Curr Treat Options Gastro (2019) 17:127–145
DOI 10.1007/s11938-019-00222-9

Inflammatory Bowel Disease (G Lichtenstein, Section Editor)

Advances in Therapeutic Drug Monitoring for Small-Molecule and Biologic Therapies in Inflammatory Bowel Disease

Christopher Ma, MD[1,2]
Robert Battat, MD[2,3]
Vipul Jairath, MD, PhD[2,4,5]
Niels Vande Casteele, PharmD, PhD[2,6,*]

Address
[1]Division of Gastroenterology and Hepatology, University of Calgary, 3280 Hospital Drive NW, Calgary, Alberta, T2N 4Z6, Canada
[2]Robarts Clinical Trials, Inc., #200, 100 Dundas Street, London, Ontario, N6A 5B6, Canada
[3]Division of Gastroenterology, University of California San Diego, 9500 Gilman Drive, #0956, La Jolla, CA, 92093, USA
[4]Department of Medicine, Division of Gastroenterology, Western University, #200, 100 Dundas Street, London, Ontario, N6A 5B6, Canada
[5]Department of Epidemiology and Biostatistics, Western University, #200, 100 Dundas Street, London, Ontario, N6A 5B6, Canada
[*,6]Department of Medicine, University of California San Diego, 9500 Gilman Drive, #0956, La Jolla, CA, 92093, USA
Email: nvandecasteele@ucsd.edu

Published online: 25 January 2019

This article is part of the Topical Collection on *Inflammatory Bowel Disease*

Keywords Biologics · Crohn's disease · Inflammatory bowel disease · Therapeutic drug monitoring · Thiopurines · Ulcerative colitis

Abstract

Purpose of review Therapeutic drug monitoring (TDM) is increasingly utilized as a strategy to optimize inflammatory bowel disease (IBD) therapeutics. As management paradigms have evolved towards treat-to-target strategies, there has been growing interest in expanding the role of TDM to guide drug optimization for achieving objective endpoints. This review summarizes the evidence for using TDM with biologic and oral small-molecule therapies, evaluates the role of reactive versus proactive TDM in treatment algorithms, and identifies potential future applications for TDM.
Recent findings Achieving therapeutic drug concentrations has been associated with

important clinical, endoscopic, and histologic outcomes in IBD. However, the optimal drug concentration varies by therapeutic agent, disease phenotype, inflammatory burden, phase of treatment, and target outcome. Traditionally, TDM has been used reactively to define pharmacokinetic versus mechanistic failures after loss of response to a tumor necrosis factor-α (TNF) antagonist and while observational data suggests a benefit to proactive TDM, this has not been definitively confirmed in prospective randomized controlled trials. The role of TDM in optimizing vedolizumab, ustekinumab, and tofacitinib remains unclear, given differences in pharmacokinetics and immunogenicity compared to TNF antagonists. Measuring drug action at the site of inflamed tissue may provide additional insights into treatment optimization.

Summary The use of TDM offers the possibility of a more personalized treatment approach for patients with IBD. High-quality studies are needed to delineate the role of proactive TDM for maintaining remission, for optimizing induction regimens, and for novel agents.

Introduction

The medical management of inflammatory bowel disease (IBD) has been revolutionized over the past few decades by an expanding therapeutic armamentarium that now features several effective biologic agents and oral small molecules targeting different components of the immune response, including antagonists to cytokines such as tumor necrosis factor-α (TNF) and the p40 common subunit of interleukin (IL)-12 and IL-23, the $\alpha_4\beta_7$ integrin on leukocytes, and the Janus kinase (JAK) intracellular signal transducers [1]. Although these advances have afforded patients with Crohn's disease (CD) and ulcerative colitis (UC) more treatment options than ever before, the role of optimizing drug therapy has also become increasingly important [2]. A substantial proportion of patients will experience either primary non-response or secondary loss of response to biologic therapy [3]. The mechanisms of treatment failure in IBD are complex, including disease-related, drug-related, and patient-related factors [4]. Given this complexity, treatment decisions directed by symptom assessment alone are unlikely to achieve optimal outcomes.

Therapeutic drug monitoring (TDM) has emerged as a promising strategy to maximize treatment response in IBD. Using measurements of serum drug or active metabolite and anti-drug antibody (ADAb) concentrations to guide therapy is based on the premise that (1) there is an exposure-response relationship wherein higher drug concentrations are positively associated with the magnitude of therapeutic efficacy [5]; (2) non-response can be mediated by pharmacokinetic failure, defined by inadequate drug exposure secondary to immune (i.e., ADAb formation) or non-immune causes (i.e., body mass index (BMI), gender, disease phenotype, concomitant immunosuppression, degree of systemic inflammation) leading to accelerated drug clearance [6, 7]; or (3) non-response can be mediated by mechanistic failure due to alternative pathways of inflammation in disease pathogenesis [8].

TDM has been increasingly adopted in clinical practice [9] and recent American Gastroenterological Association (AGA) Institute guidelines suggest the use of reactive TDM in the context of secondary loss of response to thiopurines or biologic therapy [10••]. However, many questions remain unanswered. First, it is unclear if TDM performed during induction or proactive TDM for patients in symptomatic remission improves long-term outcomes. Second, the role of TDM for small-molecule therapies and biologic agents with a non-anti-TNF-driven mechanism of action is unclear. Third, thresholds for therapeutic drug concentrations above which further dose escalation would likely prove futile have not been

fully validated. In this review, we summarize the most current evidence for incorporating TDM in treatment algorithms and propose potential future applications of TDM in clinical practice.

