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REGULATION AND GUIDELINE

Therapeutic drug monitoring of biologics in inflammatory bowel disease: An evidence-based multidisciplinary guideline

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Abstract Therapeutic drug monitoring (TDM) has emerged as a valuable tool for optimizing the use of biologics in inflammatory bowel disease (IBD). However, variations in focus, methodology, and recommendations among relevant guidelines and consensuses have contributed to inconsistencies in their quality. This guideline synthesizes current evidence to standardize TDM of biologics in IBD, and improve patient outcomes. This multidisciplinary guideline was developed in collaboration with pharmacy, gastroenterology, and pharmacology associations in China. The guideline development group included 9 experts in clinical pharmacy, 4 experts in TDM, 8 gastroenterologists, and 2 methodologists. A comprehensive search was conducted across PubMed, Embase, Web of Science, the Cochrane Library databases, as well as key gastroenterology-relevant guideline websites. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was utilized, and this guideline was registered on the Guideline International Network website. Internal and external reviews were conducted. We proposed 5 clinical questions under two overarching themes. Based on the current evidence and the clinical opinions of the core working group members, the initial recommendations were made. Following comprehensive internal and external review processes, 14 recommendations (1 strong and 13 weak) were finalized for the clinical questions. To our knowledge, this is the first evidence-based clinical practice guideline on TDM in patients with IBD developed using the GRADE approach. It addresses five key questions: whether TDM leads to better therapeutic outcomes than conventional treatment, what indicators should be monitored, when TDM should be initiated, what the therapeutic drug trough concentration thresholds are, and which TDM method (proactive or reactive) can better improve therapeutic outcomes.

1. Introduction

Inflammatory bowel disease (IBD) is a complex, chronic, and recurrent immune-mediated intestinal disorder, which includes ulcerative colitis (UC) and Crohn's disease (CD). The advent of biologics has revolutionized its treatment, leading to significantly improved patient outcomes, particularly in moderate to severe cases[1,2]. Studies have demonstrated that serum biologic concentrations in patients with IBD are highly correlated with clinical response rates, clinical remission rates, and mucosal healing[3,4]. However, up to 30% of IBD patients do not respond to initial treatment (primary non-response), and 50% develop secondary loss of response[5-7]. Sub-therapeutic drug concentrations, with or without the development of anti-drug antibodies, account for a significant proportion of these outcomes[3,8]. Therapeutic drug monitoring (TDM) defined as the measurement of drug concentrations and anti-drug antibodies, has emerged as an important tool for optimizing biologic therapy.

Guidelines and consensus statements have been developed to provide guidance on TDM of anti-tumor necrosis factor (TNF)-α biologics, such as infliximab (IFX) and adalimumab (ADA), in patients with IBD[7,9-11]. However, the development of these guidelines or consensuses did not strictly adhere to the standards of clinical practice guidelines, and systematic evidence synthesis is deficient, resulting in inconsistent reporting quality. An increasing number of studies are focusing on TDM for biologics targeting TNF-α or non-TNF-α pathways, providing a growing body of evidence to support implementation of TDM for these drugs. The Hospital Pharmacy Committee of the Chinese Pharmaceutical Association, in collaboration with the IBD Working Group of the Chinese Society of Gastroenterology, and Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society, has jointly established a multidisciplinary team comprising pharmacists, gastroenterologists, and specialists in TDM and evidence-based medicine to develop a guideline. This guideline aims to synthesize current evidence for TDM of biologics in IBD, to guide the clinical application of TDM and improve the clinical outcomes. The guideline primarily addresses biologics that have been approved and marketed for UC or CD indications, including IFX, ADA, golimumab (GOL), vedolizumab (VDZ), ustekinumab

(UST), and certolizumab pegol (CER). The intended users of this guideline are clinical and pharmaceutical healthcare professionals specializing in the field of IBD, as well as other clinicians involved in the care of the target patients.

2. Methods

2.1. Guideline development group membership

The guideline development group (GDG) comprised 23 experts with expertise in IBD, TDM, clinical pharmacy, and evidence-based medicine (all of whom are authors of this paper). Members were recruited *via* the Hospital Pharmacy Committee of the Chinese Pharmaceutical Association, in collaboration with the IBD Working Group of the Chinese Society of Gastroenterology, and Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. The organizational framework and detailed information for the GDG is provided in Supporting Information Fig. S1 and Table S1. Professor Zhang Yu was elected as the chairperson of the guideline working group. Conflicts of interest were collected and assessed using a standardized form developed in accordance with the principles outlined by the Guideline International Network (GIN). All GDG members were free from financial and intellectual conflicts of interest and were permitted full participation.

2.2. Identification of guideline questions and outcomes

The GDG, drawing upon the current research landscape and their clinical experience, identified pressing issues that need to be addressed in the field of TDM for biologics in IBD. A survey-based voting process was employed to identify and prioritize the nine most clinically relevant questions (Supporting Information Table S2). However, due to word limitations, only five intervention-related questions are presented in this paper. The remaining four questions will be addressed in a separate paper currently under preparation. Q1 addresses whether TDM can bring benefits to IBD patients, as well as three sub-questions: monitoring indicators (Q1.1), timing of monitoring (Q1.2), and concentration thresholds (Q1.3). Q2 is about the comparison between proactive TDM and reactive TDM. The critical, important, and generally important outcome indicators for each question were also determined through a voting process conducted by 21 clinical experts, with a 100% response rate (Supporting Information Table S3). Clinical remission rate, response rate, endoscopic remission rate, mucosal healing rate, biological indicators (*i.e.*, C-reactive protein (CRP) and faecal calprotectin (FCP)), corticosteroid-free remission rate, hospitalization rate, and serious adverse reactions were rated as "critical" outcomes. Surgery rate, hospitalization cost, drug cost, quality of life, and quality-adjusted life years were rated as "important" outcomes. PICO (Population, Intervention, Comparator, Outcome) questions for Q1 and Q2 are listed in Supporting Information Tables S4 and S5. When making recommendations, we prioritized the effects and certainty of evidence related to the critical outcomes.

2.3. Methodology of guideline development

This guideline adhered to the international standards for developing evidence-based clinical practice guidelines[12]. Both the Appraisal of Guidelines, Research and Evaluation (AGREE) criteria and the Reporting Items for practice Guidelines in HealThcare (RIGHT) reporting checklists were followed[13-15]. This guideline is registered on the GIN and the PROSPERO international systematic reviews Registry (CRD42023492328). Registration information can be accessed by visiting the GIN website (https://guidelines.ebmportal.com) and the PROSPERO website (https://www.crd.york.ac.uk/prospero/).

2.4. Search strategy and evidence synthesis

Information retrieval experts developed a systematic search strategy. The databases searched included PubMed, Embase, Web of Science, and the Cochrane Library. The GIN, National Institute for Health and Care Excellence (NICE), Emergency Care Research Institute (ECRI), and PROSPERO websites were searched to identify registered guidelines or systematic reviews. The search period spanned database inception to 12 December, 2023. Details of the search strategy are given in Supporting Information Appendix 1. Reviewers worked in pairs to independently screen references and extract data, with disagreements resolved through discussion or by consulting a third reviewer. Only English-language literature was searched.

The study selection criteria were (1) randomized controlled trials (RCTs); (2) if there were insufficient RCTs to make recommendations (such as only a few RCTs with low or very low certainty for certain biologics), we included comparative studies that used methods to control for potential confounders (*e.g.*, multivariate analysis, propensity score matching, or comparison of patient characteristics to show no statistically significant differences between the two groups at baseline); (3) if there was insufficient evidence from RCTs and comparative studies, existing relevant systematic reviews or guidelines were included. Animal studies, case reports, and duplicate publications were excluded. Conference abstracts were excluded if they were non-RCTs as they did not provide methodological information for rigorous peer review. The exclusion criteria for the literature are presented in Supporting Information Appendix 2. The process of literature screening is presented in the PRISMA flow diagram (Supporting Information Fig. S2). Meta-analyses were performed by the systematic review team under the guidance of the guideline core group (a subset of GDG compriming 7 experts in clinical pharmacy, TDM and IBD and two methodologists.).

2.5. Assessment of evidence certainty

The risk of bias in the included systematic reviews, meta-analyses, and network meta-analyses was assessed using AMSTAR (A MeaSurement Tool to Assess systematic Reviews)[16]. For clinical guidelines, the AGREE II appraisal tool[17] was used to evaluate the methodological quality Furthermore, for original research, the Cochrane Risk of Bias Tool (RoB)[18] was applied to evaluate the risk of bias of RCTs, and the Newcastle-Ottawa Scale (NOS)[19] was employed to assess the quality of observational studies. The results of these assessments are demonstrated in Supporting Information Tables S6−S9. The certainty of evidence then classified into high, moderate, low, or very low. High certainty indicates that further research is highly unlikely to change confidence in the estimate of effect; moderate certainty indicates that additional research may significantly influence the confidence in the effect estimate of effect and potentially change the estimate itself; low certainty indicates that further research is very likely to substantially affect confidence in the estimate of effect, and is likely to

change the estimate; very low certainty indicates that any estimate of effect is highly uncertain.

2.6. Statement drafting and internal review process

The core group held seven online meetings (2−4 h/meeting) to discuss the evidence derived from the systematic review, answer 12 methodological questions (such as balancing benefits and harms) for each recommendation based on the GRADE approach (https://www.gradepro.org/), and draft the recommendations for Q1 and Q2. The development of recommendations primarily integrated the current evidence (including balancing the magnitudes of benefits and harms of the interventions and the certainty of evidence) and patients' values and preferences, while also considering factors such as health service equity, patient and physician acceptability, and feasibility. The recommendations were categorized into strong and weak recommendations. Strong recommendations indicated that the advice applied to the vast majority, if not all, of the target population. Weak recommendations suggested that the advice should be considered in conjunction with the specific application context and be subject to joint decision-making by healthcare providers and patients, or that the recommendation should be applied conditionally to the target population. Each initial recommendation was first reviewed by the core group, which provided detailed suggestions for revision. Following subsequent modifications, the revised version was circulated among all members of the core group for consensus. Once a unanimous agreement was reached, the document was then forwarded to the GDG members for voting and revising. Each statement with an agreement rate of at least 75% were accepted (Supporting Information Table S10).

2.7. External review process

After combining GDG members' comments into the guideline draft, two online questionnaires, one for clinical and pharmaceutical experts and another for patients, were sent out to 45 potential external reviewers (40 clinicians and five patient representatives) on 11 November 2024. By 27 November, we had received review comments from 31 clinical experts (Supporting Information Table S11) and five patients. We modified the questionnaire templates for external reviewers from the Program in Evidence-based Care of McMaster University in Canada[20]. The patient reviewers found the recommendations to be unambiguous and considered the issues and addressed outcomes important to patients (Supporting Information Table S12). However, they suggested adding more explanations of medical terms to assist with understanding. The results of the questionnaire for clinicians and pharmacists are summarized in Supporting Information Table S13. The main comments regarding disagreement, concerns, and suggestions from external reviewers, along with the guideline authors' responses, are summarized in Supporting Information Table S14.

3. Results

The guideline addresses five clinical questions and provides 14 recommendations, one strong recommendation and 13 weak recommendations. The specific clinical questions and recommendations are presented in Table 1. The evidence summary for each clinical issue is detailed in the following text.

Q1 For patients with IBD receiving biologic therapy, does TDM (either proactive or reactive TDM) result in superior therapeutic outcomes compared with conventional treatment?

Statement 1

For IBD patients (including both adults and children) treated with IFX or ADA, it can be recommended to conduct TDM under the condition of informed consent and available monitoring facilities, so as to potentially improve clinical outcomes (Weak recommendation).

Statement 2

For adult patients with IBD treated with UST and VDZ, adult patients with UC treated with GOL, and adult patients with CD treated with CER, TDM may be considered under the condition that it is accessible and acceptable to both patients and clinicians to potentially improve clinical outcomes (Weak recommendation).

