supportive text for these statement is provided below and in Supplemental Digital Content #2.

Anti-TNF induction therapy—Several studies have shown an association between higher induction anti-TNF drug concentrations and favorable therapeutic outcomes in IBD implying that TDM should probably be performed early after treatment initiation. For example, higher infliximab concentrations at week 6 and 14 are associated with higher rates of positive clinical outcomes so checking drug concentrations at these time points is reasonable.[3-5] TDM during induction is important as patients during induction have active disease (often characterized by low serum albumin and high baseline CRP levels)

and consequently increased drug clearance, putting them at higher risk for inadequate drug exposure, early development of immunogenicity and treatment failure.[57-62] In addition to ADA, low albumin and high CRP levels are associated with a higher anti-TNF clearance. There is also some evidence that male gender and high body mass index are correlated with lower drug concentration.[63] In the prospective PANTS (Personalised anti-TNF therapy in Crohn's disease) study, low drug concentration at week 14 was independently associated with PNR and non-remission at week 54 for both infliximab and adalimumab. The optimal week 14 drug concentrations associated with remission at weeks 14 and 52 were 7 mg/L for infliximab and 12 mg/L for adalimumab. For both drugs, suboptimal week 14 drug concentrations were associated with immunogenicity, as was the development of ADA with subsequent low drug concentrations.[64] In a study by Verstockt *et al.*[58] patients with low adalimumab concentrations at week 4 (<8.3 μg/mL) were at significantly higher risk to have antibodies to adalimumab (ATA) by week 12 (46.7% vs 13.0%, p=0.009). The 21.4% of patients who were ATA positive by week 12 had significantly more frequent dose escalation and experienced sustained clinical benefit less frequently due to PNR or SLR.

Infliximab drug holiday—In a study from Baert *et al.*[65] among 128 consecutive patients who restarted infliximab after a median 15-month hiatus, the absence of ATI at an early sample after re-exposure to infliximab (typically before second infusion) was associated with improved short-term responses. Similarly, higher trough concentrations at an early sample after re-exposure to infliximab were associated with long-term response. Of note, ATI at an early sample after re-exposure to infliximab were associated with a higher rate of infusion reactions (with detectable ATI) after reinitiating therapy. In fact, the greatest risk for a serious acute infusion reaction is the second or third dose after a drug holiday.[65] Though data is limited, testing for ADA after the first re-induction and administering the second dose only after confirmation of absence of ADA for safety reasons is recommended. The same study showed that IMM co-treatment at restart was the only clinical predictor for preventing infusion reactions implying that an addition of an IMM when re-initiating infliximab following a drug holiday is a valid option.[65]

TDM assays—Although commercially available assays typically correlate well, absolute drug concentrations can differ among assays or even the same type of assay.[66-77] This is very important as clinical decisions are typically based on drug concentration thresholds to target. Two recent studies comparing a commercially available homogeneous mobility shift assay (HMSA) and the enzyme-linked immunosorbent assay (ELISA) to assess infliximab, adalimumab and ustekinumab concentrations demonstrated quantitative and qualitative discrepancies in drug concentrations.[72, 73] Similar discrepancies have been identified between ELISAs and point of care assays.[74] As the clinical impact of these differences has not been extensively investigated, and until commercial assays are accurately cross-validated and standardized, patients should ideally be followed and managed over time with the same TDM assay. In order to facilitate harmonization of TDM assays and quality control implementation of an international standard and use of universal calibrators should be considered.

Biosimilars—Supportive text for statement 22 is provided in Supplemental Digital Content #2.[78-80]

Immunogenicity

Statements that reached consensus regarding immunogenicity are presented in Table 4. Supportive text for these statements is provided below. Among all statements, only one did not reach consensus: 'Low-titer antibodies to adalimumab (ATA) can be defined as <4 μg/ml for the ELISA' (10% vote of ≥7).

Numerous studies have shown that ADA are associated with sub-therapeutic or undetectable drug concentrations and undesirable clinical outcomes, such as PNR, SLR and infusion reactions.[45, 57-59, 64, 81-88] These refer mostly to high-titer, neutralizing, persistent ADA that cannot be overcome with dose optimization and are associated with undetectable drug concentrations and treatment failure. It seems that ADA present when drug is still detectable by a drug tolerant assay may not be clinically relevant.[77, 86] However, there are some data suggesting that ADA, even at low concentrations and in the presence of drug, may still be a risk factor for SLR to infliximab or adalimumab and treatment discontinuation highlighting the importance of systematic TDM to look for an increase of ADA titers and/or undetectable drug concentrations and to determine if ADA can be overcome following treatment optimization.[88, 89] A recent prospective study showed that the prevalence of ATI and ATA is high when detected early using a drug-tolerant assay and their presence predicts further treatment discontinuation.[89] Time to treatment discontinuation was significantly shorter in patients with ATA ≥2.0 μg/mL or ATI ≥4.0 μg/mL at week 2 compared to patients without positive ADA. In multivariate analysis ATI or ATA at week 2 were the only factors associated with treatment discontinuation.[89]

In case of SLR to anti-TNF therapy due to the development of high titer ADA physicians should switch to a different biologic. A study more than 10 years ago showed that in patients with detectable ATI a change to another anti-TNF agent was associated with a complete or partial response in 92% of patients, whereas dose escalation resulted in a response of only 17%.[90] More recently, Yanai *et al.*[7] showed that ATA >4 μg/mL or ATI >9 μg/mL identified patients who did not respond to an increased drug dosage. Although dosage increases were more effective for patients with no or low-titer ADA patients with high-titer ADA had longer durations of response when anti-TNFs were switched than when dosage was increased.

When considering a switching within drug class the recommendation would be to add an IMM to a subsequent anti-TNF therapy to prevent the formation of ADA to the second anti-TNF. In a recent RCT, consecutive patients with IBD who developed a SLR to monotherapy with an anti-TNF due to ADA received a second anti-TNF and were randomised to receive either combination therapy with a second anti-TNF (adalimumab, 40; infliximab, 50 patients) with azathioprine (n=45) or a second anti-TNF as monotherapy (n=45). Rates of clinical failure and appearance of undetectable trough concentrations with high ADA were higher in monotherapy compared with combination therapy.[91]

However, the distinction between low and high ADA titers may be difficult as they are assay specific and as there are still limited data for assays other than the HMSA and

for biologics other than infliximab.[92] This is of great clinical importance as low-titer ADA can be overcome by treatment optimization (dose escalation, dose interval shortening and/or addition of an IMM),[93-98] while high-titer ADA can lead to undetectable or low drug concentrations, infusion reactions and treatment failure. [45, 57-59, 64, 81-88] Two studies showed that ATI >9.1 U/ml were associated with failure of dose intensification after SLR, infliximab discontinuation, and infusion reactions.[24, 85] Ben-Horin *et al.*[94] reported that in 5 patients with IBD and SLR to infliximab due to immunogenicity, ATI gradually decreased, drug concentrations increased and clinical responses were restored following the administration of IMM. Ungar *et al.*[95] showed that in almost half of patients with IBD and SLR due to immunogenicity ATA could be gradually reversed by the addition of an IMM with restoration of a clinical response.[95] Moreover, Strik *et al.*[93] showed that in 77% of IBD patients with SLR due to immunogenicity, addition of IMM resulted in undetectable ADA levels, increased serum drug concentrations and regaining of clinical response in patients treated with infliximab and adalimumab.[93] Regarding ADA titers that can be overcome with treatment optimization, Papamichael *et al.*[96] demonstrated that ATI<8.8 U/mL using the HMSA was associated with drug retention in patients with IBD in whom infliximab was optimized, either proactively or reactively, to overcome immunogenicity. Similarly, a recent study using a large database derived cohort showed that ATI≤8.55 U/mL via HMSA was associated with overcoming ATI with dose escalation.[98]