Therapeutic drug monitoring for small molecules

Therapeutic drug monitoring has routinely been used for small molecules in the treatment of IBD, to detect nonadherence to therapy or to guide dose adjustments because of lack of efficacy or adverse events. Azathioprine is a prodrug that is converted into 6-mercaptopurine, which in turn is converted into 6-methylmercaptopurine (through thiopurine methyltransferase [TPMT]), 6-thiouric acid (through xanthine oxidase), or active 6-thioguanine nucleotides [6-TGN] (through hypoxanthine-guanine phosphoribosyl-transferase). Clinical response is highly correlated with levels of 6-TGN [11], whereas patients with low or absent TPMT enzyme activity are at risk for excess production of drug-derived TGN metabolites potentially leading to life-threatening myelosuppression [12]. Current guidelines recommend routine TPMT testing (enzymatic activity or genotype) in patients starting thiopurine therapy to guide thiopurine dosing and in those patients who are treated with thiopurine therapy and who have active disease and/or adverse events thought to be due to thiopurine toxicity, to do reactive thiopurine metabolite monitoring to guide treatment changes [10••].

Tofacitinib, a recently approved oral small-molecule pan-JAK inhibitor, has shown to be effective for induction and maintenance therapy in patients with moderately-to-severely active ulcerative colitis. In the OCTAVE studies, a numerical higher proportion of patients randomized to 10 mg twice daily during maintenance therapy reached the primary endpoint of remission at week 52, compared to those randomized to 5 mg twice daily [13]. This is in line with an earlier phase 2 trial in patients with ulcerative colitis where a dose-dependent effect was observed during induction therapy [14]. These results indicate that some patients may benefit from higher doses of tofacitinib. Interestingly, data on the pharmacokinetics of tofacitinib in patients with psoriasis showed that heavier subjects and those with prior exposure to biologic therapies were predicted to require a higher dose to achieve benefit compared to lighter subjects [15]. A population pharmacokinetic analysis of tofacitinib was performed in patients with moderately-to-severely active UC showing that plasma tofacitinib concentrations increased proportionately with dose and estimated oral clearance, and the average steady-state concentrations were not significantly different between baseline and week 8 [16]. The estimated between-patient variability (% coefficient of variation) was 31.4% for clearance, which is similar to what has been observed for biologics. Clearance of tofacitinib did not significantly correlate with any of the covariates tested including baseline measurements of fecal calprotectin, C-reactive protein (CRP), albumin, and total Mayo Clinic score. Although these results indicate that baseline disease activity is likely not a determinant of tofacitinib clearance, a more extensive

covariate analysis is warranted to determine factors that can explain part of the observed interindividual variability for clearance in patients with UC. An exposure-response analysis was also conducted to evaluate the association between different measures of exposure (dose, average steady-state concentration, and steady-state trough concentration) and important clinical outcomes. It was found that the baseline Mayo Clinic score was an important determinant of efficacy at week 8 and that plasma concentrations in individual patients did not provide additional predictive value for efficacy beyond that provided by tofacitinib dose [16].

Therapeutic drug monitoring for biologics

Advances in drug and anti-drug antibody detection assays

Several assays are commercially available for measuring biologic drug and ADAb concentrations. Drug-sensitive solid-phase enzyme-linked immunosorbent assays (ELISAs) are widely available and less expensive compared to drug-tolerant tests such as the homogeneous mobility shift assay (HMSA) and electrochemiluminescence immunoassay (ECLIA). However, drug-sensitive assays are unable to detect ADAbs in the presence of drug [17]. Van Stappen et al. [18] have recently shown that an acid-based pre-treatment protocol can be used to convert the traditional solid-phase bridging ELISA to a drug-tolerant assay, improving the detection of ADAbs. Fluid-phase drug-tolerant assays have a greater sensitivity for detecting low-level, low-affinity ADAbs compared to ELISA, though neither can determine ADAb functionality. In contrast, a reporter gene assay (RGA) allows differentiation of neutralizing antibodies using an erythrocyte cell-based test [19].

Serum concentrations of TNF antagonists are generally well correlated when comparing across different assays. Marini et al. [20] evaluated infliximab levels measured using four commercial ELISAs and demonstrated that the intraclass correlation coefficient exceeded 0.89 for all tests. Similarly, golimumab levels as measured by two different ELISAs are closely correlated (Spearman's $r = 0.98$, $p < 0.0001$) [21]. When comparing different assay types, Steenholdt et al. [22] showed that ELISA, HMSA, radioimmunoassay, and functional RGA all accurately detected serum infliximab (Pearson's $r = 0.91–0.97$, $p < 0.0001$), but all assays except radioimmunoassay and RGA significantly disagreed on sample IFX concentrations and with a mean difference from 0.64 (0.15–1.12) μg/mL in ELISA and HMSA to up to 3.44 (2.49–4.39) μg/mL in RGA and ELISA. A previous study demonstrated that while correlated ($r = 0.69–0.82$), adalimumab concentrations measured by HMSA were consistently higher compared to ELISA, highlighting potential limitations of cross-assay extrapolation of absolute concentrations [23]. There is emerging data for ustekinumab on the comparison of the KU Leuven ELISAs for measuring ustekinumab and ADAb concentrations with ECLIAs developed at Janssen R&D and used in clinical studies of IBD patients showing a strong agreement [24], although comparative studies with a wider range of assays are urgently needed. For vedolizumab, a comparison between an ELISA and ultra-performance liquid chromatography tandem mass spectrometry system showed a moderate-to-good correlation [25], but comparative studies including assays used commercially in the EU and US are also urgently needed.

Measurements of ADAb concentrations across assays are poorly correlated. ADAb titers are frequently reported in different units (μg/mL, μg/mL equivalents, U/mL, arbitrary units/mL) and quantitative results are variable depending on methodology [12]. Therefore, comparison across assays should be avoided. For TNF antagonists, the presence of ADAbs is associated with accelerated drug clearance and loss of response, although drug-tolerant assays may over-detect very-low-titer, clinically irrelevant ADAbs that have limited effects on drug pharmacokinetics. Over half of ADAbs detected by drug-tolerant HMSA may not have neutralizing potential when assessed by functional RGA [22] and approximately 30% of antibodies to infliximab may be transient [26].