Evidence summary for clinical Q1

Regarding IFX and ADA, five systematic reviews[21-25], seven RCTs[26-33], and 15 comparative studies[34-49] were considered for this clinical question. The certainty of the systematic reviews is low to very low, while the certainty for the RCTs and the comparative studies is moderate (Supporting Information Tables S6, S8, and S9). The GRADE summary of findings table is presented in Table 2. Compared with the conventional treatment, the meta-analysis results of RCTs indicated a trivial or no effect on the clinical remission rate, the clinical response rate and the endoscopic remission rate in the TDM group. In contrast, the meta-analysis results of comparative studies consistently favoured the TDM group. Three RCTs[27,30,31] demonstrated that patients in the TDM group had lower levels of CRP and FCP. The meta-analysis results of seven comparative studies[35,36,40,44,45,47,48] demonstrated that TDM reduced the hospitalization rate among patients. Additionally, a meta-analysis of the nine comparative studies[35-37,39,43-45,47,48] further confirmed that TDM could decrease the surgical rate among patients. Both RCTs and comparative studies showed no significant difference in the risk of serious adverse events between TDM and conventional treatment groups. Moreover, a RCT[30] with a small sample size conducted on patients with CD revealed that TDM was associated with lower treatment costs than conventional therapy. A summary flowchart illustrating the evidence and recommendations for IFX and ADA was shown in Fig. 1.

No studies were identified that directly compared TDM with conventional therapy in patients with IBD treated with UST, VDZ, GOL, or CER. Published systematic reviews[4,50] and guidelines[7] have demonstrated a correlation between blood concentrations of UST or VDZ and clinical outcomes (Table 3). The results of comparative studies further demonstrated that the serum concentration levels of the aforementioned biologics were correlated with clinical outcomes. A systematic review[4] reported that the serum GOL concentrations in UC patients were correlated with clinical remission and clinical response. The same systematic review[4] also demonstrated a correlation between serum CER levels and clinical remission and endoscopic remission rates in CD patients.

Q1.1 When implementing TDM in patients with IBD receiving biologic therapy, which specific indicators should be monitored?

Statement 1

For patients (including both adults and children) with IBD treated with IFX or ADA, serum drug trough concentrations and serum anti-drug antibody levels should be monitored (Strong recommendation).

Table 1 Recommendations for the therapeutic drug monitoring of biologics in IBD.

Clinical questions and statements	Certainty of evidence	Strength of recommendation	Agreement
Question 1 For patients with IBD receiving biologic therapy, does TDM (either proactive or reactive TDM) result in superior therapeutic outcomes compared with conventional treatment?			
Statement 1 For IBD patients (including both adults and children) treated with IFX or ADA, it can be recommended to conduct TDM under the condition of informed consent and available monitoring facilities, so as to potentially improve clinical outcomes.	Moderate	Weak	95%
Statement 2 For adult patients with IBD treated with UST and VDZ, adult patients with UC treated with GOL, and adult patients with CD treated with CER, TDM may be considered under the condition that it is accessible and acceptable to both patients and clinicians to potentially improve clinical outcomes.	Moderate	Weak	95%
Question 1.1 When implementing TDM in patients with IBD receiving biologic therapy, which specific indicators should be monitored?			
Statement 1 For patients (including both adults and children) with IBD treated with IFX or ADA, serum drug trough concentrations and serum anti-drug antibody levels should be monitored.	Very low	Strong	95%
Statement 2 For adult patients with IBD treated with UST and VDZ, adult patients with UC treated with GOL, and adult patients with CD treated with CER, monitoring of serum drug trough concentrations may be considered.	Very low	Weak	90%
Question 1.2 When should TDM be initiated for patients with IBD receiving biologic therapy?			
Statement 1 TDM can be considered in patients (including adults and children) with IBD who are receiving biologic therapy and have developed a loss of response.	Very low	Weak	86%
Statement 2 For patients (including both adults and children) with IBD receiving IFX, TDM can be considered after the 14th week when steady state drug concentrations are achieved. Earlier TDM, around the 6th week, may be considered if conditions permit or specific clinical needs arise. During the maintenance phase, clinicians and patients may consider implementing TDM based on individual circumstances.	Very low	Weak	81%
Statement 3 For patients (including both adults and children) with IBD treated with ADA, TDM can be considered after the 8th week when steady state drug concentrations are achieved. During the maintenance phase, clinicians and patients may consider implementing TDM based on actual circumstances.	Very low	Weak	81%
Statement 4 For adult patients with IBD treated with UST, TDM can be considered after the 16th week when steady state drug concentrations are achieved. During the maintenance phase, clinicians and patients may consider implementing TDM based on actual circumstances.	Very low	Weak	76%
Statement 5 For adult patients with IBD treated with VDZ, TDM can be considered after the 22 nd week when steady state drug concentration are achieved. Earlier TDM around the 6th and 14th weeks may be considered if conditions permit or specific clinical needs arise. During the maintenance phase, clinicians and patients may consider implementing TDM based on actual circumstances.	Very low	Weak	76%
Statement 6 For adult patients with UC treated with GOL, TDM can be considered after the 14th week when steady state drug concentration are achieved. During the maintenance phase, clinicians and patients may consider implementing TDM based on actual circumstances.	Very low	Weak	81%
Statement 7 For adult patients with CD treated with CER, TDM can be considered after the 8th week when steady state drug concentration are achieved. Earlier TDM around the 6th week may be considered if conditions permit or specific clinical needs arise. During the maintenance phase, clinicians and	Very low	Weak	81%

Table 1 (*continued*)

Clinical questions and statements	Certainty of evidence	Strength of recommendation	Agreement
patients may consider implementing TDM based on actual circumstances.			
Statement 8 TDM may be considered again after adjusting the dosage of biologics and achieving a steady state of drug concentration if conditions permit or clinically necessary.	Very low	Weak	90%
Question 1.3 What are the therapeutic drug trough concentration thresholds for patients with IBD receiving biologic therapy?			
Statement 1 There is currently no consensus on the trough concentration thresholds for any biologics in patients with IBD. It is suggested that thresholds can be reasonably selected based on specific disease types, clinical outcomes, and stages of treatment to effectively guide the adjustment of biologic doses.	Very low	Weak	86%
Question 2. For patients with IBD receiving biologic therapy, which TDM method (proactive or reactive) can better improve therapeutic outcomes?			
Statement 1 For patients (both adults and children) with IBD treated with IFX or ADA, proactive TDM may be preferred when resources permit.	Low	Weak	90%

Statement 2

For adult patients with IBD treated with UST and VDZ, adult patients with UC treated with GOL, and adult patients with CD treated with CER, monitoring of serum drug trough concentrations may be considered (Weak recommendation).

Evidence summary for clinical question Q1.1

No studies have compared different indicators when implementing TDM. We collected information on indicators monitored during TDM for each biologic from all eligible studies addressing Q1 and Q2. Therefore, the certainty of evidence for each recommendation under this question is very low. Among the 26 included studies (9 RCTs[26-33,51,52] and 17 comparative studies[34-49,53,54]), serum drug trough concentrations and levels of anti-drug antibody levels were monitored in patients with IBD (including either adults and children) treated with IFX or ADA. Studies have confirmed that the serum trough concentrations of IFX and ADA were correlated with patient clinical response rates, clinical remission rates, and other outcomes. Monitoring serum trough concentrations can guide the adjustment of drug treatment regimens, thereby better ensuring therapeutic efficacy. A systematic review and meta-analysis demonstrated that pooled anti-drug antibody rates for biologic monotherapy were 28.0% for IFX, 7.5% for ADA, 3.8% for GOL, 10.9% for CER, 6.2% for UST, and 8.4% for VDZ for combo- and monotherapy combined[55]. Therefore, despite the very low certainty of evidence, the GDG believes that it is reasonable to make a strong recommendation for IFX and ADA.

Additionally, eight systematic reviews[4,50,56-61] and three guidelines[7,11,62] provided evidence that the serum drug concentration levels of UST, VDZ, GOL, and CER were correlated with clinical outcomes in patients with IBD. Currently, there is insufficient evidence to support a correlation between the levels of anti-drug antibodies for these four biologics and clinical outcomes.

Q1.2 When should TDM be initiated for patients with IBD receiving biologic therapy?

Statement 1

TDM can be considered in patients (including adults and children) with IBD who are receiving biologic therapy and have developed a loss of response (Weak recommendation).

Statement 2

For patients (including both adults and children) with IBD treated with IFX, TDM can be considered after the 14th week when steady-state drug concentrations are achieved. Earlier TDM, around the 6th week, may be considered if conditions permit or specific clinical needs arise. During the maintenance phase, clinicians and patients may consider implementing TDM based on individual circumstances (Weak recommendation).

Statement 3

For patients (including both adults and children) with IBD treated with ADA, TDM can be considered after the 8th week when steady-state drug concentrations are achieved. During the maintenance phase, clinicians and patients may consider implementing TDM based on actual circumstances (Weak recommendation).

Statement 4

For adult patients with IBD treated with UST, TDM can be considered after the 16th week when steady-state drug concentrations are achieved. During the maintenance phase, clinicians and patients may consider implementing TDM based on actual circumstances (Weak recommendation).

Statement 5

For adult patients with IBD treated with VDZ, TDM can be considered after the 22 nd week when steady-state drug concentrations are achieved. Earlier TDM around the 6th and 14th weeks may be considered if conditions permit or specific clinical needs arise. During the maintenance phase, clinicians and patients may consider implementing TDM based on actual circumstances (Weak recommendation).

Statement 6

For adult patients with UC treated with GOL, TDM can be considered after the 14th week when steady-state drug concentrations are achieved. During the maintenance phase, clinicians and patients may consider implementing TDM based on actual circumstances (Weak recommendation).

Statement 7

For adult patients with CD treated with CER, TDM can be considered after the 8th week when steady-state drug

concentrations are achieved. Earlier TDM around the 6th week may be considered if conditions permit or specific clinical needs arise. During the maintenance phase, clinicians and patients may consider implementing TDM based on actual circumstances (Weak recommendation).

Statement 8

TDM may be considered again after adjusting the dosage of biologics and achieving a steady-state of drug concentrations if conditions permit or if clinically necessary (Weak recommendation).

Evidence summary for clinical Q1.2

No studies were found to compare different timings of TDM implementation. We collected information on the timing of TDM initiation and the frequency of each biologic administration from all eligible studies addressing Q1 and Q2. Therefore, the certainty of evidence for each recommendation under this question is very low, and the GDG made weak recommendations for each biologic drug. In general, the implementation of TDM necessitates that the drug concentration reaches a steady state. Since TDM of biologics primarily involves measuring trough concentrations, the timing of sample collection is closely linked to the administration schedule. Typically, blood samples are drawn immediately prior to drug administration. We recommend the optimal timing for TDM based on the pharmacokinetic properties, the administration time, and the time reaching the steady state for different biologics.

The timing of therapeutic drug monitoring (TDM) also depends on the availability of a concentration reference range that is associated with clinical outcomes at that specific time point, which can serve as a basis for guiding dose adjustments. Current research findings indicated that early-stage TDM of biologics is correlated with clinical outcomes (Table 3). Early-stage (2−6 weeks) TDM of IFX, ADA, CER, and GOL concentrations showed correlations with clinical remission, response, and mucosal healing. UST monitoring at Week 4 and VDZ monitoring at Weeks 2, 6, and 14 were also associated with clinical outcomes such as remission and mucosal healing, as well as CRP and FCP levels. Although early TDM is associated with clinical outcomes, we considered the drug's onset time, monitoring accessibility, and cost-effectiveness in determining the appropriate time points for early monitoring across different biologics. Furthermore, specific clinical scenarios for early TDM usually include patients with a high inflammatory burden, those exhibiting an inadequate early response, and other high-risk patients.

However, there were differences in the timing of TDM across current studies. In clinical practice, the decision to implement proactive TDM should be made by considering the patient's condition, the accessibility of laboratory tests, cost−effectiveness, and the convenience of TDM, while also taking into account whether there are reference concentration thresholds for the specific monitoring time points.

Q1.3 What are the therapeutic drug trough concentration thresholds for patients with IBD receiving biologic therapy?

Statement 1

There is currently no consensus on the trough concentration thresholds for any biologics in patients with IBD. It is suggested that thresholds can be reasonably selected based on specific disease types, clinical outcomes, and stages of treatment to effectively guide the adjustment of biologic doses (Weak recommendation).