The formation of ADA cannot only be overcome, but also be prevented by the use of IMM.[64, 99-101] A retrospective multi-center study showed that thiopurines-infliximab combination therapy in patients with CD was associated with reduced ATI formation compared with infliximab monotherapy.[99] In the prospective PANTS study, combination IMM (thiopurine or methotrexate) therapy mitigated the risk of developing ATI [Hazard ratio (HR): 0.39; 95%confidence interval (CI): 0.32–0.46, p<0.001) and ATA (HR: 0.44; 95%CI: 0.31–0.64; p<0.001).[64] A meta-analysis of 35 studies showed that combined treatment with IMM is associated with reduced risk of formation of antibodies against anti-TNF in patients with IBD. The pooled risk ratio for formation of ADA in patients receiving combined therapy with IMM versus that of patients receiving anti-TNF monotherapy was 0.49 (95%CI: 0.41-0.59; p<0.001).[101] Finally, it seems that even lower doses (<1mg/Kg) of azathioprine can prevent immunogenicity of infliximab in patients with IBD receiving combination therapy.[100]

Regarding risk factors for ADA formation, a genome-wide association study found that the HLA-DQA1*05 allele increased the risk of ATI and ATA development by 2-fold in patients with CD, regardless of concomitant IMM use. The highest rates of immunogenicity, 92% at 1 year, were observed in patients treated with infliximab monotherapy who carried HLA-DQA1*05. Conversely the lowest rates of immunogenicity, 10% at 1 year, were observed in patients treated with adalimumab combination therapy who did not carry HLA-DQA1*05.[55] In the same line, HLADQA1*05 was found to be independently associated with a high risk of ATI in addition to infliximab SLR and treatment discontinuation.[56]

Immunogenicity to biologics other than anti-TNF therapy is less common. The development of ADA is relatively low for vedolizumab and ustekinumab ranging from 1 to 4.1% and 0.7 to 4.6%, respectively.[102, 103]

Biologic drug concentrations to target

Statements that reached consensus regarding drug concentrations to target are presented in Table 5 and Table 1, Supplemental Digital Content #1. Supportive text for these statements is provided below and in Supplemental Digital Content #2 (for **statements 40-48**).

Numerous exposure-response relationship studies suggest that biologic drug concentration thresholds and ranges appear to differ depending on treatment goals (Table 6), disease phenotypes and assays used.[2-5, 31-33, 39-41, 81, 104-118] In general, higher drug concentrations tend to be associated with more stringent outcomes such as endoscopic and histologic remission,[2-5] while even higher drug concentrations may be needed for IBD phenotypes characterized by a higher inflammatory burden, such as fistulising CD[119, 120] and acute severe UC.[46] However, these data mostly refer to infliximab and adalimumab.

We would like to highlight that for all statements regarding the biologic drug concentrations to target the suggested range was based on previously published association data[3-5] and the upper limit of range typically refers to drug concentration associated with more stringent therapeutic outcomes such as biochemical, endoscopic, histologic or composite remission defined as any combination of the previous.

During the on-line meeting, it was highlighted that there are only limited data about the drug concentrations to target for certolizumab pegol, golimumab, vedolizumab and ustekinumab (**statements 40-48**) and the panellists felt that robust recommendations could not be made based on so few studies and that the data be presented only as a supplementary table (Table 1, Supplemental Digital Content #1). For these biologics the suggested range was based on data from post-hoc analysis of RCTs and prospective studies, where available.[3-5]

DISCUSSION

Although most gastroenterology societies, as well as expert groups, endorse the use of reactive TDM of anti-TNF therapy, there is still a debate regarding the role of proactive TDM.[10] There is also debate regarding the application of reactive TDM for non-TNF biologics and threshold drug concentrations to target.

The panel agreed that reactive TDM should be utilized for all biologics for both PNR and SLR. It was also recommended that treatment discontinuation should not be considered for infliximab or adalimumab until a drug concentration of at least 10-15μg/ml is achieved. In the absence of high quality data and reflecting also the clinical practice of the panellists, the suggested range of 10-15 μg/mL was selected based on data from incremental gain[116] and quartile analysis[107, 110, 120] of association studies showing that drug concentrations in quartiles (Q)3 and 4 are associated with better therapeutic outcomes. For example, infliximab concentrations ≥ 12.3 μg/ml (Q4) are associated with higher rates of endoscopic and histologic healing.[110] Moreover, infliximab concentrations in Q3 (10.1-20.1 μg/ml) or Q4 (≥ 20.2 μg/ml) are associated with higher rates of mucosal or fistula healing as well as fistula closure.[120] By using a rather higher (10-15 μg/mL) than the standard infliximab (5-10 μg/mL) or adalimumab (8-12 μg/mL) concentration range to target (mostly referring to proactive TDM) we wanted to highlight that the drug should not be inappropriately

abandoned for a presumed mechanistic failure when reactive TDM is applied for SLR. This is very important as most of the SLR is attributed to PK issues because of low/sub-therapeutic drug concentrations.[2]

RCTs to test proactive TDM are more limited demonstrating inconsistent results probably also due to differences in study design and algorithms used for dose optimization.[15, 16, 121-123] The TAXIT[15] and the TAILORIX[121] (A Study investigating Tailored Treatment With Infliximab for Active Crohn's Disease) RCTs didn't reach their primary outcomes, while the PAILOT[16] and the PRECISION[123] (Precision Dosing of Infliximab Versus Conventional Dosing of Infliximab) RCTs showed that proactive TDM is associated with better therapeutic outcomes compared to standard of care. More recently, the NOR-DRUM (NORwegian DRUg Monitoring study) RCT was the first study to compare the efficacy and safety of proactive TDM starting early during the induction phase with standard infliximab therapy in patients with immune mediated inflammatory diseases, such as rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, IBD or psoriasis.[122] Although the primary end point of clinical remission at week 30 and numerous secondary outcomes were not met it is difficult to draw firm conclusions for IBD as the trial did not have the statistical power to test hypotheses within each disease subgroup. We would like to highlight that only 1/3 of the study population who received the randomized intervention had IBD, mucosal healing as a stringent objective therapeutic outcome was not investigated and the 3μg/ml infliximab concentration threshold for allowing treatment optimization seems very low based on recent data in IBD.[3-5]

The panel recommended performing proactive TDM for anti-TNF post-induction and at least once in the maintenance phase of therapy. It was felt that more data were needed to support the use of proactive TDM for other biologics. Moreover, the panel agreed that proactive TDM can efficiently guide therapeutic decisions in other clinical scenarios including treatment de-escalation, optimized anti-TNF monotherapy instead of combination therapy, verification of therapeutic drug concentrations after reactive testing, and assessment of ADA after restarting IFX following a drug holiday. The panel also suggested a range rather than a specific threshold of clinically relevant biologic drug concentrations to target, as these can vary based on the therapeutic outcome of interest, typically being higher for more stringent outcomes such as endoscopic and histologic remission or fistula healing. Biologic drug concentrations to target may also differ based on the assay used and the IBD phenotype.[2-5]