Effective implementation of TDM into clinical practice requires timely and efficient drug level and ADAb quantification. Historically, the slow turnaround time for results has precluded using drug and ADAb concentrations measured at trough for adjusting the next biologic dose, or timely decision to switch treatments if antibodies are present. A point-of-care assay has been developed for infliximab and when compared to two ELISA-based methods, the accuracy of the rapid test was high with intraclass correlation coefficients of 0.889 and 0.939 [27]. Similarly, a lateral flow-based assay with a time to result of 20 min has also shown excellent agreement with ELISA for quantification of infliximab (Pearson $r = 0.95$ during induction and $r = 0.93$ during maintenance) [28]. Adoption of rapid assays may permit the use of TDM to make "on-demand" adjustments to therapy and improve uptake for optimizing induction regimens with TNF antagonists or facilitate decision to switch out of class.

Defining therapeutic trough concentrations for TNF antagonists

The concept of defining a therapeutic target range for serum TNF antagonist trough concentrations stems from several observations. First, there is an exposure-response relationship between serum drug concentrations and clinical efficacy, wherein higher levels of infliximab [29, 30•], adalimumab [31, 32], certolizumab pegol [33], and golimumab [34] are associated with higher rates of clinical remission. Second, low drug concentrations are associated with loss of response to both infliximab and adalimumab and increase the risk of developing ADAbs [35, 36]. Third, the therapeutic drug concentration can be defined based on correlation with efficacy rather than safety outcomes as higher TNF antagonist concentrations have not been shown to correlate with the risk of adverse events [37]. Trough drug concentration thresholds in the literature have been primarily derived from retrospective cross-sectional studies that validate a chosen cutoff, maximize the area under the receiver operating characteristic (ROC) curve, analyze incremental gains with higher drug levels, or evaluate differences in the proportion of patients achieving treatment endpoints by quartile of exposure [12]. The optimal therapeutic trough level is dependent on the clinical context in which TDM is applied and varies by treatment target (clinical versus objective outcomes, response versus remission), disease state (reactive versus proactive testing), and phase of therapy (induction versus maintenance). Suggested trough concentrations according to the AGA guidelines as well as the Australian Inflammatory Bowel Diseases Consensus Working Group are summarized in Table 1.

Treatment targets in both CD and UC have shifted from achieving symptomatic remission towards targeting objective endoscopic, biomarker, and

Table 1. Suggested target trough concentrations for therapeutic drug monitoring of TNF antagonists

Drug	2017 American Gastroenterological Association Guideline Suggestions	2017 Australian Inflammatory Bowel Diseases Consensus Working Group Suggestions
Infliximab	≥ 5 μg/mL	3–8 μg/mL
Adalimumab	≥ 7.5 μg/mL	5–12 μg/mL
Certolizumab	≥ 20 μg/mL	Not stated
Golimumab	Unknown	Not stated

histologic endpoints [38]. Higher drug concentrations may be required to achieve these more robust, objective outcomes [32, 39–41]. For example, Ungar et al. [39] have recently described that a therapeutic window of 6–10 μg/mL for infliximab and 8–12 μg/mL for adalimumab is associated with mucosal healing in 80–90% of patients with IBD. Juncadella et al. [42] found that threshold adalimumab concentrations of 11.8, 12.0, and 12.2 μg/mL in CD and 10.5, 16.2, and 16.2 μg/mL in UC stratified patients with and without biochemical (CRP ≤ 5 mg/L), endoscopic (absence of ulcerations/erosions, Rutgeerts score ≤ i1, or Mayo endoscopic subscore ≤ 1), and histologic remission (absence of active inflammation). Similarly, higher infliximab concentrations are associated with endoscopic (9.7 μg/mL) and histologic (9.8 μg/mL) healing in CD [43]. Infliximab serum concentrations ≥ 5.1 μg/mL at week 14 and ≥ 2.3 μg/mL at week 30 were associated with week 30 Mayo Clinic endoscopic subscore ≤ 1, whereas higher concentrations of ≥ 6.7 μg/mL and ≥ 3.8 μg/mL, respectively, were associated with a subscore of 0 [44]. Cumulatively, these results suggest that better outcomes can be achieved with higher drug trough concentrations, although determination of causality in cross-sectional studies is challenging because better disease control may result in higher trough levels secondary to reduced drug clearance.

Disease phenotype also influences the optimal therapeutic trough level associated with remission. Patients with highly aggressive fistulizing CD may require higher drug levels to achieve response. Yarur et al. [45] evaluated 117 CD patients with perianal fistulizing disease treated with infliximab for a minimum of 24 weeks; those achieving fistula healing had significantly higher median serum drug concentrations compared to those with persistently active disease (15.8 vs. 4.4 μg/mL, $p < 0.0001$). In quartile analysis, the highest rate of fistula healing (86%) was achieved by patients in the top quartile of infliximab exposure (trough level 20.2–50 μg/mL) and levels associated with fistula healing and closure were higher than those previously correlated with luminal mucosal healing.

Less is known about the optimal drug concentration during induction therapy prior to achievement of steady state. There is great interest in using early optimization to distinguish patients who are primary non-responders to TNF antagonists (due to mechanistic failure) from those patients who require more aggressive dosing (due to pharmacokinetic failure) [46]. Patients at risk for accelerated drug clearance could be identified before initiating therapy by using a population pharmacokinetic approach, as a linear relationship was found between baseline infliximab clearance and week 8 Mayo Clinic

endoscopic subscore ($p < 0.001$) [44]. A threshold infliximab clearance of < 0.397 L/day was associated with week 8 Mayo Clinic endoscopic subscore ≤ 1 with a sensitivity, specificity, positive predictive value, and an area under ROC curve of 75%, 48%, 68%, and 0.64 (95% CI, 0.59–0.69) ($p < 0.0001$), respectively. Observational studies demonstrate that higher infliximab and adalimumab serum concentrations as early as 2 to 6 weeks after the first TNF antagonist dose are associated with improved rates of clinical response and remission [30•, 47], mucosal healing [28, 48], and long-term drug retention and surgery-free survival [49]. Infliximab concentration ≥ 15 μg/mL at week 6 is associated with a 4.6-fold increase in likelihood of achieving weeks 10–14 endoscopic mucosal healing [48]. Conversely, infliximab levels below 6.8 μg/mL or early antibodies to infliximab (> 4.3 μg/mL) before the second infusion are associated with primary non-response [50]. During the induction phase, the high rate of drug clearance, early development of ADAbs, and heavy inflammatory burden are important mediators of serum drug levels. Patients with moderate-to-severe UC for example have highly accelerated infliximab drug clearance from demonstrable infliximab fecal losses [51]. Furthermore, high inflammatory burden (defined by CRP > 50 mg/L) predicts those UC patients with lower total infliximab exposure (587 vs. 1361 mg/L/day, $p = 0.001$) [52]. Using an incremental gain analysis, therapeutic windows of 30–36 μg/mL at week 2 and 24–30 μg/mL at week 6 for infliximab have been proposed to maximize likelihood of early mucosal healing although these thresholds require prospective validation [46].