Evidence summary for Q1.3

In addition to the eight included systematic reviews, our literature search identified three additional guidelines that provided relevant information[7,11,62]. Studies included in the systematic reviews and guidelines identified correlations between biologic drug concentrations, anti-drug antibody levels, and clinical outcomes in IBD patients through multivariate analysis. There was considerable variation in the reported serum drug concentration thresholds for biologics across studies, making it currently infeasible to establish a unified statement for IBD patients. Therefore, the certainty of evidence for this research question was very low. A summary table of therapeutic drug concentration thresholds for biologics in IBD from 11 existing systematic reviews and guidelines is presented in Table 3. Given the substantial variation in trough concentration thresholds for biologics across these studies, the GDG concluded that it is not yet feasible to establish a clear threshold for each biologic drug at this time. In clinical practice, judgments should be made based on the patient's disease type, the timing of TDM, the specific stage of treatment, and clinical outcomes. To facilitate the visualization of blood drug concentration thresholds across different time points and outcome indicators, we generated plots for IFX, ADA, and VDZ. Detailed information can be found in Figs. 2−4. Due to substantial variations in TDM time points and outcome indicators among other drugs, a comparative graphical representation could not be constructed. It is important to conduct high-quality clinical studies on serum drug concentration thresholds for different biologics in the future. Due to the differences in tests or assay kits used across various studies, there was variation in the positive thresholds for anti-drug antibodies. As a result, it is not feasible to provide recommendations on the concentration thresholds for anti-drug antibodies associated with biologics.

Justification for the recommendations of Q1, Q1.1, Q1.2, and Q1.3

The GDG made the above recommendations, based on the currently available evidence and the practical experience of the GDG members, considering clinical realities, patients' values, equity issues, acceptability to patients and clinicians, feasibility, and resources. Details of considerations based on the 12 issues from the GRADEpro website are presented in the Supporting Information Table S15.

Q2 For patients with IBD receiving biologic therapy, which TDM method (proactive or reactive) can better improve therapeutic outcomes?

Statement 1

For patients (including adults and children) with IBD treated with IFX or ADA, proactive TDM may be preferred when resources permit (Weak recommendation).

Evidence summary for clinical Q2

TDM can be conducted in the manner of either proactivly or reactively. Proactive TDM involves the routine monitoring of drug trough concentrations and anti-drug antibodies irrespective of disease control, aiming to achieve optimal therapeutic levels. In contrast, reactive TDM entails measuring drug concentrations and anti-drug antibodies triggered by a clinical event, such as primary non-response or a secondary loss of response. Four systematic reviews[22,24,25,63], two RCTs[51,52], and four comparative studies[43,49,53,54] were relevant to this research question. The certainty of the included systematic reviews is low to very low, and the overall certainty for both RCTs and comparative studies is low. This uncertainty precluded us from making a strong recommendation for proactive TDM in these patients. The GRADE summary of the findings table is presented in Table 4. One RCT[52] suggested that proactive TDM may reduce the clinical remission rate compared with reactive TDM in adult patients with IBD receiving IFX. Another RCT[51] indicated that proactive TDM might reduce

Table 2 GRADEpro summary of findings table for clinical Q1.

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TDM	conventional management/ standard of care	Relative (95% CI)	Absolute (95% CI)		
Clinical remission (12w, 30w, 56w)												
6[27,29,30–33]	randomised trials	serious[a]	not serious	not serious	not serious	none	279/467 (59.7%)	346/692 (50.0%)	RR 1.04 (0.91 to 1.18)	20 more per 1000 (from 45 fewer to 90 more)	⨁⨁⨁◯ Moderate[a]	CRITICAL
Clinical remission (6m, 1y)												
4[36,40,42,48]	cohort studies	serious[b,c]	not serious	not serious	not serious	none	339/533 (63.6%)	283/526 (53.8%)	RR 1.23 (1.08 to 1.40)	124 more per 1000 (from 43 more to 215 more)	⨁⨁⨁◯ Moderate[b,c]	CRITICAL
Clinical response (12w, 56w)												
3[27,29,30]	randomised trials	not serious[d]	serious[e]	not serious	not serious[f]	none	144/199 (72.4%)	281/425 (66.1%)	RR 1.06 (0.95 to 1.19)	40 more per 1000 (from 33 fewer to 126 more)	⨁⨁⨁◯ Moderate[d,e,f]	CRITICAL
Clinical response (12w)												
2[38,48]	cohort studies	serious[c]	serious[e]	not serious	Extremely serious[g,h]	none	74/128 (57.8%)	74/158 (46.8%)	RR 1.29 (0.72 to 2.29)	136 more per 1000 (from 131 fewer to 604 more)	⨁◯◯◯ Very low[c,e,g,h]	CRITICAL
Clinical response (6m)												
2[40,48]	cohort studies	serious[c]	not serious	not serious	serious[g]	none	127/179 (70.9%)	155/253 (61.3%)	RR 1.19 (1.04 to 1.37)	116 more per 1000 (from 25 more to 227 more)	⨁⨁◯◯ Low[c,g]	CRITICAL
Clinical response (1y)												
1[49]	cohort studies	serious[c]	not serious	not serious	serious[g]	none	91/163 (55.8%)	40/72 (55.6%)	RR 1.00 (0.78 to 1.29)	0 fewer per 1000 (from 122 fewer to 161 more)	⨁⨁◯◯ Low[c,g]	CRITICAL
Clinical response (2y)												
1[49]	cohort studies	serious[c]	not serious	not serious	serious[g]	none	84/151 (55.6%)	34/72 (47.2%)	RR 1.18 (0.89 to 1.56)	85 more per 1000 (from 52 fewer to 264 more)	⨁⨁◯◯ Low[c,g]	CRITICAL
Endoscopic remission (56w)												
3[26,27,29]	randomised trials	not serious[d]	not serious	not serious	serious[g]	none	92/248 (37.1%)	167/429 (38.9%)	RR 0.88 (0.70 to 1.10)	47 fewer per 1000 (from 117 fewer to 39 more)	⨁⨁⨁◯ Moderate[d,g]	CRITICAL
Endoscopic remission (6m, 1yr)												
2[40,46]	cohort studies	not serious[b]	not serious	not serious	serious[g]	none	118/205 (57.6%)	93/211 (44.1%)	RR 1.33 (1.10 to 1.61)	145 more per 1000 (from 44 more to 269 more)	⨁⨁⨁◯ Moderate[b,g]	CRITICAL

(*continued on next page*)

Table 2 (*continued*)

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TDM	conventional management/ standard of care	Relative (95% CI)	Absolute (95% CI)		
Mucosal healing (2y, 41m)												
2[35,45]	cohort studies	serious[c]	serious[e]	not serious	Extremely serious[g,h]	none	93/126 (73.8%)	107/204 (52.5%)	RR 1.25 (0.53 to 2.91)	131 more per 1000 (from 247 fewer to 1000 more)	⨁◯◯◯ Very low[c,e,g,h]	CRITICAL
CRP (mg/L) (12w, 30w)												
2[30,31]	randomised trials	serious[a]	not serious	not serious	Very serious[i]	none	101	105	–	MD 1.68 lower (6.09 lower to 2.73 higher)	⨁◯◯◯ Very low[a,i]	CRITICAL
FCP (μg/g) (56w)												
1[27]	randomised trials	not serious[j]	not serious	not serious	Very serious[i]	none	92	92	–	MD 56.2 lower (701.87 lower to 589.47 higher)	⨁⨁◯◯ Low[i,j]	CRITICAL
Corticosteroid-free remission (56w)												
4[26–29]	randomised trials	serious[a]	not serious	not serious	not serious[g]	none	136/242 (56.2%)	148/322 (46.0%)	RR 1.07 (0.92 to 1.24)	32 more per 1000 (from 37 fewer to 110 more)	⨁⨁⨁◯ Moderate[a,g]	CRITICAL
Corticosteroid-free remission (1y)												
2[41,42]	cohort studies	serious[b,c]	serious[e]	not serious	Extremely serious[g,h]	none	166/268 (61.9%)	124/186 (66.7%)	RR 0.86 (0.45 to 1.64)	93 fewer per 1000 (from 367 fewer to 427 more)	⨁◯◯◯ Very low[b,c,e,g,h]	CRITICAL
Hospitalization rate (26w, 1y, 2y, 3y, 41m)												
7[35,36,40,44,45,47,48]	cohort studies	serious[b,c]	not serious	not serious	serious[g]	none	92/599 (15.4%)	190/825 (23.0%)	RR 0.69 (0.54 to 0.88)	71 fewer per 1000 (from 106 fewer to 28 fewer)	⨁⨁◯◯ Low[b,c,g]	CRITICAL
Serious adverse events (56w)												
4[26,27,29,33]	randomised trials	serious[a]	not serious	not serious	serious[g]	none	49/470 (10.4%)	106/967 (11.0%)	RR 0.92 (0.64 to 1.33)	9 fewer per 1000 (from 39 fewer to 36 more)	⨁⨁◯◯ Low[a,g]	CRITICAL
Serious adverse events (3y)												
1[44]	cohort studies	serious[b,c]	not serious	not serious	Extremely serious[g,h]	none	1/33 (3.0%)	6/69 (8.7%)	RR 0.35 (0.04 to 2.78)	57 fewer per 1000 (from 83 fewer to 155 more)	⨁◯◯◯ Very low[b,c,g,h]	CRITICAL
Serious TEAE (56w)												
2[27,29]	randomised trials	not serious[d]	not serious	not serious	Extremely serious[g,h]	none	17/260 (6.5%)	81/804 (10.1%)	RR 0.73 (0.42 to 1.29)	27 fewer per 1000 (from 58 fewer to 29 more)	⨁◯◯◯ Very low[d,g,h]	CRITICAL
Surgery rate (26w, 1y, 2y, 3y, 41m, 5y)												
9[35–37,39,43–45,47,48]	cohort studies	serious[b,c]	not serious	not serious	serious[g]	none	67/895 (7.5%)	108/1087 (9.9%)	RR 0.62 (0.45 to 0.84)	38 fewer per 1000 (from 55 fewer to 16 fewer)	⨁⨁◯◯ Low[b,c,g]	IMPORTANT

Cost of CD (1000€) (12w)											
1[30]	randomised trials	serious[a]	not serious	not serious	Very serious[i]	none	33	36	—	MD 3.14 lower (4.71 lower to 1.57 lower)	⨁◯◯◯ Very low[a,i]	IMPORTANT
Change of IBDQ score (20w, 30w, 48w) (ranging 32-224, higher the better)											
3[30–32]	randomised trials	serious[a]	not serious	not serious	serious[k]	none	173	180	—	MD 0.8 lower (5.36 lower to 3.75 higher)	⨁⨁◯◯ Low[a,k]	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio.
[a]Downgraded by 1 level due to risk of bias: there are some concerns of risk of bias in Randomization and Blinding domains.
[b]Downgraded by 0.5 levels due to risk of bias in Comparability domain.
[c]Downgraded by 1 level due to risk of bias: did not use the ROBINS-I tool.
[d]Downgraded by 0.5 levels due to risk of bias: there are some concerns of risk of bias in Randomization domain.
[e]Downgraded by 1 level due to inconsistency.
[f]Downgraded by 0.5 levels due to imprecision: small sample size (600−750).
[g]Downgraded by 1 level due to imprecision: low event rate (<300).
[h]Downgraded by 2 levels due to imprecision: RR value: high limit/low limit >3.
[i]Downgraded by 2 levels due to imprecision: very' small sample size (<240).
[j]Downgraded by 0.5 levels due to risk of bias: there are some concerns of risk of bias in Blinding domain.
[k]Downgraded by 1 level due to imprecision: small sample size (240−600).

FCP levels at 72 weeks and improve steroid-free clinical remission rates in pediatric patients with CD treated with ADA, and found no impact of proactive TDM on the risk of serious adverse events. Additionally, one comparative study[54] indicated that proactive TDM may improve clinical remission rates at 30 weeks and 54 weeks and improve the endoscopic remission rate in both pediatric and adult CD patients receiving IFX. Two comparative studies[53,54] indicated that proactive TDM might reduce the hospitalization rate in pediatric and adult IBD patients. Additionally, one comparative study[53] indicated that proactive TDM might lower the risk of serious adverse events in adult IBD patients. Furthermore, a meta-analysis of 2 comparative studies[53,54] indicated that proactive TDM may reduce the surgery rate in adult IBD patients receiving IFX. Given the low certainty of the evidence, the patient burden associated with potential additional clinic visits for blood sampling and monitoring, and the accessibility of TDM, a weak recommendation was made in favour of proactive TDM. Reactive TDM can still be implemented when necessary in clinical practice, as it is currently the most feasible approach. No relevant evidence was available for proactive TDM of other biologic drugs other than IFX and ADA. A summary flowchart illustrating the evidence and recommendations for proactive and reactive TDM was shown in Fig. 5.