Nevertheless, additional data from prospective studies and RCTs concerning the use of proactive TDM, particularly during the induction phase, incorporating point-of-care assays[58] and/or PK dashboards[123, 124] are warranted. Point-of-care assays will provide a rapid assessment of drug concentrations and allow an immediate adjustment of drug dosage. PK dashboards integrate individual clinical and PK data to forecast dosing recommendations to target pre-specified drug concentrations for individual patients and allow for more personalised care. PK modeling and pharmacogenetics to identify patients with a high risk of accelerated drug clearance and a genetic predisposition of ADA formation,[55, 56] respectively, would allow a selection of those patients who would benefit more from proactive TDM. Another important area that needs further investigation is the role of TDM

in biologics other than infliximab and adalimumab, as recommendations for these drugs are only based on exposure-outcome association studies which are limited. Finally, there is a gap in knowledge regarding the measurement of peak drug concentrations[39] and total drug exposure.[125]

In conclusion, TDM of biologics is a useful tool in optimizing the care of patients with IBD. We hope that these consensus statements based on interpretation of the available literature can assist physicians in improving the care of patients with IBD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Katsanos KH, Papamichael K, Feuerstein JD, et al. Biological therapies in inflammatory bowel disease: Beyond anti-TNF therapies. Clin Immunol 2019;206:9–14 [PubMed: 29545207]
2. Vande Casteele N, Herfarth H, Katz J, et al. American Gastroenterological Association institute technical review on the role of therapeutic drug monitoring in the management of inflammatory bowel Diseases. Gastroenterology 2017;153:835–857. [PubMed: 28774547]
3. Sparrow MP, Papamichael K, Ward MG, et al. Therapeutic drug monitoring of biologics during induction to prevent primary non-response. J Crohns Colitis 2020;14:542–556. [PubMed: 31549158]
4. Vermeire S, Dreesen E, Papamichael K, et al. How, when, and for whom should we perform therapeutic drug monitoring? Clin Gastroenterol Hepatol 2020;18:1291–1299. [PubMed: 31589978]
5. Papamichael K, Cheifetz AS, Melmed GY, et al. Appropriate therapeutic drug monitoring of biologic agents for patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2019;17:1655–1668. [PubMed: 30928454]
6. Roblin X, Rinaudo M, Tedesco E, et al. Development of an algorithm incorporating pharmacokinetics of adalimumab in inflammatory bowel diseases. Am J Gastroenterol 2014;109:1250–1256. [PubMed: 24913041]
7. Yanai H, Lichtenstein L, Assa A, et al. Levels of drug and antidrug antibodies are associated with outcome of interventions after loss of response to infliximab or adalimumab. Clin Gastroenterol Hepatol 2015;13:522–530. [PubMed: 25066837]
8. Kelly OB, Donnell SO, Stempak JM, et al. Therapeutic drug monitoring to guide infliximab dose adjustment is associated with better endoscopic outcomes than clinical decision making alone in active inflammatory bowel disease. Inflamm Bowel Dis 2017;23:1202–1209. [PubMed: 28498155]
9. Restellini S, Chao CY, Lakatos PL, et al. Therapeutic drug monitoring guides the management of Crohn's patients with secondary loss of response to adalimumab. Inflamm Bowel Dis 2018;24:1531–1538. [PubMed: 29668893]
10. Papamichael K, Cheifetz AS. Therapeutic drug monitoring in patients on biologics: lessons from gastroenterology. Curr Opin Rheumatol 2020;32:371–379. [PubMed: 32412995]
11. Syed N, Tolaymat M, Brown SA, et al. Proactive drug monitoring is associated with higher persistence to infliximab and adalimumab treatment and lower healthcare utilization compared with reactive and clinical monitoring. Crohns Colitis 360 2020;2:otaa050. [PubMed: 32743546]
12. Papamichael K, Chachu KA, Vajravelu RK, et al. Improved long-term outcomes of patients with inflammatory bowel disease receiving proactive compared with reactive monitoring of

serum concentrations of infliximab. Clin Gastroenterol Hepatol 2017;15:1580–1588. [PubMed: 28365486]

13. Vaughn BP, Martinez-Vazquez M, Patwardhan VR, et al. Proactive therapeutic concentration monitoring of infliximab may improve outcomes for patients with inflammatory bowel disease: results from a pilot observational study. Inflamm Bowel Dis 2014;20:1996–2003. [PubMed: 25192499]
14. Lyles JL, Mulgund AA, Bauman LE, et al. Effect of a practice-wide anti-TNF proactive therapeutic drug monitoring program on outcomes in pediatric patients with inflammatory bowel disease. Inflamm Bowel Dis 2021;27:482–492. [PubMed: 32448898]
15. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology 2015;148:1320–1329. [PubMed: 25724455]
16. Assa A, Matar M, Turner D, et al. Proactive monitoring of adalimumab trough concentration associated with increased clinical remission in children with Crohn's disease compared with reactive monitoring Gastroenterology 2019;157:985–996. [PubMed: 31194979]
17. Sánchez-Hernández JG, Rebollo N, Martin-Suarez A, et al. A 3-year prospective study of a multidisciplinary early proactive therapeutic drug monitoring programme of infliximab treatments in inflammatory bowel disease. Br J Clin Pharmacol 2020;86:1165–1175. [PubMed: 32022291]
18. Papamichael K, Juncadella A, Wong D, et al. Proactive therapeutic drug monitoring of adalimumab is associated with better long-term outcomes compared to standard of care in patients with inflammatory bowel disease. J Crohns Colitis 2020;14:878–879 [PubMed: 31761938]
19. Papamichael K, Vajravelu RK, Vaughn BP, et al. Proactive infliximab monitoring following reactive testing is associated with better clinical outcomes than reactive testing alone in patients with inflammatory bowel disease. J Crohns Colitis 2018;12:804–810 [PubMed: 29590345]
20. Amiot A, Hulin A, Belhassan M, et al. Therapeutic drug monitoring is predictive of loss of response after de-escalation of infliximab therapy in patients with inflammatory bowel disease in clinical remission. Clin Res Hepatol Gastroenterol 2016;40:90–98. [PubMed: 26138132]
21. Lucidarme C, Petitcollin A, Brochard C, et al. Predictors of relapse following infliximab de-escalation in patients with inflammatory bowel disease: the value of a strategy based on therapeutic drug monitoring. Aliment Pharmacol Ther 2019;49:147–154. [PubMed: 30589970]
22. Petitcollin A, Brochard C, Siproudhis L, et al. Pharmacokinetic parameters of infliximab influence the rate of relapse after de-escalation in adults with inflammatory bowel diseases. Clin Pharmacol Ther 2019;106:605–615. [PubMed: 30860594]
23. Aguas Peris M, Bosó V, Navarro B, et al. , Serum adalimumab levels predict successful remission and safe deintensification in inflammatory bowel disease patients in clinical practice. Inflamm Bowel Dis 2017;23:1454–1460. [PubMed: 28708805]
24. Lega S, Phan BL, Rosenthal CJ, et al. Proactively optimized infliximab monotherapy is as effective as combination therapy in IBD. Inflamm Bowel Dis 2019;25:134–141. [PubMed: 29868777]
25. Drobne D, Kurent T, Golob S, et al. Optimised infliximab monotherapy is as effective as optimised combination therapy, but is associated with higher drug consumption in inflammatory bowel disease. Aliment Pharmacol Ther 2019;49:880–889. [PubMed: 30784100]
26. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE): Determining therapeutic goals for treat-to-target. Am J Gastroenterol 2015;110:1324–1338. [PubMed: 26303131]
27. Yao J, Jiang X, Joyce H, You JHS, et al. A systematic review on cost-effectiveness analyses of therapeutic drug monitoring for patients with inflammatory bowel disease: from immunosuppressive to anti-TNF therapy. Inflamm Bowel Dis 2021;27:275–282. [PubMed: 32311018]
28. Singh S, George J, Boland BS, et al. Primary non-response to tumor necrosis factor antagonists is associated with inferior response to second-line biologics in patients with inflammatory bowel diseases: a systematic review and meta-analysis. J Crohns Colitis 2018;12:635–643. [PubMed: 29370397]