In maintenance treatment with TNF antagonists, based on a meta-analysis, the AGA guidelines suggest trough concentrations of infliximab ≥ 5 μg/mL, adalimumab ≥ 7.5 μg/mL, and certolizumab pegol ≥ 20 μg/mL to be associated with clinical remission [10]. Insufficient evidence was available to establish a target trough for golimumab. These cutoffs were chosen based on the proportion of patients not in remission for incremental increases in drug trough concentration: however, 8% of patients with an infliximab trough concentration ≥ 5 μg/mL, 10% of patients with an adalimumab trough concentration ≥ 7.5 μg/mL, and 26% of patients with a certolizumab pegol trough concentration ≥ 20 μg/mL will not be in clinical remission, and a subset of these patients may still respond by targeting higher concentrations.

Treatment algorithms incorporating reactive and/or proactive TDM

Prior to the adoption of TDM, patients experiencing secondary loss of response to TNF antagonists were typically managed by empiric dose escalation. Although this approach exhausts the therapeutic potential of each treatment and is sensible when limited options are available, it may delay initiation of effective therapy and increase potentially unnecessary drug exposure among patients with immune-mediated pharmacokinetic treatment failure or mechanistic treatment failure [53]. The use of reactive TDM can direct more personalized and efficient treatment decisions by distinguishing patients with pharmacokinetic failure due to inadequate drug levels from those whose disease is not driven by TNF-mediated pathways (Fig. 1). The use of reactive TDM is more cost-effective compared to empiric dose escalation [54, 55] and allows earlier implementation of effective treatment decisions. For example, in a retrospective cohort study of 247 IBD patients developing 330 loss-of-response events to

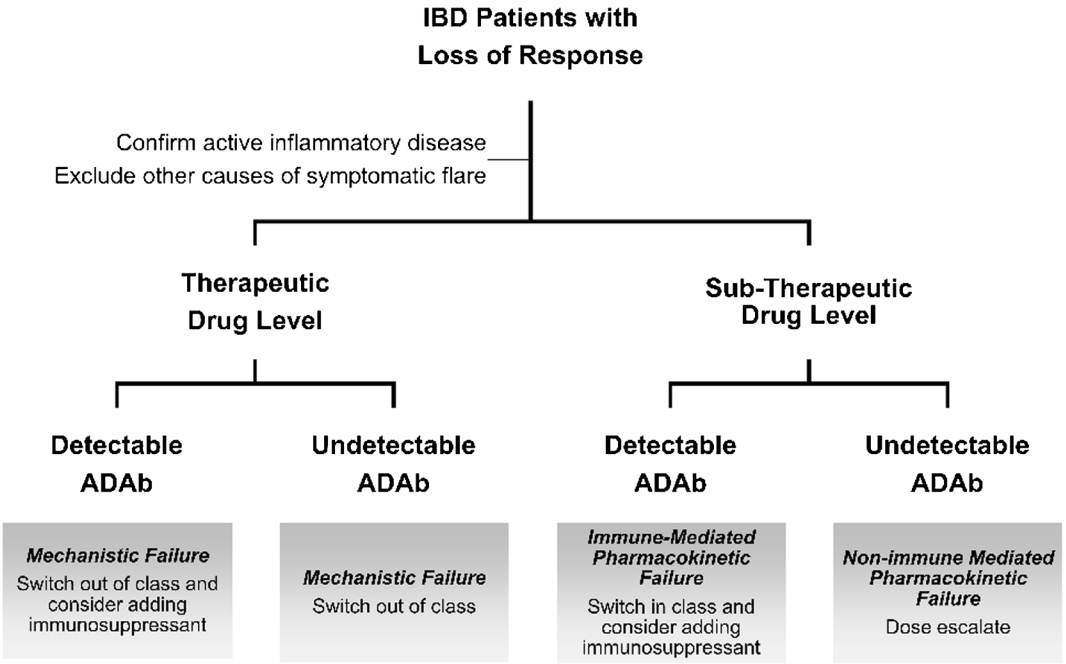

Fig. 1. Algorithm for use of reactive therapeutic drug monitoring in IBD patients with secondary loss of response to TNF antagonists.

infliximab or adalimumab, Yanai et al. [56] identified that the presence of either therapeutic trough levels (adalimumab > 4.5 μg/mL, infliximab >3.8 μg/mL) or high-titer ADAbs (anti-adalimumab > 4 μg/mL equivalent, anti-infliximab > 9 μg/mL equivalent) predicted failure to respond to dose escalation with 90% specificity and had longer duration of response when switched to a different class of treatment.

While reactive TDM has an established role for managing secondary loss of response, integrating TDM into clinical practice proactively for patients in stable remission remains controversial. In a multicenter retrospective study of 264 consecutive IBD patients receiving infliximab maintenance therapy, Papamichael et al. [57] compared proactive versus reactive drug monitoring based on measurements of first infliximab concentration and ADAb. In multivariable Cox regression, proactive drug monitoring was associated with a reduced risk for treatment failure (hazard ratio HR 0.16 [95% CI, 0.09–0.27]), IBD-related surgery (HR 0.30 [95% CI, 0.11–0.80]), IBD-related hospitalization (HR 0.16 [95% CI, 0.07–0.33]), and serious infusion reactions (HR 0.17 [95% CI, 0.04–0.78]). However, this retrospective comparison is limited by potential differences in patient characteristics wherein patients undergoing proactive testing were asymptomatic compared to those patients potentially experiencing a symptomatic disease flare in the reactive group.