Justification for the recommendations of Q2

The GDG concluded that while proactive TDM for IFX and ADA may provide greater clinical benefits, it also increased the monitoring frequency and costs. In clinical practice, decisions regarding the implementation of proactive versus reactive TDM should take into account patient preferences and financial capabilities, as well as ensure equity among patients and maintain feasibility. Details of the considerations based on the 12 issues from the GRADEpro website are presented in Supporting Information Table S16.

4. Discussion

TDM remains a crucial tool in optimizing the management of patients with IBD, thereby contributing to improved clinical outcomes. Several medical societies and TDM expert groups have made guidelines or consenusus statements for TDM of biologics in IBD[7,9-11,64]. These published consensus statements primarily address the key issues associated with the TDM implementation in patients with IBD, with a specific focus on anti-TNFα agents, IFX and ADA. Delphi method was mainly used to establish these consensuses without systematic literature search, evidence synthesis and evaluation. Due to the differences in time period for incorporating literature evidence among various guidelines, there is a certain degree of inconsistency in the recommendations. This guideline incorporates comprehensive and up-to-date evidence synthesis and represents the first clinical practice recommendation for TDM in patients with IBD, based on a systematic review using GRADE approach. More importantly, this guideline encompasses not only anti-TNF-α drugs but also a broader range of biologics, thereby better aligning with actual clinical requirements. It addresses five critical questions: whether TDM results in superior therapeutic outcomes to conventional treatment, which indicators should be monitored, when TDM should be initiated, what the therapeutic drug trough concentration thresholds are, and which TDM method (proactive or reactive) can better improve therapeutic outcomes. These recommendations provide current, evidence-based guidance for intended users to consider in clinical practice.

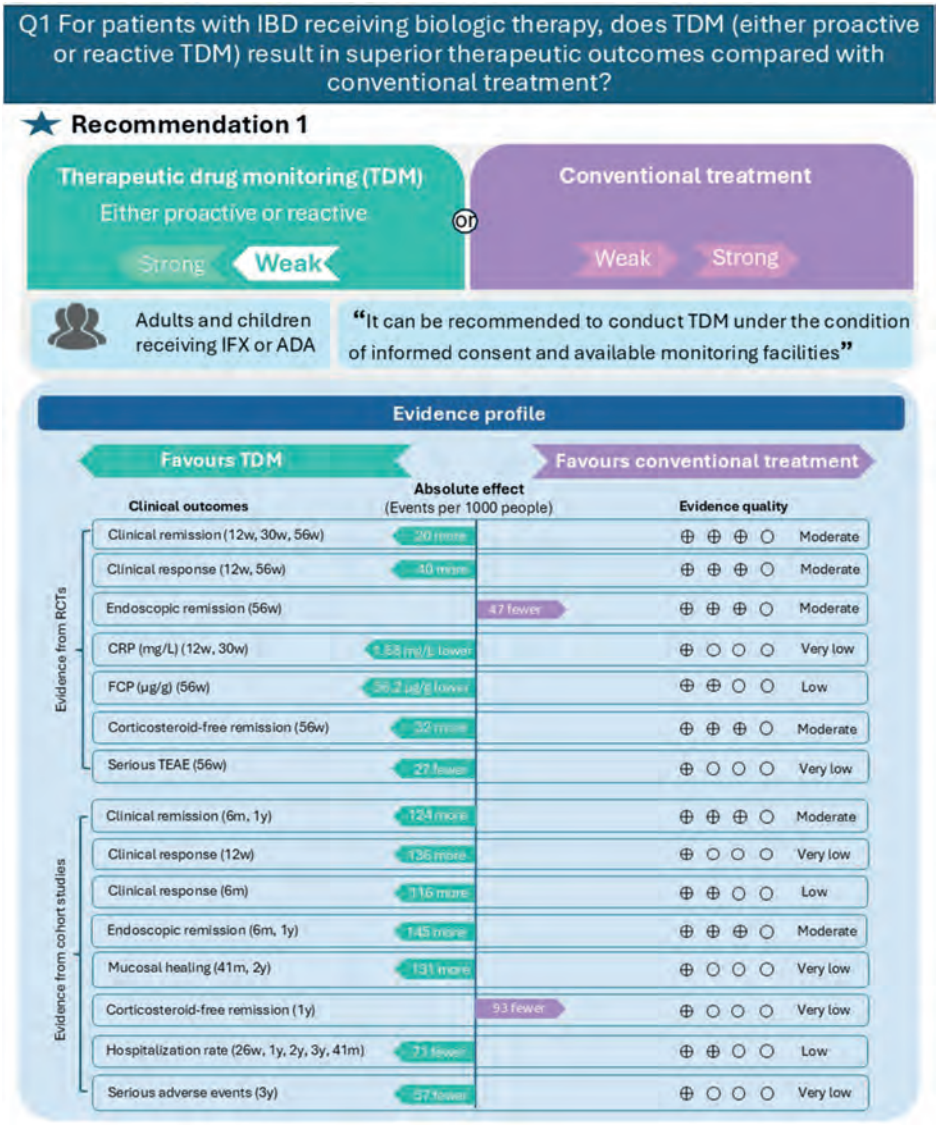

Figure 1 The recommendation and evidence for clinical Q1.

However, as described in the Evidence Summary section, for Q1.1, Q1.2, and Q1.3, there is no direct comparative evidence to support the recommendations. For Q1, the existing evidence from RCTs and comparative studies is inconsistent. Two main RCTs (TAXIT and TAILORIX trials) were incorporated in Q1[26,33]. However, trials failed to reach their primary end points due to methodological flaws. In the TAXIT trial, only patients in remission were randomized, and they first underwent an intervention of dose optimization. In the TAILORIX trial, dose intensification only started after Week 14 and when a low serum concentration was measured; dose escalation was only implemented 8 weeks later. However, if the IFX concentration was <1 μg/mL, an additional IFX infusion was given at the Week 4 interval. Moreover, patients in the control group received 'liberal' dose escalation as per investigator's discretion. The trial may also have been underpowered, and the cut-off used to escalate the dose was 3 μg/mL, a threshold that was probably too low in light of other observations. Therefore, in such scenarios, the formulation of recommendations should be based on the findings of cohort studies.

Although serum drug concentrations have been demonstrated to be associated with clinical outcomes, a major concern when treating patients with biologics is the development of anti-drug antibodies, which are associated with lower serum drug concentrations, loss of response, and adverse effects such as infusion and injection site reactions[65]. Thus, serum concentrations and anti-drug antibody levels are usually as combined as indicators for TDM. The incidence of immunogenicity demonstrates substantial variability across studies and biologic agents. The immunogenicity of biologics is associated with their degree of humanization, with the human-mouse chimeric antibody IFX exhibiting the highest immunogenic potential, followed by the ADA. UST and VDZ are fully humanized antibodies, which exhibit a relatively low rate of anti-drug antibody production. In clinical settings, immunogenicity may arise from multiple factors, encompassing both patient-related factors (*e.g.*, underlying chronic diseases, systemic immune status—including prior failure of biologic therapies—and [epi]genetic background) and treatment-related factors (*e.g.*, dosage and administration regimens, drug molecular structure, photostability, storage temperature, and exposure to

Table 3 Summary of therapeutic drug concentration thresholds for biologics in IBD.

Drug type	Disease type	TDM method	TDM time point	Threshold (μg/mL)	Clinical outcome	Therapeutic outcome time point	Ref (Study ID)
ADA	CD	ELISA	Week 2	6.7	Clinical remission	Week 14	Papamichael 2022 (SR)[4] Ungar 2018(POETIC)
ADA	IBD	ELISA	Week 4	13.85	Clinical remission	Week 52	Pigneur 2022 (SR)[59] Lucafo 2021
ADA	IBD	ELISA	Week 4	3.5	Clinical response	Week 4	Papamichael 2022 (SR)[4] Tighe 2017
ADA	CD	ELISA	Week 4	12	CRP normalization (≤5 mg/L)	Week 12	Papamichael 2022 (SR)[4] Verstockt 2018 (POETIC)
ADA	CD	ELISA	Week 4	22.5	PCDAI<10, CRP normalization (≤5 mg/L) and FCP normalization (≤250 g/g)	Week 24	Papamichael 2022 (SR)[4] Rinawi 2021
ADA	CD	ELISA	Week 8	12.5	PCDAI<10, CRP normalization (≤5 mg/L) and FCP normalization (≤250 g/g)	Week 24	Papamichael 2022 (SR)[4] Rinawi 2021
ADA	CD	ELISA	Week 14	12	Clinical remission	Week 14 and 54	Papamichael 2022 (SR)[4] Kennedy 2019 (PANTS)
ADA	CD	ELISA	Week 14	3.65	CRP normalization	Week 14	Papamichael 2022 (SR)[4] Ungar 2018(POETIC)
ADA	CD	ELISA	Week 16	8.76	Mucosal healing	Week 16	Papamichael 2022 (SR)[4] Choi 2020
ADA	IBD	ELISA	Week 22	7.54	Clinical remission	Week 82	Pigneur 2022 (SR)[59] Lucafo 2021
ADA	CD	ELISA	Week 26	5	Clinical remission	Week 52	Papamichael 2022 (SR)[4] Nakase 2017 (DIAMOND)
ADA	CD	ELISA	Week 26	7.2	Mucosal healing	NR	Pigneur 2022 (SR)[59] Chaparro 2019
ADA	IBD	NR	Maintenance	8.25	Clinical remission	NR	Pigneur 2022 (SR)[59] Ritter 2021
ADA	CD	ELISA	Maintenance	7.9	Mucosal healing	NR	Cheifetz 2021 (GD)[7] Morita 2016
ADA	CD	ELISA	Maintenance	9.8	Fistula closure	Maintenance	Cheifetz 2021 (GD)[7] Plevris 2020
ADA	CD	ELISA	Maintenance	6.8	Fistula healing	Maintenance	Cheifetz 2021 (GD)[7] Plevris 2020
ADA	CD	ELISA	Maintenance	5.6	CRP normalization (≤3 g/L)	Maintenance	Cheifetz 2021 (GD)[7] Morita 2016
ADA	IBD	ELISA	Maintenance	6.6	CRP normalization (≤3 g/L)	Maintenance	Cheifetz 2021 (GD)[7] Ungar 2016
ADA	CD	Validated in-house assay	Maintenance	6.8	CRP normalization (≤3 g/L)	Maintenance	Cheifetz 2021 (GD)[7] Carlsen 2019
ADA	CD	ELISA	Maintenance	10.5	CRP normalization (≤3 g/L) and FCP normalization (≤100 g/g)	Maintenance	Cheifetz 2021 (GD)[7] Plevris 2018
ADA	CD	ELISA	Maintenance	8.5	CRP normalization (≤3 g/L) and FCP normalization (≤250 g/g)	Maintenance	Cheifetz 2021 (GD)[7] Plevris 2018
ADA	CD	Validated in-house assay	Maintenance	6.8	CRP normalization (≤3 g/L) and FCP normalization (≤50 g/g)	Maintenance	Cheifetz 2021 (GD)[7] Carlsen 2019

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Table 3 (*continued*)