29. Sands BE, Feagan BG, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. Gastroenterology 2014;147:618–627. [PubMed: 24859203]
30. Verstockt B, Mertens E, Dreesen E, et al. Influence of drug exposure on vedolizumab-induced endoscopic remission in anti-TNF naïve and anti-TNF exposed IBD patients. J Crohns Colitis. 2020;14:332–341. [PubMed: 31504343]
31. Dreesen E, Verstockt B, Bian S, et al. Evidence to support monitoring of vedolizumab trough concentrations in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2018;16:1937–1946. [PubMed: 29704680]
32. Ungaro R, Yarur A, Jossen J, et al. Higher trough vedolizumab concentrations during maintenance therapy are associated with corticosteroid-free remission in inflammatory bowel disease vedolizumab. J Crohns Colitis 2019;13:963–969. [PubMed: 31087100]
33. Verstockt B, Dreesen E, Noman M, et al. Ustekinumab exposure-outcome analysis in Cohn's disease only in part explains limited endoscopic remission rates. J Crohns Colitis 2019;13:864–872. [PubMed: 30715258]
34. Al-Bawardy B, Ramos GP, Willrich MAV, et al. Vedolizumab drug level correlation with clinical remission, biomarker normalization, and mucosal healing in inflammatory bowel disease. Inflamm Bowel Dis 2019;25:580–586. [PubMed: 30165638]
35. Yacoub W, Williet N, Pouillon L, et al. Early vedolizumab trough levels predict mucosal healing in inflammatory bowel disease: a multicentre prospective observational study. Aliment Pharmacol Ther 2018;47:906–912. [PubMed: 29384209]
36. Pouillon L, Rousseau H, Busby-Venner et al. Vedolizumab trough levels and histological healing during maintenance therapy in ulcerative colitis. J Crohns Colitis 2019;13:970–975 [PubMed: 30698684]
37. Osterman MT, Rosario M, Lasch K, et al. Vedolizumab exposure levels and clinical outcomes in ulcerative colitis: determining the potential for dose optimisation. Aliment Pharmacol Ther 2019;49:408–418. [PubMed: 30663076]
38. Williet N, Boschetti G, Fovet M, et al. Association between low trough levels of vedolizumab during induction therapy for inflammatory bowel diseases and need for additional doses within 6 months. Clin Gastroenterol Hepatol 2017;15:1750–1757. [PubMed: 27890854]
39. Hanžel J, Zdovc J, Kurent T, et al. Peak concentrations of ustekinumab after intravenous induction therapy identify patients with Crohn's disease likely to achieve endoscopic and biochemical remission. Clin Gastroenterol Hepatol 2021;19:111–118 [PubMed: 32109630]
40. Gomez Espin R, De Prado IN, Candel MG, et al. Association between ustekinumab trough concentrations and biochemical outcomes in patients with Crohn's disease. A real life study. Rev Esp Enferm Dig 2021;113:110–115. [PubMed: 33213170]
41. Adedokun OJ, Xu Z, Marano C, et al. Ustekinumab pharmacokinetics and exposure response in a phase 3 randomized trial of patients with ulcerative colitis: ustekinumab PK and exposure-response in UC. Clin Gastroenterol Hepatol 2020;18:2244–2255. [PubMed: 31816446]
42. Battat R, Kopylov U, Bessissow T, et al. Association between ustekinumab trough concentrations and clinical, biomarker, and endoscopic outcomes in patients with Crohn's disease. Clin Gastroenterol Hepatol 2017;15:1427–1434. [PubMed: 28365485]
43. Adedokun OJ, Xu Z, Gasink C, et al. Pharmacokinetics and exposure response relationships of ustekinumab in patients with Crohn's disease. Gastroenterology 2018;154:1660–1671. [PubMed: 29409871]
44. Vaughn BP, Yarur AJ, Graziano E, et al. Vedolizumab serum trough concentrations and response to dose escalation in inflammatory bowel disease. J Clin Med 2020;9:3142.
45. Brandse JF, Mathot RA, van der Kleij D, et al. Pharmacokinetic features and presence of anti-drug antibodies associate with response to infliximab induction therapy in patients with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol 2016;14:251–258. [PubMed: 26545802]
46. Ungar B, Mazor Y, Weisshof R, et al. Induction infliximab levels among patients with acute severe ulcerative colitis compared with patients with moderately severe ulcerative colitis. Aliment Pharmacol Ther 2016;43:1293–1299. [PubMed: 27091119]