A second purported benefit to proactive drug optimization is the potential to circumvent the need for concomitant immunosuppression with azathioprine or methotrexate. Combination therapy with infliximab and azathioprine is superior to infliximab monotherapy in CD [58] and UC [59], mediated by a reduction in ADAb formation and higher trough infliximab levels. However,

concomitant immunosuppression is associated with an increased risk of adverse events [60]. In a comparison of 16 patients managed with week 10 proactive infliximab TDM and 35 patients on combination infliximab and immunosuppressant therapy, Lega et al. [61] demonstrated that proactive "optimized monotherapy" achieved comparable endpoints to combination therapy with respect to median infliximab trough concentration (9.1 vs. 7.7 μg/mL, $p = 0.24$), probability of anti-infliximab antibody-free survival ($p = 0.27$), and frequency of infliximab discontinuation (0% vs. 3%, $p = 1.0$). Correspondingly, post hoc analysis of the SONIC (the Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease) trial showed comparable outcomes are achieved regardless of concomitant azathioprine when patients are stratified by infliximab trough quartiles [62].

Although observational evidence supports the use of proactive TDM, two randomized controlled trials have been inconclusive. The TAXIT study (Trough Level Adapted Infliximab Treatment study) was a 1-year trial that evaluated 178 CD patients and 85 UC patients with stable response to infliximab maintenance therapy who were then randomized to receive infliximab dosing either based on clinical features or based on proactive TDM [63••]. Importantly, all patients initially underwent an optimization phase where infliximab dosing was escalated or reduced to reach a trough level range of 3–7 μg/mL prior to randomization. At 12 months, the proportion of patients with combined clinical and biochemical remission was similar between the clinically based and proactive TDM-based dosing groups (66%vs. 69%, $p = 0.686$). At the end of the study, similar rates of mucosal healing were observed in patients randomized to clinically based compared to proactive TDM-based dosing (91% vs. 90%) [64]. During long-term follow-up after TAXIT (median 41 months), there were no differences in IBD-related hospitalization (13% vs. 15%), abdominal surgery (6% vs. 7%), or corticosteroid use (13% vs. 8%) in those patients previously randomized to clinically based compared to proactive TDM-based dosing, respectively, although proactive TDM was continued approximately once per year in all patients. Interestingly, proactive TDM-based dose optimization in all patients before randomization, to achieve trough concentrations in the 3–7-μg/mL range, was associated with significant reductions in CRP and an increase in the proportion of CD patients in remission—potentially negating some of the benefits associated with TDM—and a 28% reduction in drug costs among patients with a trough level > 7 μg/mL who were able to undergo dose reduction. Although the trial did not meet its primary endpoint, important differences in secondary outcomes were achieved between the proactive TDM-based and clinically based dosing groups including a lower proportion of patients who required rescue therapy due to loss of response (7% vs. 17%, $p = 0.018$) and a higher proportion of patients who stayed within the target trough level range (74% vs. 57%, $p = 0.001$).

Treatment with infliximab incorporating proactive TDM was also evaluated in the TAILORIX (A Randomized Controlled Trial Investigating Tailored Treatment With Infliximab for Active Luminal Crohn's Disease) randomized controlled trial [65••] that evaluated a treatment algorithm based on clinical symptoms, biomarkers, and infliximab TDM compared to symptom-based management alone. In the two dose intensification strategy (DIS) groups, dose escalation was prompted by the following criteria: (1) Crohn's Disease Activity Index (CDAI) > 220 with a CRP > 5 mg/L and/or

fecal calprotectin (FC) > 250 μg/g; (2) CDAI 150–220 for two consecutive weeks with an elevated CRP and/or FC; (3) infliximab serum concentration at trough < 1 μg/mL; (4) infliximab trough level 1–3 μg/mL; and (5) infliximab trough level 3–10 μg/mL with a drop by > 50% compared with the week 14 infliximab concentration. The control group received infliximab dose escalation based on clinical symptoms (CDAI > 220 or a CDAI 150–220 in the two prior visits) alone. A stringent primary endpoint of corticosteroid-free clinical remission without ulcers, need for surgery, or the development of fistulas between weeks 22 to 54 was used.

The primary endpoint was achieved in 33% (15/45), 27% (10/37), and 40% (16/40) of patients in the DIS1, DIS2, and the control groups, respectively (p = 0.50). Furthermore, no significant differences were observed in the proportion of patients achieving secondary endpoints of absence of ulcers, endoscopic remission, or endoscopic improvement at both weeks 12 and 54. Although outcomes did not differ between the DIS and control groups, dose escalation algorithms in TAILORIX were complex and incorporated symptoms, biomarkers, and TDM: separating the independent effects of each of these components is not possible. Second, only 47% (21/45) and 46% (17/37) of patients in the DIS1 and DIS2 groups sustained therapeutic infliximab trough concentrations > 3 mg/mL between weeks 12 and 54, respectively. Also, only 5 (25%) and 7 (30%) patients in DIS1 and DIS2 groups, respectively, underwent dose escalation because of TDM.

The AGA guidelines conditionally recommend the use of reactive TDM to guide therapeutic decisions in patients with active IBD treated with TNF antagonists, recognizing that the quality of evidence is very low [10]. However, no recommendation is made regarding the use of routine proactive TDM for patients with quiescent disease. Rather, this area is characterized as a knowledge gap. Additional concerns regarding proactive TDM were also raised, including (1) the potential for inappropriate treatment changes in the context of low-titer ADAbs that are of uncertain clinical significance, (2) the unclear frequency with which TDM should be repeated, and (3) the cost associated with both testing and downstream treatment changes.

These guidelines have come under scrutiny [66] and are contrasted with recent expert consensus statements that support using TDM reactively in secondary loss of response, in patients with primary induction non-response, and periodically in patients in clinical remission, with the caveat that proactive testing should only be performed if the results are likely to impact management [67••]. Furthermore, it is suggested that patients with supra-therapeutic drug trough levels be considered for dose reduction whereas high-risk patients with sub-therapeutic trough levels and undetectable or low ADAbs should have immunomodulators added/optimized and/or dose escalation. Eighty-six percent of panelists agreed that patients in clinical remission with high-risk features, undetectable trough drug levels, and persistently high titers of ADAbs be considered for switching within or out-of-class.