Drug type	Disease type	TDM method	TDM time point	Threshold (μg/mL)	Clinical outcome	Therapeutic outcome time point	Ref (Study ID)
ADA	UC	ELISA	NR	11.1	Endoscopic remission	NR	Pigneur 2022 (SR)[59] Kato 2021
CER	CD	ELISA	Week 6	31.8	CDAI remission	Week 6	Papamichael 2022 (SR)[4] Vande 2018
CER	CD	ELISA	Week 6	31.8	CDAI response	Week 6	Papamichael 2022 (SR)[4] Vande 2018
CER	CD	ELISA	Week 6	34.5	CDAI ≤150 and FCP normalization (≤250 g/g)	Week 6	Papamichael 2022 (SR)[4] Vande 2018
CER	CD	ELISA	Week 6	36.1	CDAI ≤150 and FCP normalization (≤250 g/g)	Week 26	Papamichael 2022 (SR)[4] Vande 2018
CER	CD	ELISA	Week 6	31.9	CRP normalization (≤5 g/L)	Week 6	Papamichael 2022 (SR)[4] Vande 2018
CER	CD	ELISA	Week 6	32.7	FCP normalization (≤250 g/g)	Week 6	Papamichael 2022 (SR)[4] Vande 2018
CER	CD	NR	Week 8	23.3	Endoscopic remission	Week 10	Papamichael 2022 (SR)[4] Colombel 2014
CER	CD	ELISA	Week 12	13.8	FCP normalization (≤250 g/g)	Week 26	Papamichael 2022 (SR)[4] Vande 2018
CER	CD	ELISA	Week 12	14.8	FCP normalization (≤250 g/g)	Week 26	Papamichael 2022 (SR)[4] Vande 2018
GOL	UC	ECLIA	Week 2	8.9	Clinical response	Week 6	Papamichael 2022 (SR)[4] Adedokun 2017
GOL	UC	ECLIA	Week 4	7.4	Clinical response	Week 6	Papamichael 2022 (SR)[4] Adedokun 2017
GOL	UC	ELISA	Week 6	3.2	Clinical response	Week 6	Papamichael 2022 (SR)[4] Samaan 2020
GOL	UC	ECLIA	Week 6	2.5	Clinical response	Week 6	Papamichael 2022 (SR)[4] Adedokun 2017
GOL	UC	ELISA	Week 6	3.8	Combined clinical-biochemical remission	Week 6	Papamichael 2022 (SR)[4] Samaan 2020
GOL	UC	ECLIA	Week 28	0.9	Clinical remission	Weeks 30 and 54	Papamichael 2022 (SR)[4] Adedokun 2017
GOL	UC	ECLIA	Week 44	1.4	Clinical remission	Weeks 30 and 54	Papamichael 2022 (SR)[4] Adedokun 2017
GOL	UC	ECLIA	Week 54	3.7	Clinical remission	Weeks 30 and 54	Papamichael 2022 (SR)[4] Adedokun 2017
GOL	UC	ELISA	Maintenance	2.4	Combined clinical-biochemical remission	Maintenance	Papamichael 2022 (SR)[4] Samaan 2020
IFX	CD	ELISA	Week 2	20.4	Clinical remission	Week 14	Cheifetz 2021 (GD)[7] Gonczi 2017
IFX	UC	ELISA	Week 2	15.3	Clinical remission	Week 14	Cheifetz 2021 (GD)[7] Gonczi 2017
IFX	UC	ELISA	Week 2	14.5	Clinical remission	Week 30	Cheifetz 2021 (GD)[7] Gonczi 2017
IFX	UC	ELISA	Week 2	21.3	Clinical remission	Week 14	Alsoud 2024 (GD)[62] Kobayashi 2016 (JAPIC)
IFX	CD	ELISA	Week 2	16.9	Clinical response	Week 14	Cheifetz 2021 (GD)[7] Gonczi 2017
IFX	UC	ELISA	Week 2	11.5	Clinical response	Week 14	Cheifetz 2021 (GD)[7] Gonczi 2017
IFX	UC	ELISA	Week 2	11.5	Clinical response	Week 30	Cheifetz 2021 (GD)[7] Gonczi 2017
IFX	IBD	AIFA	Week 2	22.9	Clinical response	Week 14	Alsoud 2024 (GD)[62] Buhl 2020
IFX	CD	ELISA	Week 2	26.7	Clinical response	Week 14	Alsoud 2024 (GD)[62] Clarkston 2019

Table 3 (*continued*)

Drug type	Disease type	TDM method	TDM time point	Threshold (μg/mL)	Clinical outcome	Therapeutic outcome time point	Ref (Study ID)
IFX	CD	ELISA	Week 2	23.1	Endoscopic remission	Week 12	Alsoud 2024 (GD)[62] Dreesen 2020 (TAILORIX)
IFX	IBD	AIFA	Week 6	11.8	Clinical response	Week 14	Alsoud 2024 (GD)[62] Buhl 2020
IFX	UC	ELISA	Week 6	22	Clinical response	Week 8	Alsoud 2024 (GD)[62] Adedokun 2014 (ACT 1/2)
IFX	CD	ELISA	Week 6	15.9	Clinical response	Week 14	Alsoud 2024 (GD)[62] Clarkston 2019
IFX	UC	ELISA	Week 6	6.6	Endoscopic healing	Week 8	Alsoud 2024 (GD)[62] Brandse 2016
IFX	CD	ELISA	Week 6	10	Endoscopic remission	Week 12	Alsoud 2024 (GD)[62] Dreesen 2020 (TAILORIX)
IFX	UC	ELISA	Week 6	15	Mucosal healing	Weeks 10-14	Cao 2021 (SR)[57] Papamichael 2016
IFX	UC	ELISA	Week 8	41.2	Clinical response	Week 8	Alsoud 2024 (GD)[62] Adedokun 2014 (ACT 1/2)
IFX	CD	ELISA	Week 10	7.1	Clinical remission	Week 10	Alsoud 2024 (GD)[62] Cheifetz 2023 (REACH)
IFX	CD	ELISA	Week 10	6.5	Clinical response	Week 30	Alsoud 2024 (GD)[62] Cheifetz 2023 (REACH)
IFX	CD	ELISA	Week 12	10.6	Mucosal healing	Week 54	Alsoud 2024 (GD)[62] Dreesen 2020 (TAILORIX)
IFX	IBD	ELISA	Week 14	4	Clinical remission	Week 30 and 54	Alsoud 2024 (GD)[62] Park 2023
IFX	CD	ELISA	Week 14	7	Clinical remission	Week 14 and 54	Alsoud 2024 (GD)[62] Kennedy 2019 (PANTS)
IFX	CD	ELISA	Week 14	3.5	Clinical response	Week 54	Alsoud 2024 (GD)[62] Cornillie 2014 (ACCENT I)
IFX	IBD	ELISA	Week 14	4.8	Clinical response	Week 14	Papamichael 2022 (SR)[4] Tighe 2017
IFX	UC	ELISA	Week 14	5.1	Clinical response	Week 30	Alsoud 2024 (GD)[62] Adedokun 2014 (ACT 1/2)
IFX	UC	ELISA	Week 14	3.5	Clinical response	Week 54	Alsoud 2024 (GD)[62] Adedokun 2014 (ACT 1/2)
IFX	IBD	ELISA	Week 14	4	Endoscopic remission	Week 54	Alsoud 2024 (GD)[62] Park 2023
IFX	CD	ELISA	Week 14	2	CRP normalization	Week 14	Cheifetz 2021 (GD)[7] Papamichael 2021-b
IFX	CD	ECLIA	Week 14	9.4	FCP normalization (≤250 g/g)	Week 14	Alsoud 2024 (GD)[62] Colman 2021
IFX	CD	ECLIA	Week 14	11.5	FCP normalization (<100 g/kg)	Week 14	Alsoud 2024 (GD)[62] Colman 2021
IFX	UC	ELISA	Week 14	2.1	Mucosal healing	Weeks 10-14	Cao 2021 (SR)[57] Papamichael 2016
IFX	CD	ELISA	Week 14	4.85	Mucosal healing	NR	Cao 2021 (SR)[57] Feng 2019
IFX	UC	ELISA	Week 14	5.1	Mucosal healing (MES<2)	Week 30	Cheifetz 2021 (GD)[7] Vande Casteele 2019
IFX	UC	ELISA	Week 14	6.7	Mucosal healing (MES = 0)	Week 30	Cheifetz 2021 (GD)[7] Vande Casteele 2019

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Table 3 (*continued*)

Drug type	Disease type	TDM method	TDM time point	Threshold (μg/mL)	Clinical outcome	Therapeutic outcome time point	Ref (Study ID)
IFX	CD	ELISA	Week 14	6.1	Complete fistula response	Week 14	Cheifetz 2021 (GD)[7] Papamichael 2021-b
IFX	CD	ELISA	Week 14	7.2	Complete fistula response and CRP normalization	Week 14	Cheifetz 2021 (GD)[7] Papamichael 2021-b
IFX	IBD	ELISA	Induction	6	Mucosal healing	Induction	Cao 2021 (SR)[57] Ungar 2016
IFX	IBD	ELISA	Induction	6.8	CRP normalization	Induction	Cao 2021 (SR)[57] Ungar 2016
IFX	UC	ELISA	Week 30	3.7	Clinical response	Week 30	Alsoud 2024 (GD)[62] Adedokun 2014 (ACT 1/2)
IFX	UC	ELISA	Week 30	2.4	Clinical response	Week 54	Alsoud 2024 (GD)[62] Adedokun 2014 (ACT 1/2)
IFX	CD	ELISA	Week 30	2.85	Mucosal healing	NR	Cao 2021 (SR)[57] Feng 2019
IFX	CD	ELISA	Week 30	3	Mucosal healing	Week 26	Alsoud 2024 (GD)[62] Reinisch 2015 (SONIC)
IFX	UC	ELISA	Week 46	2.7	Mucosal healing	Week 46	Cao 2021 (SR)[57] Morita 2016
IFX	IBD	ELISA	Week 46	3.4	Mucosal healing	Week 46	Cao 2021 (SR)[57] Chaparro 2018
IFX	UC	ELISA	Week 46	7.5	Endoscopic healing	Week 46	Cheifetz 2021 (GD)[7] Papamichael 2018-b
IFX	UC	ELISA	Week 54	1.7	Clinical response	Week 54	Alsoud 2024 (GD)[62] Adedokun 2014 (ACT 1/2)
IFX	CD	ELISA	Maintenance	1.5	Clinical remission	Maintenance	Cheifetz 2021 (GD)[7] Ward 2017
IFX	IBD	ELISA	Maintenance	2.1	Clinical remission	Maintenance	Cheifetz 2021 (GD)[7] Roblin 2017
IFX	IBD	ELISA	Maintenance	2.9	Clinical remission	Maintenance	Cheifetz 2021 (GD)[7] Roblin 2017
IFX	IBD	ELISA	Maintenance	3.9	Clinical remission	Maintenance	Cheifetz 2021 (GD)[7] Roblin 2017
IFX	IBD	ELISA	Maintenance	4.9	Clinical remission	Maintenance	Cheifetz 2021 (GD)[7] Roblin 2017
IFX	CD	ELISA	Maintenance	3.26	Clinical remission	Maintenance	Cao 2021 (SR)[57] Kang 2019
IFX	CD	ELISA	Maintenance	4	Mucosal healing	Maintenance	Cheifetz 2021 (GD)[7] Imaeda 2014
IFX	CD	ELISA	Maintenance	4	Mucosal healing	Maintenance	Cao 2021 (SR)[57] Imaeda 2014
IFX	CD	ELISA	Maintenance	4.2	Mucosal healing	Maintenance	Cao 2021 (SR)[57] Kang 2019
IFX	CD	ELISA	Maintenance	3.7	Partial mucosal healing	Maintenance	Cao 2021 (SR)[57] Kang 2019
IFX	CD	ELISA	Maintenance	9.7	Endoscopic remission	Maintenance	Cheifetz 2021 (GD)[7] Papamichael 2018-a
IFX	CD	ELISA	Maintenance	1.1	FCP normalization ($\leq$300 g/g)	Maintenance	Cheifetz 2021 (GD)[7] Imaeda 2014
IFX	CD	ELISA	Maintenance	5.7	FCP normalization	Maintenance	Cheifetz 2021 (GD)[7] Ward 2017
IFX	CD	ELISA	Maintenance	0.6	CRP normalization	Maintenance	Cheifetz 2021 (GD)[7] Imaeda 2014
IFX	CD	ELISA	Maintenance	3.4	CRP normalization	Maintenance	Cheifetz 2021 (GD)[7] Ward 2017
IFX	CD	ELISA	Maintenance	2.2	CRP normalization	Maintenance	Cheifetz 2021 (GD)[7] Papamichael 2018-a

Table 3 (*continued*)