47. Brandse JF, van den Brink GR, Wildenberg ME, et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. Gastroenterology 2015;149:350–355. [PubMed: 25917786]
48. Battat R, Hemperly A, Truong S, et al. Baseline clearance of infliximab is associated with requirement for colectomy in patients with acute severe ulcerative colitis. Clin Gastroenterol Hepatol 2021;19:511–518. [PubMed: 32348905]
49. Jongsma MME, Winter DA, Huynh HQ, et al. Infliximab in young paediatric IBD patients: it is all about the dosing. Eur J Pediatr 2020;179:1935–1944. [PubMed: 32813123]
50. Winter DA, Joosse ME, Wildt SN, et al. Pharmacokinetics, pharmacodynamics, and immunogenicity of infliximab in pediatric inflammatory bowel disease: a systematic review and revised dosing considerations. J Pediatr Gastroenterol Nutr 2020;70:763–776. [PubMed: 32443029]
51. Colombel JF, Adedokun OJ, Gasink C, et al. Combination therapy with infliximab and azathioprine improves infliximab pharmacokinetic features and efficacy-a post-hoc analysis. Clin Gastroenterol Hepatol 2019;17:1525–1532. [PubMed: 30267864]
52. Drobne D, Bossuyt P, Breynaert C, et al. Withdrawal of immunomodulators after co-treatment does not reduce trough level of infliximab in patients with Crohn's disease. Clin Gastroenterol Hepatol 2015;13:514–521. [PubMed: 25066841]
53. Siegel CA, Thompson KD, Walls D, et al. Crohn's disease patients' and gastroenterologists' perspectives towards de-escalating inflammatory bowel disease therapy: a comparative European and American survey. Clin Gastroenterol Hepatol 2021;19:403–405. [PubMed: 31887442]
54. Holmer A, Singh S. Overall and comparative safety of biologic and immunosuppressive therapy in inflammatory bowel diseases. Expert Rev Clin Immunol 2019;15:969–979. [PubMed: 31322018]
55. Sazonovs A, Kennedy NA, Moutsianas L, et al. HLA-DQA1*05 carriage associated with development of anti-drug antibodies to infliximab and adalimumab in patients with Crohn's disease. Gastroenterology 2020;158:189–199. [PubMed: 31600487]
56. Wilson A, Peel C, Wang Q, et al. HLADQA1*05 genotype predicts anti-drug antibody formation and loss of response during infliximab therapy for inflammatory bowel disease. Aliment Pharmacol Ther 2020;51:356–363. [PubMed: 31650614]
57. Brandse JF, Mould D, Smeekes O, et al. A real-life population pharmacokinetic study reveals factors associated with clearance and immunogenicity of infliximab in inflammatory bowel disease. Inflamm Bowel Dis 2017;23:650–660. [PubMed: 28195852]
58. Verstockt B, Moors G, Bian S, et al. Influence of early adalimumab serum levels on immunogenicity and long-term outcome of anti-TNF naive Crohn's disease patients: the usefulness of rapid testing. Aliment Pharmacol Ther 2018;48:731–739. [PubMed: 30109889]
59. Fasanmade AA, Adedokun OJ, Blank M, et al. Pharmacokinetic properties of infliximab in children and adults with Crohn's disease: a retrospective analysis of data from 2 phase III clinical trials. Clin Ther 2011;33:946–964. [PubMed: 21741088]
60. Fasanmade AA, Adedokun OJ, Olson A, et al. Serum albumin concentration: a predictive factor of infliximab pharmacokinetics and clinical response in patients with ulcerative colitis. Int J Clin Pharmacol Ther. 2010;48:297–308. [PubMed: 20420786]
61. Vande Casteele N, Baert F, Bian S, et al. Subcutaneous absorption contributes to observed interindividual variability in adalimumab serum concentrations in Crohn's disease: a prospective multicentre study. J Crohns Colitis 2019;13:1248–1256. [PubMed: 30820530]
62. Santacana E, Rodríguez-Alonso L, Padullés A, et al. Predictors of infliximab trough concentrations in inflammatory bowel disease patients using a repeated-measures design. Ther Drug Monit 2020;42:102–110. [PubMed: 31283556]
63. Ordás I, Mould DR, Feagan BG, et al. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. Clin Pharmacol Ther 2012;91:635–46. [PubMed: 22357456]
64. Kennedy NA, Heap GA, Green HD, et al. Predictors of anti-TNF treatment failure in anti-TNF-naive patients with active luminal Crohn's disease: a prospective, multicentre, cohort study. Lancet Gastroenterol Hepatol 2019;4:341–353. [PubMed: 30824404]

65. Baert F, Drobne D, Gils A, et al. Early trough levels and antibodies to infliximab predict safety and success of re-initiation of infliximab therapy. Clin Gastroenterol Hepatol 2014;12:1474–81. [PubMed: 24486408]
66. Gils A, Van Stappen T, Dreesen E, et al. Harmonization of infliximab and anti-infliximab assays facilitates the comparison between originators and biosimilars in clinical samples. Inflamm Bowel Dis 2016;22:969–975. [PubMed: 26954707]
67. Neveu B, Kunst A, Prosser C, et al. An in vitro comparison of four different immunoassays for the monitoring of Infliximab biosimilars drug levels. Clin Biochem 2020;78:58–62. [PubMed: 31982376]
68. Vande Casteele N, Buurman DJ, Sturkenboom MG, et al. Detection of infliximab levels and anti-infliximab antibodies: a comparison of three different assays. Aliment Pharmacol Ther 2012;36:765–771. [PubMed: 22928581]
69. Marini JC, Sendecki J, Cornillie F, et al. Comparisons of serum infliximab and antibodies-to-infliximab tests used in inflammatory bowel disease clinical trials of Remicade®. AAPS J 2017;19:161–171. [PubMed: 27600137]
70. Sam MJ, Connor SJ, Ng WW, et al. Comparative evaluation of 4 commercially available ELISA kits for measuring adalimumab and anti-adalimumab antibodies. Ther Drug Monit 2020;42:821–828. [PubMed: 32947553]
71. Berger AE, Duru G, de Vries A, et al. Comparison of immunoassays for measuring serum levels of golimumab and antibodies against golimumab in ulcerative colitis: a retrospective observational Study. Ther Drug Monit 2019;41:459–66. [PubMed: 30817702]
72. Papamichael K, Clarke WT, Casteele NV, et al. Comparison of assays for therapeutic monitoring of infliximab and adalimumab in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2021;19:839–841 [PubMed: 32147594]
73. Verdon C, Vande Casteele N, Heron V, et al. Comparison of serum concentrations of ustekinumab obtained by three commercial assays in patients with Crohn's disease. J Can Assoc Gastroenterol 2021;4:73–77. [PubMed: 33855264]
74. Cherry M, Dutzer D, Nasser Y, et al. Point-of-care assays could be useful for therapeutic drug monitoring of IBD patients in a proactive strategy with adalimumab. J Clin Med 2020;9:2739.
75. Steenholdt C, Ainsworth MA, Tovey M, et al. Comparison of techniques for monitoring infliximab and antibodies against infliximab in Crohn's disease. Therapeutic Drug Monitor 2013;35:530–538.
76. Bertin D, Serrero M, Grimaud JC, et al. Monitoring of infliximab trough levels and anti-infliximab antibodies in inflammatory bowel diseases: A comparison of three commercially available ELISA kits. Cytokine. 2020;126:154859. [PubMed: 31629989]
77. Steenholdt C, Bendtzen K, Brynskov J, et al. Clinical implications of measuring drug and anti-drug antibodies by different assays when optimizing infliximab treatment failure in Crohn's disease: post hoc analysis of a randomized controlled trial. Am J Gastroenterol 2014;109:1055–1064. [PubMed: 24796769]
78. Jentzer A, Emmanuelle Berger A, Labetoulle R, et al. Short Communication: Evaluation of infliximab and anti-infliximab LISA-TRACKER immunoassays for the therapeutic drug monitoring of SB2 infliximab biosimilar. Ther Drug Monit. 2018;40:749–753. [PubMed: 30439790]
79. Afonso J, de Sousa HT, Rosa I, et al. Therapeutic drug monitoring of CT-P13: a comparison of four different immunoassays. Therap Adv Gastroenterol 2017;10:661–671.
80. Schulze K, Koppka N, Lutter F, et al. CT-P13 (Inflectra™, Remsima™) monitoring in patients with inflammatory bowel disease. Biologicals. 2016;44:463–466. [PubMed: 27435444]
81. Gonczi L, Vegh Z, Golovics PA, et al. Prediction of short- and medium-term efficacy of biosimilar infliximab therapy. Do trough levels and antidrug antibody levels or clinical and biochemical markers play the more important role? J Crohns Colitis 2017;11:697–705. [PubMed: 27838610]
82. Ungar B, Engel T, Yablecovitch D, et al. Prospective observational evaluation of time-dependency of adalimumab immunogenicity and drug concentrations: The Poetic Study. Am J Gastroenterol. 2018;113:890–898. [PubMed: 29867175]