Differences in the AGA guidelines and expert consensus recommendations may in part reflect differences in methodology. The AGA guidelines were developed using standards set by the Institute of Medicine and the Grading of Recommendations Assessment, Development and Evaluation framework, whereas Mitrev et al. developed the consensus statements using a modified 3-

iteriation Delphi to achieve agreement. Nevertheless, both groups reiterated the need for high-quality, controlled, prospective long-term studies to better clarify the role TDM in clinical practice.

Using TDM for non-TNF-antagonist biologics

The role of measuring drug and ADAb levels for novel biologic agents such as vedolizumab, an $\alpha_4\beta_7$ integrin antagonist, and ustekinumab, a monoclonal antibody targeting the common p40 subunit of IL-12/-23, is less clear. Interindividual variability in drug clearance for both treatments has been demonstrated, with differences in serum albumin, body weight, and inflammatory burden affecting drug pharmacokinetics [68, 69]. Persistent antibody presence also increases drug clearance although, interestingly, immunogenicity to ustekinumab and vedolizumab appears attenuated compared to therapy with TNF antagonists. In CD, the incidence of ustekinumab antibody formation after 1 year of treatment in the IM-UNITI phase III trial program was only 2.3% using a purportedly drug-tolerant assay [70]. Approximately 12% of patients randomized to placebo in the maintenance arm of the GEMINI trials developed ADAb to vedolizumab after exposure in induction, and 10% developed antibodies in the active treatment arm at week 66 (14 weeks after the last dose of vedolizumab) [68].

An exposure-response relationship for vedolizumab has been demonstrated in both UC and CD. In the GEMINI-1 trial, UC patients with vedolizumab trough levels in the lowest quartile (< 17 μg/mL) had clinical remission rates of only 6% compared to 37% of patients in the highest quartile (> 35.7 μg/mL) [71]. A similar exposure-response relationship was demonstrated in GEMINI-2 among CD patients although this was less robust (difference in clinical remission rates of 22% vs. 6% comparing the highest quartile > 33.7 μg/mL and the lowest quartile < 16 μg/mL) [72]. In maintenance treatment, a dose-response relationship was evident in both CD and UC patients on every 8-week dosing; however, this response was less evident in patients on every 4-week dosing where the lowest trough concentration quartile overlapped with the highest quartile of the 8-week group in terms of serum concentrations.

Interpreting the exposure-response relationship for vedolizumab is further confounded by the fact that there is complete saturation of the α4β7 receptors on peripheral lymphocytes even at every 8-week maintenance dosing and at drug concentrations as low as 1 μg/mL [73]. This suggests that higher serum concentrations would not be associated with improved efficacy but are contrasted by the clinical observation that a substantial proportion of patients recapture response with vedolizumab dose escalation [74]. Therefore, receptor saturation may not be the only mechanism mediating vedolizumab efficacy. Furthermore, given that vedolizumab purportedly affects gut-specific leukocyte trafficking, it is unclear if serum levels are an accurate approximation of drug efficacy.

Exposure-response relationships have also been described with ustekinumab [75]. Clinical remission at week 8 after induction in the UNITI-1 and UNITI-2 trial programs was positively associated with serum drug concentrations [70]. Ustekinumab concentrations of 0.9–1.2 μg/mL in quartile

analysis were associated with higher rates of clinical remission and the optimal cutoff determined in ROC analysis was a trough concentration of 1 μg/mL (area under the curve 0.64, $p < 0.003$). Higher trough concentrations were associated with increased rates of CRP normalization (52% vs. 25%, $p < 0.0001$ for trough concentration of above 1.1 μg/mL) and endoscopic response (40% vs. 8%, $p < 0.003$ for trough concentration of above 0.5 μg/mL) [75]. A higher serum trough concentration of > 4.5 μg/mL measured using a drug-tolerant HMSA after 26 weeks of treatment was reported to be associated with improved biomarker and endoscopic response in a real-world cohort, although this study did not incorporate intravenous induction and timing of assessment was not standardized [76].

In summary, although exposure-response relationships have been demonstrated with both ustekinumab and vedolizumab, the utility of TDM for optimizing treatment with these agents is still to be delineated, particularly given important differences in mode of action, immunogenicity, and drug pharmacokinetics of these novel agents compared to TNF antagonists.

Measuring drug at the site of action

Little is known about colonic mucosal concentrations of infliximab and TNF in IBD patients and whether this correlates with either (1) serum or stool drug concentrations or (2) clinically important outcomes. The recent proof of concept ATLAS (Anti-TNF Tissue Level and Antibodies in Serum) study demonstrated that serum TNF antagonist concentrations correlated with tissue concentrations in uninflamed, but not inflamed tissue [77]. Furthermore, TNF antagonist concentrations in tissue correlated with the degree of endoscopic inflammation, except for tissue with severe inflammation. Patients with active mucosal disease had high rates of serum-to-tissue drug concentration mismatch. This study demonstrated that in patients with active disease, serum concentrations may not accurately guide clinical management of IBD.

A recent study by Yoshihara et al. [78] confirmed the correlation of serum TNF antagonist with tissue TNF concentration in non-inflamed tissue. A total of 25 CD patients were treated with infliximab ($n = 15$) or adalimumab ($n = 10$). During maintenance therapy, tissue concentrations were measured 2 weeks after drug administration. Inflamed tissue had higher TNF antagonist concentrations and lower TNF concentrations than uninflamed tissue. No correlation between tissue concentrations and prospectively scored clinical or endoscopic outcomes was found. Drug concentrations only correlated between uninflamed tissue and serum. Using a non-conventional outcome (therapeutic intervention requirement after 6 months), the optimal cutoff concentration in non-inflamed tissue was 1.3 μg/g. In patients with a TNF antagonist concentration > 1.3 μg/g in non-inflamed tissue, the time to therapeutic intervention was longer compared to that in patients with lower concentrations.