Drug type	Disease type	TDM method	TDM time point	Threshold (μg/mL)	Clinical outcome	Therapeutic outcome time point	Ref (Study ID)
IFX	CD	ELISA	Maintenance	2.52	CRP normalization (≤3 g/L)	Maintenance	Cao 2021 (SR)[57] Kang 2019
IFX	IBD	ELISA	Maintenance	4.9	CRP normalization and FCP normalization (≤50 g/g)	Maintenance	Cheifetz 2021 (GD)[7] Roblin 2017
IFX	CD	ELISA	Maintenance	5	Fistula closure	Maintenance	Cao 2021 (SR)[57] Strik 2019
IFX	CD	ELISA	Maintenance	7.1	Fistula closure	Maintenance	Cao 2021 (SR)[57] Plevris 2020
IFX	CD	ELISA	Maintenance	7.1	Fistula healing	Maintenance	Cao 2021 (SR)[57] Plevris 2020
IFX	IBD	ELISA	Maintenance	3.9	Clinical remission and FCP normalization (≤250 g/g)	Maintenance	Cheifetz 2021 (GD)[7] Roblin 2017
IFX	IBD	ELISA	Maintenance	2.9	Clinical remission and CRP normalization	Maintenance	Cheifetz 2021 (GD)[7] Roblin 2017
IFX	IBD	ELISA	NR	2.3	Clinical remission	NR	Cheifetz 2021 (GD)[7] Roblin 2017
IFX	IBD	HMSA/ ELISA	NR	6−10	Clinical response	NR	Marquez-Megias 2022 (SR)[58] Mitrev 2017
IFX	CD	ELISA	NR	12.7	Fistula healing	NR	Cao 2021 (SR)[57] EI-Matary 2019
UST	CD	ELISA	Week 2	24.7	FCP normalization (≤100 g/g)	Week 8	Cheifetz 2021 (GD)[7] Hanzel 2021
UST	CD	ELISA	Week 2	24.7	FCP normalization (≤100 g/g)	Week 16	Cheifetz 2021 (GD)[7] Hanzel 2021
UST	CD	ELISA	Week 2	27.2	FCP normalization (≤100 g/g)	Week 24	Cheifetz 2021 (GD)[7] Hanzel 2021
UST	UC	ELISA	Week 4	17.1	Clinical response	NR	Vieujean 2023 (SR)[50] Alsoud 2022
UST	CD	ELISA	Week 4	15	FCP normalization (≤100 g/g)	Week 8	Cheifetz 2021 (GD)[7] Hanzel 2021
UST	CD	ELISA	Week 4	15	FCP normalization (≤100 g/g)	Week 16	Cheifetz 2021 (GD)[7] Hanzel 2021
UST	CD	ELISA	Week 4	15	FCP normalization (≤100 g/g)	Week 24	Cheifetz 2021 (GD)[7] Hanzel 2021
UST	CD	ELISA	Week 4	13	CRP normalization (≤5 mg/L) and FCP normalization (≤250 g/g)	Week 16	Papamichael 2022 (SR)[4] Soufflet 2019
UST	UC	ELISA	Week 4	21.3	Mucosal improvement.	NR	Vieujean 2023 (SR)[50] Alsoud 2022
UST	UC	ELISA	Week 6	24.4	Clinical remission	Week 14	Papamichael 2022 (SR)[4] Verstockt 2019
UST	CD	ELISA	Week 6	28.7	Clinical remission	Week 24	Papamichael 2022 (SR)[4] Verstockt 2019
UST	UC	ELISA	Week 6	20.9	Endoscopic improvement	Week 14	Papamichael 2022 (SR)[4] Verstockt 2019
UST	CD	ELISA	Week 6	13.8	Endoscopic improvement	Week 24	Papamichael 2022 (SR)[4] Verstockt 2019
UST	CD	ELISA	Week 8	3.3	Clinical remission	Week 8	Papamichael 2022 (SR)[4] Adedokun 2018
UST	UC	HMSA	Week 8	3.7	Clinical response	Week 8	Vieujean 2023 (SR)[50] Adedokun 2020
UST	UC	ELISA	Week 8	5.9	Clinical response	NR	Vieujean 2023 (SR)[50] Alsoud 2022
UST	CD	ELISA	Week 8	6.85	FCP normalization (≤100 g/g)	Week 8	Cheifetz 2021 (GD)[7] Hanzel 2021
UST	CD	ELISA	Week 8	4.37	FCP normalization (≤100 g/g)	Week 16	Cheifetz 2021 (GD)[7] Hanzel 2021

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Table 3 (*continued*)

Drug type	Disease type	TDM method	TDM time point	Threshold (μg/mL)	Clinical outcome	Therapeutic outcome time point	Ref (Study ID)
UST	CD	ELISA	Week 8	6.85	FCP normalization (≤100 g/g)	Week 24	Cheifetz 2021 (GD)[7] Hanzel 2021
UST	CD	ELISA	Week 8	2	CRP normalization (≤5 mg/L) and FCP normalization (≤250 g/g)	Week 16	Papamichael 2022 (SR)[4] Soufflet 2019
UST	CD	ELISA	Week 8	11.1	Mucosal healing	Week 8	Cheifetz 2021 (GD)[7] Hanzel 2021
UST	UC	ELISA	Week 8	8.4	Mucosal improvement.	NR	Vieujean 2023 (SR)[50] Alsoud 2022
UST	CD	ELISA	Week 12	1.1	CRP normalization (≤5 mg/L)	Week 26	Papamichael 2022 (SR)[4] Painchart 2020
UST	UC	ELISA	Week 14	10.1	Clinical remission	Week 14	Papamichael 2022 (SR)[4] Verstockt 2019
UST	CD	ELISA	Week 14	21.2	Clinical remission	Week 24	Papamichael 2022 (SR)[4] Verstockt 2019
UST	UC	ELISA	Week 14	10.1	Endoscopic improvement	Week 14	Papamichael 2022 (SR)[4] Verstockt 2019
UST	CD	ELISA	Week 14	30.1	Endoscopic improvement	Week 24	Papamichael 2022 (SR)[4] Verstockt 2019
UST	CD	ELISA	Week 16	1.4	CRP normalization (≤5 mg/L) and FCP normalization (≤250 g/g)	Week 16	Papamichael 2022 (SR)[4] Soufflet 2019
UST	CD	ELISA	Week 16	2.3	Endoscopic response	Maintenance	Papamichael 2022 (SR)[4] Verstockt 2019
UST	CD	ELISA	Week 24	0.8	Clinical remission	Week 24	Papamichael 2022 (SR)[4] Adedokun 2018
UST	CD	ELISA	Week 24	1.9	Endoscopic response	Maintenance	Papamichael 2022 (SR)[4] Verstockt 2019
UST	CD	ELISA	Week 40	1.4	Clinical remission	Week 44	Papamichael 2022 (SR)[4] Adedokun 2018
UST	CD	ELISA	Maintenance	5.2	Clinical remission	Maintenance	Papamichael 2022 (SR)[4] Verstockt 2019
UST	UC	HMSA	Maintenance	1.3	Clinical remission	Maintenance	Vieujean 2023 (SR)[50] Adedokun 2020
UST	CD	ELISA	Maintenance	1.4	Clinical remission	Maintenance	Cheifetz 2021 (GD)[7] Gomez 2021
UST	CD	ELISA	Maintenance	10.1	Endoscopic improvement	Maintenance	Papamichael 2022 (SR)[4] Verstockt 2019
VDZ	UC	ELISA	Week 2	28.9	Clinical response	Week 14	Cheifetz 2021 (GD)[7] Dreesen 2018
VDZ	UC	ELISA	Week 2	20.8	Clinical response	Week 14	Cheifetz 2021 (GD)[7] Dreesen 2018
VDZ	IBD	HMSA	Week 2	23.2	Endoscopic remission	Week 52	Papamichael 2022 (SR)[4] Yarur 2019
VDZ	UC	ELISA	Week 2	28.9	Mucosal healing	Week 14	Cheifetz 2021 (GD)[7] Dreesen 2018
VDZ	UC	ELISA	Week 6	24.4	Clinical remission	Week 14	Cheifetz 2021 (GD)[7] Verstockt 2020
VDZ	IBD	ELISA	Week 6	29.9	Clinical remission	Week 14	Papamichael 2022 (SR)[4] guidi 2019
VDZ	UC	ELISA	Week 6	37.1	Clinical remission	Week 14 and 52	Papamichael 2022 (SR)[4] Osterman 2019
VDZ	CD	ELISA	Week 6	28.7	Clinical remission	Week 24	Cheifetz 2021 (GD)[7] Verstockt 2020
VDZ	UC	ELISA	Week 6	23.5	Endoscopic improvement	Week 14	Cheifetz 2021 (GD)[7] Verstockt 2020
VDZ	CD	ELISA	Week 6	26.2	Endoscopic improvement	Week 24	Cheifetz 2021 (GD)[7] Verstockt 2020
VDZ	IBD	HMSA	Week 6	19·8	Endoscopic remission	Week 52	Papamichael 2022 (SR)[4] Yarur 2019

Table 3 (*continued*)

Drug type	Disease type	TDM method	TDM time point	Threshold (μg/mL)	Clinical outcome	Therapeutic outcome time point	Ref (Study ID)
VDZ	IBD	ELISA	Week 6	22	Combined endoscopic and clinical remission	Week 54	Papamichael 2022 (SR)[4] Hanžel 2019
VDZ	IBD	ELISA	Week 6	18	Mucosal healing	Week 52	Papamichael 2022 (SR)[4] Yacoub 2018
VDZ	UC	ELISA	Week 14	10.1	Clinical remission	Week 14	Cheifetz 2021 (GD)[7] Verstockt 2020
VDZ	UC	ELISA	Week 14	18.4	Clinical remission	Week 14	Papamichael 2022 (SR)[4] Osterman 2019
VDZ	CD	ELISA	Week 14	24.9	Clinical remission	Week 24	Cheifetz 2021 (GD)[7] Verstockt 2020
VDZ	UC	ELISA	Week 14	13.9	Clinical response	Week 14	Cheifetz 2021 (GD)[7] Dreesen 2018
VDZ	UC	ELISA	Week 14	10.1	Endoscopic improvement	Week 14	Cheifetz 2021 (GD)[7] Verstockt 2020
VDZ	CD	ELISA	Week 14	29.2	Endoscopic improvement	Week 24	Cheifetz 2021 (GD)[7] Verstockt 2020
VDZ	UC	ELISA	Week 14	10.4	Mucosal healing	Week 14	Cheifetz 2021 (GD)[7] Dreesen 2018
VDZ	CD	ELISA	Week 22	8	Clinical response	Week 22	Cheifetz 2021 (GD)[7] Dreesen 2018
VDZ	CD	ELISA	Week 22	10	Endoscopic remission	Week 26	Papamichael 2022 (SR)[4] Löwenberg 2019
VDZ	IBD	ELISA	Week 22	8	Combined endoscopic and clinical remission	Week 54	Papamichael 2022 (SR)[4] Hanžel 2019
VDZ	UC	ELISA	Week 22	13.6	Mucosal healing	Week 22	Cheifetz 2021 (GD)[7] Dreesen 2018
VDZ	CD	ELISA	Week 30	11.3	Mucosal healing	Week 30	Cheifetz 2021 (GD)[7] Dreesen 2018
VDZ	CD	ELISA	Maintenance	11.8	Clinical remission	Maintenance	Cheifetz 2021 (GD)[7] Verstockt 2020
VDZ	UC	ELISA	Maintenance	12.7	Clinical remission	Maintenance	Papamichael 2022 (SR)[4] Osterman 2019
VDZ	CD	ELISA	Maintenance	10.1	Endoscopic improvement	Maintenance	Cheifetz 2021 (GD)[7] Verstockt 2020
VDZ	IBD	HMSA	Maintenance	10.7	Endoscopic remission	Maintenance	Cheifetz 2021 (GD)[7] Ungaro 2019
VDZ	IBD	HMSA	Maintenance	11.5	Corticosteroid-free clinical and bio chemical remission	Maintenance	Cheifetz 2021 (GD)[7] Ungaro 2019
VDZ	IBD	HMSA	Maintenance	14.8	Corticosteroids-free deep remission	Maintenance	Cheifetz 2021 (GD)[7] Ungaro 2019

AIFA, Automated immunofluorometric assays; CDAI, Crohn's Disease Activity Index; ECLIA, Electrochemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; HMSA, homogeneous mobility shift assay; PCDAI, Pediatric CDAI; NR, not reported.

agitation)[66]. According to the current literature, several knowledge gaps remain. For example, little known about how anti-drug antibody titres are associated with serum drug concentrations, or what anti-drug antibody titers result in sub-therapeutic serum drug concentration. Moreover, drug-sensitive assays only show anti-drug antibody when serum drug concentrations are low or undetectable; thus, an inverse correlation between both measures is a self-fulfilling prophecy. Another difficulty is the correct interpretation of anti-drug antibody titres across different assays, such as the commonly used ELISA method, the homogeneous mobility shift assay, and electrochemiluminescence immunoassay. Additionally, anti-drug antibodies titres are often expressed in arbitrary units and cannot be compared directly among assays. This limitation is important as physicians might inappropriately discontinue a biologic due to hypothetical high-titre anti-drug antibodies. Thus, studies with drug-tolerant assays should be conducted.