83. Baert F, Kondragunta V, Lockton S, et al. Antibodies to adalimumab are associated with future inflammation in Crohn's patients receiving maintenance adalimumab therapy: a post hoc analysis of the Karmiris trial. Gut 2016;65:1126–1131. [PubMed: 25862647]
84. Ungar B, Chowers Y, Yavzori M, et al. The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab. Gut 2014;63:1258–1264. [PubMed: 24041539]
85. Vande Casteele N, Gils A, Singh S, et al. Antibody response to infliximab and its impact on pharmacokinetics can be transient. Am J Gastroenterol 2013;108:962–971. [PubMed: 23419382]
86. Van Stappen T, Vande Casteele N, Van Assche G, et al. Clinical relevance of detecting anti-infliximab antibodies with a drug-tolerant assay: post hoc analysis of the TAXIT trial. Gut 2018;67:818–826. [PubMed: 28450388]
87. Awadie H, Waterman M. Intermittent appearance of antibodies to infliximab is not associated with reduced efficacy in patients with inflammatory bowel diseases J Clin Gastroenterol 2020 Nov 25. doi: 10.1097/MCG.0000000000001469. Online ahead of print.
88. Vande Casteele N, Khanna R, Levesque BG, et al. The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease. Gut 2015;64:1539–1545 [PubMed: 25336114]
89. Tournier Q, Paul S, Williet N, et al. Early detection of anti-drug antibodies during initiation of anti-tumour necrosis factor therapy predicts treatment discontinuation in inflammatory bowel disease. Aliment Pharmacol Ther 2021;53:1190–1200. [PubMed: 33872404]
90. Afif W, Loftus EV Jr, Faubion WA, et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. Am J Gastroenterol 2010;105:1133–1139. [PubMed: 20145610]
91. Roblin X, Williet N, Boschetti G, et al. Addition of azathioprine to the switch of anti-TNF in patients with IBD in clinical relapse with undetectable anti-TNF trough levels and antidrug antibodies: a prospective randomised trial Gut 2020;69:1206–1212. [PubMed: 31980448]
92. Imbrechts M, Van Stappen T, Compernolle G, et al. Anti-infliximab antibodies: How to compare old and new data? J Pharm Biomed Anal 2020;177:112842. [PubMed: 31526960]
93. Strik AS, van den Brink GR, Ponsioen C, et al. Suppression of anti-drug antibodies to infliximab or adalimumab with the addition of an immunomodulator in patients with inflammatory bowel disease. Aliment Pharmacol Ther 2017;45:1128–1134. [PubMed: 28230306]
94. Ben-Horin S, Waterman M, Kopylov U, et al. Addition of an immunomodulator to infliximab therapy eliminates antidrug antibodies in serum and restores clinical response of patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2013;11:444–447. [PubMed: 23103905]
95. Ungar B, Kopylov U, Engel T, et al. Addition of an immunomodulator can reverse antibody formation and loss of response in patients treated with adalimumab. Aliment Pharmacol Ther 2017;45:276–282. [PubMed: 27862102]
96. Papamichael K, Vajravelu RK, Osterman MT, Cheifetz AS. Long-term outcome of infliximab optimization for overcoming immunogenicity in patients with inflammatory bowel disease. Dig Dis Sci 2018;63:761–767 [PubMed: 29340807]
97. Cohen RZ, Schoen BT, Kugathasan S, Sauer CG. Management of anti-drug antibodies to biologic medications in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2019;69:551–556. [PubMed: 31335833]
98. Battat R, Lukin D, Scherl EJ, et al. Immunogenicity of tumor necrosis factor antagonists and effect of dose escalation on anti-drug antibodies and serum drug concentrations in inflammatory bowel disease. Inflamm Bowel Dis. 2020 Nov 30:izaa313. doi: 10.1093/ibd/izaa313. Online ahead of print.
99. Bar-Yoseph H, Waterman M, Almog R, et al. Prevention of antidrug antibody formation to infliximab in Crohn's patients with prior failure of thiopurines. Clin Gastroenterol Hepatol 2017;15:69–75. [PubMed: 27404966]
100. Arieira C, Dias de Castro F, Cúrdia Gonçalves T, et al. Combination therapy in inflammatory bowel disease patients: do we need to maximize the dose of azathioprine? Scand J Gastroenterol. 2020;55:920–923. [PubMed: 32689833]

101. Qiu Y, Mao R, Chen B-L, et al. Effects of combination therapy with immunomodulators on trough levels and antibodies against tumor necrosis factor antagonists in patients with inflammatory bowel disease: a meta-analysis. Clin Gastroenterol Hepatol 2017;15:1359–1372. [PubMed: 28232073]
102. Vermeire S, Gils A, Accossato P, Lula S, Marren A. Immunogenicity of biologics in inflammatory bowel disease. Ther Adv Gastroenterol. 2018;11:1756283X1775035.
103. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2019;381:1201–1214. [PubMed: 31553833]
104. Vande Casteele N, Jeyarajah J, Jairath V, et al. Infliximab exposure-response relationship and thresholds associated with endoscopic healing in patients with ulcerative colitis. Clin Gastroenterol Hepatol 2019;17:1814–1821 [PubMed: 30613004]
105. Papamichael K, Vande Casteele N, Jeyarajah J et al. Higher postinduction infliximab concentrations are associated with improved clinical outcomes in fistulizing Crohn's disease: An ACCENT-II post-hoc analysis. Am J Gastroenterol 2021;116:1007–1014. [PubMed: 33929379]
106. Colman RJ, Tsai Y-T, Jackson K, et al. Achieving target infliximab drug concentrations improves blood and fecal neutrophil biomarkers in Crohn's disease. Inflamm Bowel Dis 2020 Sep 18;izaa241.
107. Papamichael K, Rakowsky S, Rivera C, Cheifetz AS, Osterman MT. Association between serum infliximab trough concentrations during maintenance therapy and biochemical, endoscopic and histologic remission in Crohn's disease. Inflamm Bowel Dis 2018;24:2266–2271. [PubMed: 29718327]
108. Imaeda H, Bamba S, Takahashi K, et al. Relationship between serum infliximab trough levels and endoscopic activities in patients with Crohn's disease under scheduled maintenance treatment. J Gastroenterol 2014;49:674–682. [PubMed: 23666424]
109. Ward MG, Warner B, Unsworth N, et al. Infliximab and adalimumab drug levels in Crohn's disease: contrasting associations with disease activity and influencing factors. Aliment Pharmacol Ther 2017;46:150–161. [PubMed: 28481014]
110. Papamichael K, Rakowsky S, Rivera C, et al. Infliximab trough concentrations during maintenance therapy are associated with endoscopic and histologic healing in ulcerative colitis. Aliment Pharmacol Ther 2018;47:478–484. [PubMed: 29210094]
111. Roblin X, Boschetti G, Duru G, Williet N, et al. Distinct thresholds of infliximab trough level are associated with different therapeutic outcomes in patients with inflammatory bowel disease: A prospective observational study. Inflamm Bowel Dis 2017;23:2048–2053. [PubMed: 28945636]
112. Morita Y, Imaeda H, Nishida A, et al. Association between serum adalimumab concentrations and endoscopic disease activity in patients with Crohn's disease. J Gastroenterol Hepatol 2016;31:1831–1836. [PubMed: 27043158]
113. Plevris N, Lyons M, Philip Jenkinson PW, et al. Higher adalimumab drug levels during maintenance therapy for Crohn's disease are associated with biologic remission. Inflamm Bow Dis 2018;18:1271–1279.
114. Plevris N, Jenkinson PW, Arnott ID, Jones GR, Lees CW. Higher anti-tumor necrosis factor levels are associated with perianal fistula healing and fistula closure in Crohn's disease. Eur J Gastroenterol Hepatol 2020;32:32–37. [PubMed: 31567638]
115. Carlsen A, Omdal R, Karlsen L, et al. Determination of lower cut-off levels of adalimumab associated with biochemical remission in Crohn's disease. JGH Open 2019;4:410–416. [PubMed: 32514446]
116. Ungar B, Levy I, Yavne Y, et al. Optimizing Anti-TNF-α Therapy: Serum levels of infliximab and adalimumab are associated with mucosal healing in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol 2016;14:550–557. [PubMed: 26538204]
117. Vande Casteele N, Feagan BG, Vermeire S, et al. Exposure–response relationship of certolizumab pegol induction and maintenance therapy in patients with Crohn's disease. Aliment Pharmacol Ther 2018;47:229–237 [PubMed: 29159893]
118. Samaan MA, Cunningham G, Tamilarasan AG, et al. Therapeutic thresholds for golimumab serum concentrations during induction and maintenance therapy in ulcerative colitis: results from the GO-LEVEL study. Aliment Pharmacol Ther 2020;52:292–302. [PubMed: 32506695]