However, further work on this subject is needed for several reasons. The ATLAS study did not provide quantitative data on TNF antagonist concentrations. Only 12 patients were on infliximab, with an unknown proportion of CD and UC within this group. Only 6 patients with UC were included in

the study, of which an unspecified portion received infliximab or adalimumab. Furthermore, while 43 uninflamed biopsies were analyzed, only 17 inflamed biopsies were analyzed and an unknown proportion of these were from either infliximab- or adalimumab-treated patients. Lastly, neither objective endoscopic nor histologic scores were assessed. In the study by Yoshihara et al., tissue concentrations of individual therapies were not provided, and only one patient receiving adalimumab had measurable concentrations in non-inflamed tissue.

Drug development of locally acting agents

A better understanding of the disposition of systemically absorbed drugs into the mucosal tissue and the correlation with clinically important outcomes will be key for developing compounds with proven mechanism of action that are being designed to act locally in the gut and limit systemic absorption. Sandborn et al. [79] recently presented the results of a Phase 2b randomized, double-blind, placebo-controlled induction study in patients with moderately-to-severely active UC who were treated with PTG-100, an orally administered gut-restricted peptide $\alpha_4\beta_7$ antagonist. PTG-100 showed a dose-dependent increase in clinical remission, endoscopic response, and histologic remission with maximal efficacy at the 900-mg dose. These efficacy results require confirmation in subsequent trials, including systemic and local exposure-response analyses to understand inter- and intra-individual variability in pharmacokinetics and pharmacodynamics. Panes et al. recently presented the results of a Phase 1b randomized, double-blind, placebo-controlled study in patients with moderately-to-severely active UC who were treated with TD-1473, an orally administered and intestinally restricted pan-JAK inhibitor [80]. TD-1473 was generally well tolerated over 4 weeks with evidence of signals for clinical and biomarker activity and colonic tissue concentrations of TD-1473 that were higher than plasma concentrations and in the range needed for JAK inhibition. Based on these early results, the local delivery of compounds (both peptides and small molecules) with proven systemic mechanism of action may prove to be a promising strategy leading to orally administered, effective, yet safer drugs because of limited systemic exposure. Understanding drug disposition after systemic or oral administration will be key for efficient dose finding and early drug development.

Conclusions

The adoption of TDM for patients with IBD undergoing treatment with thiopurines or TNF antagonists has offered a more personalized approach to optimizing therapy. The benefits of reactive TDM for defining mechanisms of loss of response or adverse events have been well established. Despite these advances, our review also highlights areas that require further investigation. First, although many clinicians employ proactive TDM for TNF antagonists, the evidence to support this practice is primarily observational. Second, the role of TDM for patients treated with biologics with

alternative mechanisms of action other than TNF blockade is unclear, as these agents have different immunogenicity and pharmacokinetic profiles. Third, recent drug development of effective locally acting therapies may change our approach from measuring systemic drug concentrations to measuring drug at site of action. The development of these concepts will mark another important step forward in personalized IBD care.

Authorship contributions

CM, RB, VJ, and, NVC contributed to the study design, manuscript drafting, and manuscript editing. All authors approve the final version of the manuscript.

Funding Support

Dr. Christopher Ma is supported by a Clinician Fellowship from the Canadian Institutes of Health Research and the Canadian Association of Gastroenterology. Dr. Niels Vande Casteele is supported by a Research Scholar Award from the American Gastroenterological Association.

Compliance with Ethical Standards

Conflict of Interest

Christopher Ma and Robert Battat have no conflicts of interest to declare.

Vipul Jairath has received consulting fees from AbbVie, Eli Lilly, GlaxoSmithKline, Arena pharmaceuticals, Genetech, Pendopharm, Sandoz, Merck, Takeda, Janssen, Robarts Clinical Trials, Topivert, and Celltrion, and speaker's fees from Takeda, Janssen, Shire, Ferring, Abbvie, and Pfizer.

Niels Vande Casteele has received grant/research support from R-Biopharm and Takeda, and consulting fees from Pfizer, Progenity, Prometheus, and Takeda.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Publisher's Note

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Duijvestein M, Battat R, Vande Casteele N, D'Haens GR, Sandborn WJ, Khanna R, et al. Novel therapies and treatment strategies for patients with inflammatory bowel disease. Curr Treat Options Gastroenterol.