One of the most important unmet needs is a reliable process to identify optimal drug trough concentrations to target, as these depend on the therapeutic outcome, assay, timing, IBD phenotype, and individual patient. In practice and in many trials, TDM has been combined with clinical activity parameters and biomarkers to guide dose adaptation. Consequently, the ideal threshold concentrations for each drug, patient profile, and end point have not yet been identified and have changed substantially with the implementation of end points such as endoscopic, histological and fistula healing. Moreover, suitable or optimal target serum concentrations during active disease differ from those required during maintenance treatment due to a change in inflammatory

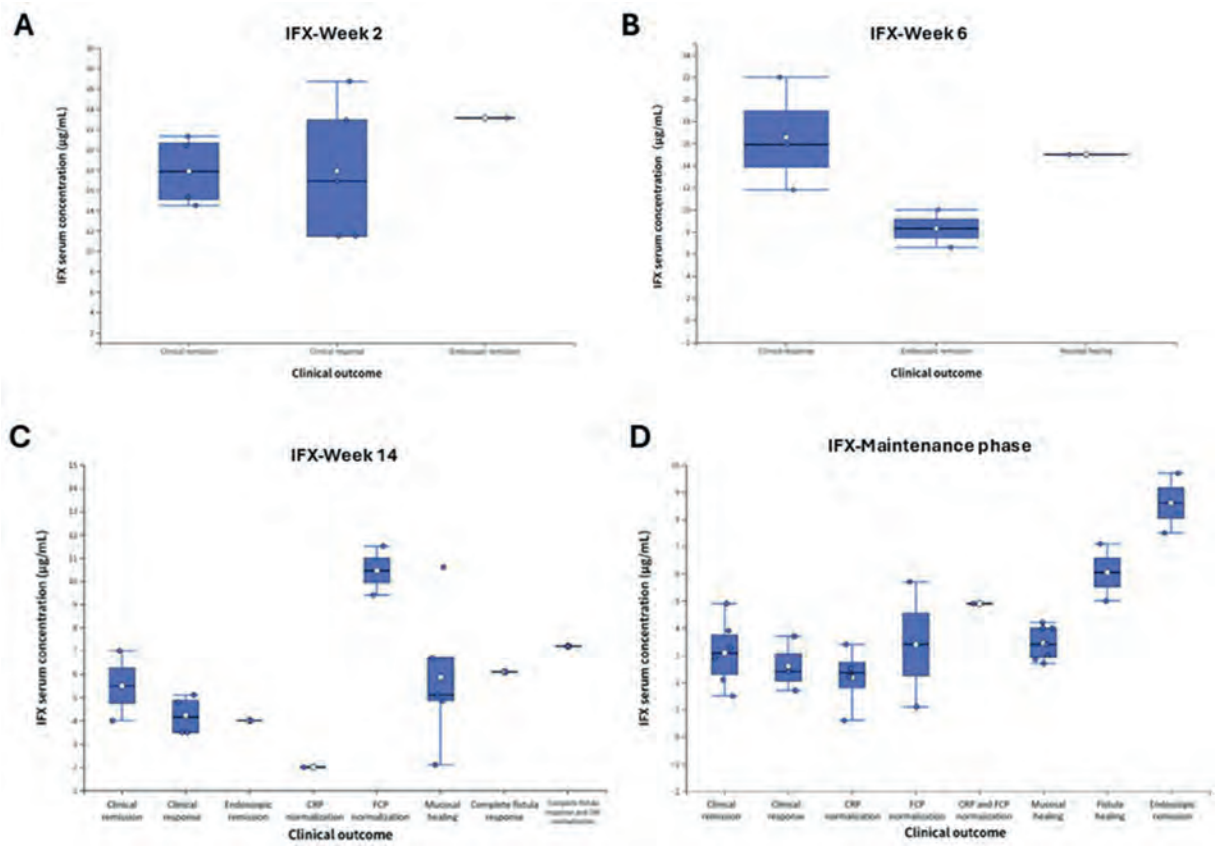

Figure 2 IFX serum concentration thresholds based on different time point and clinical outcomes.

burden. We believe that target concentrations should be individualized on the basis of a patient's disease severity, extent and phenotype, as well as the target end point. Although this guideline is unable to provide definitive recommendations regarding the effective concentrations of each biologic, we have objectively summarized the data in a tabular format and constructed threshold plots for IFX, ADA, and VZD based on various monitoring time points and clinical outcomes, thereby facilitating easier interpretation and comprehension.

The standard strategy for managing secondary loss of response is to first intensify the current treatment and switch to another biologic if this fails. However, this empirical approach is often suboptimal, exposing patients to the risks of allergic reactions and high costs. Therefore, a TDM-based strategy may be advantageous. First, it avoids unnecessary drug concentration in patients who do not need intensification (in the case of high concentrations). Second, it does not put patients who may have developed high-titer antibodies at risk of infusion reactions. Reactive TDM can indeed be helpful for distinguish between immunogenic, pharmacokinetic and pharmacodynamic loss of response. Reactive TDM is emerging as a new standard of care for optimizing biologic therapy in IBD. For proactive TDM, debate is ongoing regarding its role in clinical practice, and further data are needed from well-designed perspective studies and RCTs. For Q2, the

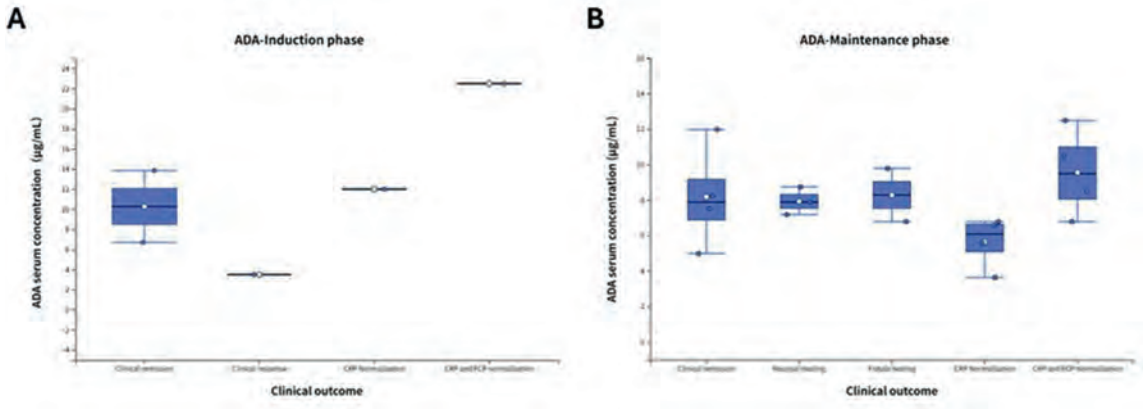

Figure 3 ADA serum concentration thresholds based on different time point and clinical outcomes.

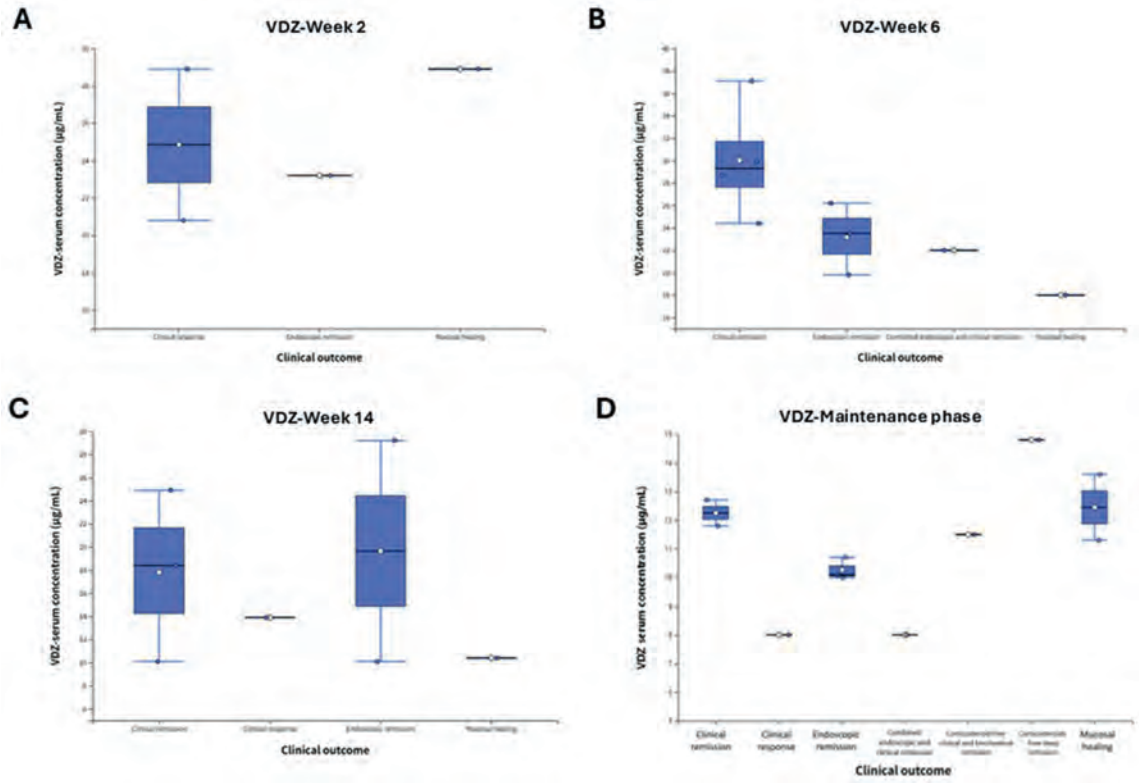

Figure 4 VDZ serum concentration thresholds based on different time point and clinical outcomes.

available evidence is restricted to only two of the six biologic agents (IFX and ADA), with low certainty. These limitations in the evidence base preclude the development of robust recommendations. Recently, a clinical practice guideline provided three conditional recommendations for proactive TDM of anti-TNFα biologics in adult patients with chronic immune-mediated inflammatory diseases[67]. Consistent with our approach, their guideline development utilized the GRADE system, and the strength of the recommendations was rated as weak, similar to ours. According to the results of the latest published retrospective study, for IBD patients receiving VDZ or UST treatment, proactive TDM can increase drug persistence and reduce hospitalization duration compared with reactive TDM[68,69]. Future research should prioritize conducting more RCTs to compare the efficacy of reactive versus proactive TDM strategies for biologics in the treatment of IBD.

Model-informed TDM or model-informed precision dosing (MIPD) has been suggested as a strategy for dose optimization. Individual pharmacokinetic parameters can be estimated (by empirical Bayes estimates) from patient characteristics and drug concentration measurements and subsequently be used to predict the next dose required for that patient to achieve a predefined exposure target. The clinical efficacy of a MIPD dashboard was shown in the PRECISION trial, in which pharmacokinetic dashboard-driven IFX dosing was superior to standard dosing in patients with IBD in terms of clinical remission at 1 year[70]. Two RCTs of MIPD are currently in progress. The OPTIMIZE study (proactive IFX optimization using a pharmacokinetic dashboard versus standard-of-care dosing in patients with CD) is comparing proactive TDM combined with pharmacokinetic dashboard-driven IFX dosing with standard-of-care dosing in patients with moderately to severely active CD[71]. The REMODEL-CD trial aims to investigate a precision dosing strategy starting from induction and targeting dose-specific pharmacokinetic and pharmacodynamic endpoints throughout therapy will significantly improve outcomes compared with a conventional dosing strategy in paediatric CD[72].

According to the current evidence, remaining challenges are hindering the widespread implementation of TDM in clinical practice. These barriers include identification of the optimal drug concentrations to target, timing of TDM initiation, and cut-off values for every anti-drug antibody. Further unmet needs include well-designed high-quality RCTs to provide high-certainty evidence, enabling guideline developers to make strong and actionable recommendations regarding these research questions in future studies.