119. El-Matary W, Walters TD, Huynh HQ, et al. Higher postinduction infliximab serum trough levels are associated with healing of fistulizing perianal Crohn's disease in children. Inflamm Bowel Dis 2019;25:150–155. [PubMed: 29912413]

120. Yarur AJ, Kanagala V, Stein DJ, et al. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. Aliment Pharmacol Ther 2017;45:933–940. [PubMed: 28211593]

121. D'Haens G, Vermeire S, Lambrecht G, et al. Increasing infliximab dose based on symptoms, biomarkers, and serum drug concentrations does not increase clinical, endoscopic, and corticosteroid-free remission in patients with active luminal Crohn's disease. Gastroenterology 2018;154:1343–1351. [PubMed: 29317275]

122. Syversen SW, Goll GL, Jørgensen KK, et al. Effect of therapeutic drug monitoring vs standard therapy during infliximab induction on disease remission in patients with chronic immune-mediated inflammatory diseases: A randomized clinical trial. JAMA 2021;325:1744–1754. [PubMed: 33944876]

123. Strik AS, Löwenberg M, Mould DM, et al. Efficacy of dashboard driven dosing of infliximab in inflammatory bowel disease patients; a randomized controlled trial. Scand J Gastroenterol 2021;56:145–154. [PubMed: 33290108]

124. Vande Casteele N, Jairath V, Jeyarajah J, et al. Development and validation of a clinical decision support tool that incorporates pharmacokinetic data to predict endoscopic healing in patients treated with infliximab. Clin Gastroenterol Hepatol 2021;19:1209–1217. [PubMed: 32376505]

125. Landemaine A, Petitcollin A, Brochard C, et al. Cumulative exposure to infliximab, but not trough concentrations, correlates with rate of infection. Clin Gastroenterol Hepatol 2021;19:288–295. [PubMed: 32200087]

Table 1.

Statements regarding reactive therapeutic drug monitoring of biologics

Statement	Vote agreement, %	Strength of recommendation *
1. Reactive TDM should be performed in patients with confirmed ** primary non-response to anti-TNF therapy.	100	9.7
2. Reactive TDM should be performed in patients with confirmed ** secondary loss of response to anti-TNF therapy.	100	9.8
3. Reactive TDM has been proven more cost-effective than empiric anti-TNF therapy optimization.	100	8.6
4. When performing reactive TDM for secondary loss of response to infliximab, treatment discontinuation should not be considered until a drug concentration of at least 10-15μg/ml is achieved. ***	90	8.5
5. When performing reactive TDM for secondary loss of response to adalimumab, treatment discontinuation should not be considered until a drug concentration of at least 10-15μg/ml is achieved. ***	90	8.3
6. Reactive TDM should be performed in patients with confirmed ** primary non-response to vedolizumab prior to switching therapy.	100	8.3
7. Reactive TDM should be performed in patients with confirmed ** primary non-response to ustekinumab prior to switching therapy.	90	7.4
8. Reactive TDM should be performed in patients with confirmed ** secondary loss of response to vedolizumab.	100	8.9
9. Reactive TDM should be performed in patients with confirmed ** secondary loss of response to ustekinumab.	90	8.5

* Mean score of rating of the statements.

** PNR and SLR should not be defined by clinical symptoms alone, but ongoing inflammation needs to be confirmed objectively with laboratory testing (i.e. CRP, FC), imaging and/or endoscopy.

*** A range rather than a threshold is provided as drug concentrations may differ among assays.

TDM: therapeutic drug monitoring; TNF: tumor necrosis factor.

Table 2.

Statements regarding proactive therapeutic drug monitoring of biologics.

Statement	Vote agreement, %	Strength of recommendation *
10. Proactive TDM should be performed post induction for patients treated with anti-TNF therapy.	90	9
11. Proactive TDM should be performed at least once during maintenance therapy for patients treated with anti-TNF therapy.	90	8.8
12. Proactive TDM should be utilized after reactive TDM of anti-TNF therapy.	80	8.1
13. Proactive TDM is most important in more severely active patients and in patients who have higher drug clearance.	90	8.5
14. When infliximab de-escalation (dose reduction) is considered in patients in remission, proactive TDM both prior to and after de-escalation should be performed.	100	9.2
15. Proactive TDM for optimizing anti-TNF monotherapy is better than unoptimized anti-TNF monotherapy.	100	9
16. Proactive TDM for optimizing anti-TNF monotherapy in select patients is an alternative to combination anti-TNF therapy with an immunomodulator.	90	8.5
17. More data are needed to support the use of proactive TDM for biologics other than anti-TNF therapies.	100	9.2

* Mean score of rating of the statements.

TDM: therapeutic drug monitoring; TNF: tumor necrosis factor.

Table 3.

General statements regarding therapeutic drug monitoring of biologics.

Statement	Vote agreement, %	Strength of recommendation *
18. There is clinical utility for TDM to be performed in patients treated with anti-TNF therapy during induction.	80	8
19. Increased anti-TNF clearance is associated with anti-drug antibodies, male gender, low albumin, high baseline CRP and high BMI.	90	9.2
20. TDM (drug concentration and antibodies to infliximab) should be performed following a drug holiday in patients treated with infliximab prior to second dose after re-starting.	100	9
21. Patients should be followed over time with the same TDM assay, if possible, until commercial assays are accurately cross-validated and standardized.	80	8.1
22. There are no differences in performing and interpreting the results of TDM between biosimilars and originator biologic drugs.	100	9.4

* Mean score of rating of the statements.

TDM: therapeutic drug monitoring; TNF: tumor necrosis factor; CRP: C-reactive protein; BMI: body mass index.

Table 4.

Statements regarding immunogenicity of biologics.

Statement	Vote agreement, %	Strength of recommendation *
23. Anti-drug antibodies are more clinically relevant when trough drug concentrations are undetectable.	90	9.1
24. Patients with secondary loss of response to anti-TNF therapy due to the development of high-titer anti-drug antibodies should not be dose-escalated, but instead should be switched to a different therapy (within-class or out of class).	100	9.4
25. When considering switching within drug class in case of secondary loss of response to a first anti-TNF drug due to the development of anti-drug antibodies, an immunomodulator should be added to a subsequent anti-TNF therapy.	90	8.5
26. All commercially available assays are appropriate to use for TDM, however, for antibody measurement, beyond the homogeneous mobility shift assay there are not sufficient data to support specific clinically relevant cut-offs to define high-titer antibodies.	100	8.3
27. Low-titer antibodies to infliximab can be defined as <10 U/ml for the homogeneous mobility shift assay.	90	8.1
28. Low titer anti-drug antibodies can be overcome by treatment optimization (dose escalation, dose interval shortening and/or addition of an immunomodulator).	100	8.4
29. The formation of antibodies to infliximab or adalimumab can be reduced by the use of immunomodulators.	100	9.1
30. HLA-DQA1*05 is associated increased risk of development of antibodies to infliximab and adalimumab.	100	9.3
31. Vedolizumab is associated with less immunogenicity than anti-TNFs.	100	9.2
32. Ustekinumab is associated with less immunogenicity than anti-TNFs.	100	9.9

* Mean score of rating of the statements.

TDM: therapeutic drug monitoring; TNF: tumor necrosis factor; HLA: Human leukocyte antigen.

Table 5.

Statements regarding infliximab and adalimumab concentrations to target.

Statement*	Vote agreement, %	Strength of recommendation**
33. The target drug concentration may vary depending on disease phenotype, assay used and desired therapeutic outcome.	100	9.2
34. Infliximab concentrations to target at week 2 should be at least 20-25 μg/ml.	80	8.3
35. Infliximab concentrations to target at week 6 should be at least 15-20 μg/ml.	90	8.5
36. Infliximab concentrations to target at week 14 should be at least 7-10μg/ml.	100	8.3
37. Infliximab concentrations to target during maintenance therapy should be at least 5-10 μg/ml.	90	8.5
38. Adalimumab concentrations to target at week 4 should be at least 8-12 μg/ml.	80	8.2
39. Adalimumab concentrations to target during maintenance therapy should be at least 8-12 μg/ml.	80	8.3

*For all statements the upper limit of range typically refers to drug concentration associated with more stringent therapeutic outcomes such as biochemical, endoscopic, histologic and composite remission defined as any combination of the previous.

**Mean score of rating of the statements.

Table 6.

Biologic drug concentration thresholds can vary based on the desired therapeutic outcome to target.

Drug type	IBD type	TDM time point	Threshold (μg/ml)	Therapeutic outcome*	Therapeutic outcome time point	Ref.
IFX[a]	CD UC	Week 2	>16.9 >20.4 >11.5 >15.3	Clinical response Clinical remission Clinical response Clinical remission	Week 14	81
IFX	UC	Week 14	≥5.1 ≥6.7	Mucosal healing (MES<2) Mucosal healing (MES=0)	Week 30	104
IFX	CD	Week 14	≥2 ≥6.1 ≥7.2	CRP normalization Complete fistula response Complete fistula response & CRP normalization	Week 14	105
IFX	CD	Week 14	>9.4 >11.5	FC<250μg/g FC<100μg/g	Week 14	106
IFX	CD	Maintenance	≥2.2 ≥9.7 ≥9.8	Normal CRP Endoscopic remission Histologic remission	Maintenance	107
IFX	CD	Maintenance	>0.6 >1.1 >4	Normal CRP[b] Normal FC[c] Mucosal healing	Maintenance	108
IFX	CD	Maintenance	>1.5 >3.4 >5.7	Clinical remission Normal CRP Normal FC[d]	Maintenance	109
IFX	UC	Maintenance	≥7.5 ≥10.5	Endoscopic healing Histologic healing	Maintenance	110
IFX	CD/UC	Maintenance	>2.1 >2.9 >3.9 >4.9	Clinical remission Clinical remission & normal CRP Clinical remission & FC <250μg/g Clinical remission, normal CRP & FC<50 μg/g	Maintenance	111
ADM	CD	Maintenance	>5.6 >7.9	Normal CRP[b] Mucosal healing	Maintenance	111
ADM	CD	Maintenance	>8.5 >10.5	Normal CRP & FC <250 μg/g Normal CRP & FC <100 μg/g	Maintenance	113
ADM	CD	Maintenance	>6.8 >9.8	Perianal fistula healing Perianal fistula closure	Maintenance	114
ADM	CD	Maintenance	>6.8 >9.8	Normal CRP Normal CRP & FC[e]	Maintenance	115
ADM	CD/UC	Maintenance	>6.6 >7.1	Normal CRP Mucosal healing	Maintenance	116
CZP	CD	Week 6	>31.8 >32.7 >34.5	Clinical remission[f] Normal FC[g] Clinical remission & normal FC	Week 6	117
GOL	UC	Week 6	>3.2 >3.8	Clinical remission Clinical & biochemical remission	Week 6	118
VDZ	CD	Week 14	>21.2 >25.2 >30.1	Clinical remission Biological remission Endoscopic improvement	Week 24	30
VDZ	UC	Week 14	>12.6 >17	Clinical response Mucosal healing	Week 14	31

Drug type	IBD type	TDM time point	Threshold (μg/ml)	Therapeutic outcome*	Therapeutic outcome time point	Ref.
VDZ	CD/UC	Maintenance	>10.7 >14.8	CS-free endoscopic remission CS-free deep remission	Maintenance	32
UST	CD	Week 8	>4.2 >7.2	50% decrease in FC Biological remission	Week 8	33
UST	CD	Week 8	>6.9 >11.1	Normal FC[h] Endoscopic remission	Week 24	39
UST	CD	Maintenance	>1.4 >2 >2.2	Clinical remission[i] Biochemical remission[k] Clinical & biochemical remission	Maintenance	40
UST	UC	Week 8 Maintenance	≥3.5 ≥3.7 ≥1.1 ≥1.3	Endoscopic improvement Histologic improvement Endoscopic improvement Histologic improvement	Week 8 Week 44	41

*Higher drug concentrations are typically associated with more stringent outcomes going from clinical to biochemical, endoscopic, histologic and composite remission defined as any combination of the previous.

[a]Infliximab biosimilar CT-P13

[b]≤3mg/L

[c]<300μg/g

[d]<59μg/g

[e]<50μg/g

[f]CDAI<150

[g]<250μg/g

[h]<100μg/g

[i]HBI<5

[k]<150μg/g.

IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; IFX: infliximab; ADM: adalimumab; GOL: golimumab; CZP: certolizumab pegol; VDZ: vedolizumab; UST: ustekinumab; CRP: C-reactive protein, FC: fecal calprotectin; MES: Mayo endoscopic score; CS: corticosteroids; CDAI: Crohn's disease activity index; HBI: Harvey-Bradshaw index; ref: reference.