Given that most of our recommendations are graded as “weak” due to very low to moderate certainty of evidence, it is essential to interpret them within a shared decision-making framework. Weak recommendations emphasized the requirement for individualized clinical judgment. Clinicians should engage patients in discussions that consider their values, preferences, disease severity, treatment history, and access to care. This patient-centered approach ensures that therapeutic decisions are tailored to each individual’s context.

While this guideline distinguishes recommendations between adults and children where appropriate, we identified a lack of high-quality evidence specifically addressing older adults. Given the unique physiological characteristics, comorbidities, and treatment considerations in this population, future research should prioritize randomized controlled trials and subgroup analyses that include elderly individuals. Such efforts will help inform more tailored recommendations and improve the applicability of guidelines across age groups.

Table 4 GRADE pro Summary of Findings Table for clinical Q2.

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Proactive TDM	Reactive TDM	Relative (95% CI)	Absolute (95% CI)		
Clinical remission (30w)												
1[54]	cohort studies	serious[a]	not serious	not serious	serious[b]	none	84/95 (88.4%)	26/38 (68.4%)	RR 1.29 (1.03 to 1.62)	198 more per 1000 (from 21 more to 424 more)	⨁⨁◯◯ Low[a,b]	CRITICAL
Clinical remission (54w)												
1[54]	cohort studies	serious[a]	not serious	not serious	serious[b]	none	78/95 (82.1%)	21/38 (55.3%)	RR 1.49 (1.10 to 2.01)	271 more per 1000 (from 55 more to 558 more)	⨁⨁◯◯ Low[a,b]	CRITICAL
Sustained clinical remission (2y)												
1[52]	RCTs	not serious[c]	not serious	not serious	serious[b]	none	86/115 (74.8%)	60/72 (83.3%)	RR 0.90 (0.77 to 1.04)	83 fewer per 1000 (from 192 fewer to 33 more)	⨁⨁⨁◯ Moderate[b,c]	CRITICAL
Clinical response (30w)												
1[54]	cohort studies	serious[a]	not serious	not serious	serious[b]	none	95/99 (96.0%)	31/43 (72.1%)	RR 1.33 (1.10 to 1.61)	238 more per 1000 (from 72 more to 440 more)	⨁⨁◯◯ Low[a,b]	CRITICAL
Clinical response (54w)												
2[49,54]	cohort studies	serious[a]	not serious	not serious	serious[b]	none	145/181 (80.1%)	53/124 (42.7%)	RR 1.76 (1.13 to 2.75)	325 more per 1000 (from 56 more to 748 more)	⨁⨁◯◯ Low[a,b]	CRITICAL
Endoscopic remission (30w)												
1[54]	cohort studies	not serious[d]	not serious	not serious	Extremely serious[b,e]	none	28/99 (28.3%)	9/43 (20.9%)	RR 1.35 (0.70 to 2.62)	73 more per 1000 (from 63 fewer to 339 more)	⨁◯◯◯ Very low[b,d,e]	CRITICAL
Endoscopic remission (54w)												
1[54]	cohort studies	not serious[d]	not serious	not serious	serious[b]	none	81/99 (81.8%)	22/43 (51.2%)	RR 1.60 (1.18 to 2.17)	307 more per 1000 (from 92 more to 599 more)	⨁⨁⨁◯ Moderate[b,d]	CRITICAL
FCP (μg/g) (72w)												
1[51]	RCTs	not serious[f]	not serious	not serious	Very serious[g]	none	40	40	–	MD 407.84 lower (604.98 lower to 210.7 lower)	⨁⨁◯◯ Low[f,g]	CRITICAL
Sustained corticosteroid-free clinical remission (72w)												
1[51]	RCTs	not serious[f]	not serious	not serious	Extremely serious[h,i]	none	31/38 (81.6%)	19/40 (47.5%)	RR 1.72 (1.20 to 2.46)	342 more per 1000 (from 95 more to 694 more)	⨁◯◯◯ Very low[f,h,i]	CRITICAL

Hospitalization rate (54w, 2.4y)											
2[53,54]	cohort studies	serious[a,j]	not serious	not serious	serious[i]	none	12/229 (5.2%)	39/177 (22.0%)	RR 0.27 (0.14 to 0.49)	161 fewer per 1000 (from 189 fewer to 112 fewer)	⨁⨁◯◯ Low[a,i,j]	CRITICAL
Serious adverse events (72w)											
1[51]	RCTs	not serious[f]	not serious	not serious	Extremely serious[e,h]	none	4/38 (10.5%)	4/40 (10.0%)	RR 1.05 (0.28 to 3.91)	5 more per 1000 (from 72 fewer to 291 more)	⨁◯◯◯ Very low[e,f,h]	CRITICAL
Serious adverse events (2.4y)											
1[53]	cohort studies	serious[a]	not serious	not serious	Very serious[e,k]	none	4/130 (3.1%)	15/134 (11.2%)	RR 0.27 (0.09 to 0.81)	82 fewer per 1000 (from 102 fewer to 21 fewer)	⨁◯◯◯ Very low[a,e,k]	CRITICAL
Adverse events (54w)											
1[54]	cohort studies	serious[a]	not serious	not serious	Extremely serious[b,e]	none	13/99 (13.1%)	7/43 (16.3%)	RR 0.81 (0.35 to 1.88)	31 fewer per 1000 (from 106 fewer to 143 more)	⨁◯◯◯ Very low[a,b,e]	CRITICAL
Surgery rate (1y, 2.4y, 3.1y)											
3[43,53,54]	cohort studies	serious[a]	not serious	not serious	Very serious[e]	none	9/229 (3.9%)	29/177 (16.4%)	RR 0.29 (0.14 to 0.60)	116 fewer per 1000 (from 141 fewer to 66 fewer)	⨁◯◯◯ Very low[a,e]	IMPORTANT

CI: confidence interval; MD: mean difference; RCT: randomized controlled trial; RR: risk ratio.

[a]Downgraded by 1 level due to risk of bias in comparability domain and selection domain.

[b]Downgraded by 1 level due to imprecision: low event rate.

[c]Downgraded by 0.5 levels due to risk of bias in randomization domain.

[d]Downgraded by 0.5 levels due to risk of bias in outcome domain.

[e]Downgraded by 2 levels due to imprecision: the 95% confidence interval for the RR value is too wide: high limit/low limit >3.

[f]Downgraded by 0.5 levels due to risk of bias in blinding domain.

[g]Downgraded by 2 levels due to imprecision: very small sample size.

[h]Downgraded by 1.5 levels due to imprecision: low event rate.

[i]Downgraded by 1 level due to imprecision: the 95% confidence interval for the RR value is too wide: high limit/low limit >2.

[j]Downgraded by 0.5 levels due to risk of bias in comparability domain.

[k]Downgraded by 0.5 levels due to imprecision: low event rate.

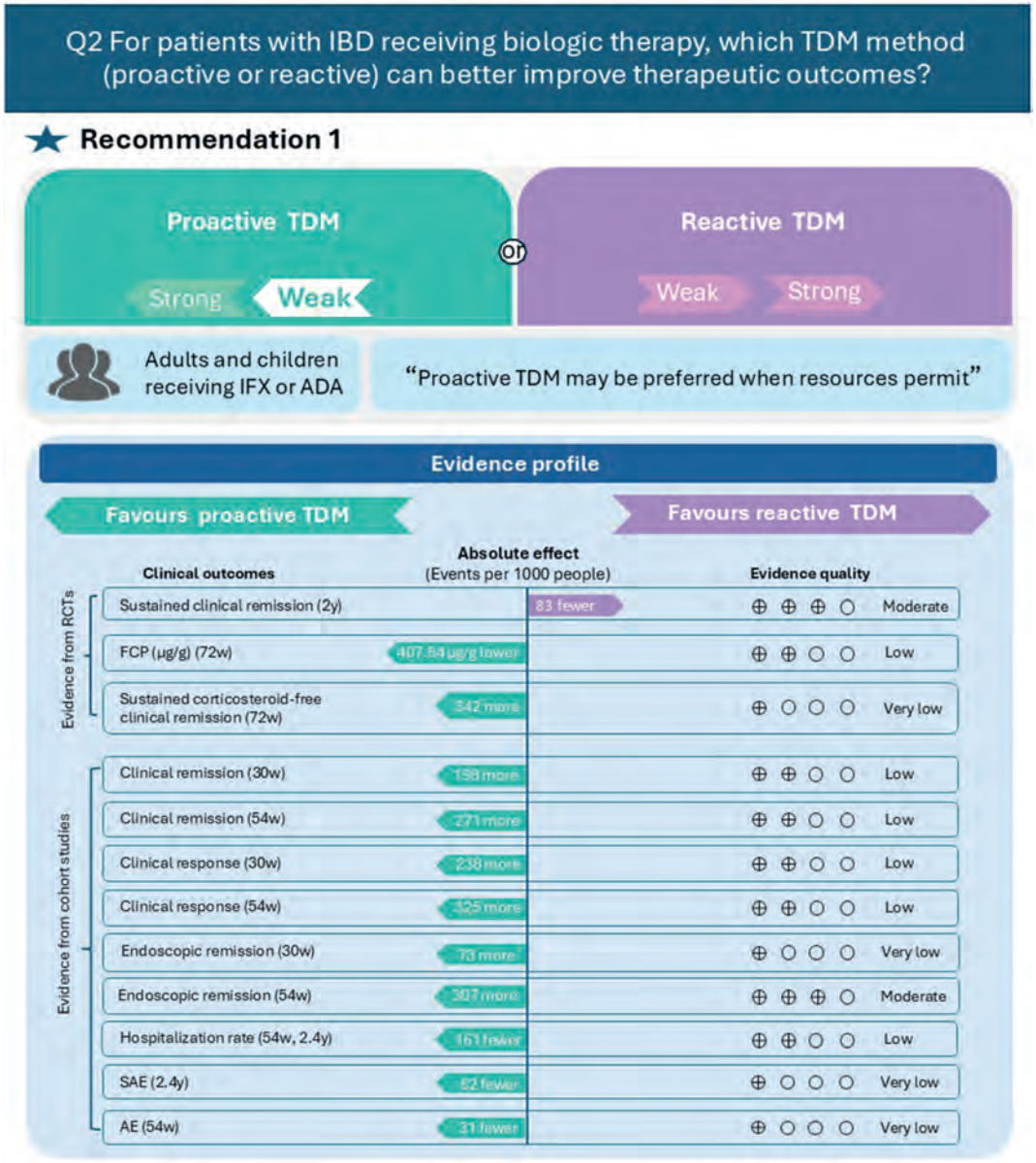

Figure 5 The recommendation and evidence for clinical Q2.

4.1. Guideline limitation

The GDG members and external reviewers are predominantly from China, which may limit the generalizability of the recommendations for end users in other countries, especially in European and American countries. GOL and CER mentioned in the guideline have not yet been approved for use in IBD indications in China. Therefore, experts' clinical experience in TDM for this drug treatment is limited, which may cause certain bias in the relevant recommendations. Other countries and regions can, based on the evidence used as the basis for this guideline and in combination with local actual conditions, formulate the most suitable TDM implementation plans for themselves. Additionally, while the guideline is China-led, it does not extensively incorporate local cohort data or address healthcare system constraints such as the accessibility of TDM services within China. These factors may affect the feasibility and implementation of certain recommendations. However, we have maintained transparency throughout the guideline development process, with details of the evidence provided in the Appendix. This will enable end users to critically assess and adapt the 14 recommendations to their local context, considering factors such as resource availability, clinical infrastructure, and patient population characteristics. This guideline restricts literature to English-language publications, which may have a high risk of omitting key evidence from non-English sources. We will specifically consider the issue of language restrictions in the search strategy during future updates of this guideline.

4.2. Guideline update plan

The GDG is committed to maintaining the relevance and accuracy of the recommendations through a structured update process. Medical literature databases will be searched regularly on an

annual basis, contingent on available resources. A formal guideline update (either full or partial) will be triggered when new evidence emerges that could potentially change any of the 14 current recommendations.

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Appendix A. Supporting information

Supporting information to this article can be found online at https://doi.org/10.1016/j.apsb.2025.11.025.

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