2018;16(1):129–46. https://doi.org/10.1007/s11938-018-0175-1.
2. Van Assche G. Optimizing biologic therapy for treatment of inflammatory bowel disease. Gastroenterol Hepatol (N Y). 2013;9(7):462–4.
3. Roda G, Jharap B, Neeraj N, Colombel JF. Loss of response to anti-TNFs: definition, epidemiology, and management. Clin Transl Gastroenterol. 2016;7:e135. https://doi.org/10.1038/ctg.2015.63.
4. Yanai H, Hanauer SB. Assessing response and loss of response to biological therapies in IBD. Am J Gastroenterol. 2011;106(4):685–98. https://doi.org/10.1038/ajg.2011.103.
5. Vande Casteele N, Khanna R, Levesque BG, Stitt L, Zou GY, Singh S, et al. The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease. Gut. 2015;64(10):1539–45. https://doi.org/10.1136/gutjnl-2014-307883.
6. Wang W, Wang EQ, Balthasar JP. Monoclonal antibody pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther. 2008;84(5):548–58. https://doi.org/10.1038/clpt.2008.170.
7. Ordas I, Feagan BG, Sandborn WJ. Therapeutic drug monitoring of tumor necrosis factor antagonists in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2012;10(10):1079–87.
quiz e85–6. https://doi.org/10.1016/j.cgh.2012.06.032.
8. Yarur AJ, Rubin DT. Therapeutic drug monitoring of anti-tumor necrosis factor agents in patients with inflammatory bowel diseases. Inflamm Bowel Dis. 2015;21(7):1709–18. https://doi.org/10.1097/MIB.0000000000000380.
9. Grossberg LB, Papamichael K, Feuerstein JD, Siegel CA, Ullman TA, Cheifetz AS. A survey study of gastroenterologists' attitudes and barriers toward therapeutic drug monitoring of anti-TNF therapy in inflammatory bowel disease. Inflamm Bowel Dis. 2017;24(1):191–7. https://doi.org/10.1093/ibd/izx023.
10.•• Feuerstein JD, Nguyen GC, Kupfer SS, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute Clinical Guidelines C. American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. Gastroenterology. 2017;153(3):827–34. https://doi.org/10.1053/j.gastro.2017.07.032
Clinical guidelines from the American Gastroenterological Association for use of therapeutic drug monitoring.
11. Dubinsky MC, Lamothe S, Yang HY, Targan SR, Sinnett D, Theoret Y, et al. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. Gastroenterology. 2000;118(4):705–13.
12. Vande Casteele N, Herfarth H, Katz J, Falck-Ytter Y, Singh S. American Gastroenterological Association Institute Technical Review on the Role of Therapeutic Drug Monitoring in the Management of Inflammatory Bowel Diseases. Gastroenterology. 2017;153(3):835–5.
e6. https://doi.org/10.1053/j.gastro.2017.07.031.
13. Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2017;376(18):1723–36. https://doi.org/10.1056/NEJMoa1606910.
14. Sandborn WJ, Ghosh S, Panes J, Vranic I, Su C, Rousell S, et al. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. N Engl J Med. 2012;367(7):616–24. https://doi.org/10.1056/NEJMoa1112168.
15. Hutmacher MM, Papp K, Krishnaswami S, Ito K, Tan H, Wolk R, et al. Evaluating dosage optimality for tofacitinib, an oral Janus kinase inhibitor, in plaque psoriasis, and the influence of body weight. CPT Pharmacometrics Syst Pharmacol. 2017;6(5):322–30. https://doi.org/10.1002/psp4.12182.
16. Mukherjee A, Hazra A, Smith MK, Martin SW, Mould DR, Su C, et al. Exposure-response characterization of tofacitinib efficacy in moderate to severe ulcerative colitis: results from a dose-ranging phase 2 trial. Br J Clin Pharmacol. 2018;84(6):1136–45. https://doi.org/10.1111/bcp.13523.
17. Vaughn BP, Sandborn WJ, Cheifetz AS. Biologic concentration testing in inflammatory bowel disease. Inflamm Bowel Dis. 2015;21(6):1435–42. https://doi.org/10.1097/MIB.0000000000000312.
18. Van Stappen T, Brouwers E, Vermeire S, Gils A. Validation of a sample pretreatment protocol to convert a drug-sensitive into a drug-tolerant anti-infliximab antibody immunoassay. Drug Test Anal. 2017;9(2):243–7. https://doi.org/10.1002/dta.1968.
19. Pavlov IY, Carper J, Lazar-Molnar E, Delgado JC. Clinical laboratory application of a reporter-gene assay for measurement of functional activity and neutralizing antibody response to infliximab. Clin Chim Acta. 2016;453:147–53. https://doi.org/10.1016/j.cca.2015.12.015.
20. Marini JC, Sendecki J, Cornillie F, Popp JW Jr, Black S, Blank M, et al. Comparisons of serum infliximab and antibodies-to-infliximab tests used in inflammatory bowel disease clinical trials of Remicade(R). AAPS J. 2017;19(1):161–71. https://doi.org/10.1208/s12248-016-9981-3.
21. Martin S, del Agua AR, Torres N, Pascual-Salcedo D, Plasencia C, Ruiz-Arguello B, et al. Comparison study of two commercially available methods for the determination of golimumab and anti-golimumab antibody levels in patients with rheumatic diseases. Clin Chem Lab Med. 2015;53(11):e297–9. https://doi.org/10.1515/cclm-2015-0266.
22. Steenholdt C, Bendtzen K, Brynskov J, Thomsen OO, Ainsworth MA. 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(7):1055–64. https://doi.org/10.1038/ajg.2014.106.
23. Bodini G, Giannini EG, Furnari M, Marabotto E, Baldissarro I, Del Nero L, et al. Comparison of two different techniques to assess adalimumab trough

levels in patients with Crohn's disease. J Gastrointestin Liver Dis. 2015;24(4):451–6. https://doi.org/10.15403/jgld.2014.1121.244.adb.

24. Marini JC, Gils A, Shankar G, Peeters M, Brouwers E, van Iperen P, et al. P649 Comparison of the KU Leuven ustekinumab concentration assay and the antibodies-to-ustekinumab assay with assays developed at Janssen R & D and used in clinical studies of IBD patients. J Crohn's Colitis. 2018;12(supplement_1):S439. https://doi.org/10.1093/ecco-jcc/jjx180.776.
25. Berger C, Christ C, Armbruster FP, Schulze H, Dignass A, Stein J, et al. P717 Comparison of two different techniques to assess vedolizumab trough levels in adult patients with IBD. J Crohn's Colitis. 2018;12(supplement_1):S474. https://doi.org/10.1093/ecco-jcc/jjx180.844.
26. Vande Casteele N, Gils A, Singh S, Ohrmund L, Hauenstein S, Rutgeerts P, et al. Antibody response to infliximab and its impact on pharmacokinetics can be transient. Am J Gastroenterol. 2013;108(6):962–71. https://doi.org/10.1038/ajg.2013.12.
27. Afonso J, Lopes S, Goncalves R, Caldeira P, Lago P, Tavares de Sousa H, et al. Proactive therapeutic drug monitoring of infliximab: a comparative study of a new point-of-care quantitative test with two established ELISA assays. Aliment Pharmacol Ther. 2016;44(7):684–92. https://doi.org/10.1111/apt.13757.
28. Van Stappen T, Bollen L, Vande Casteele N, Papamichael K, Van Assche G, Ferrante M, et al. Rapid test for infliximab drug concentration allows immediate dose adaptation. Clin Transl Gastroenterol. 2016;7(12):e206. https://doi.org/10.1038/ctg.2016.62.
29. Cornillie F, Hanauer SB, Diamond RH, Wang J, Tang KL, Xu Z, et al. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. Gut. 2014;63(11):1721–7. https://doi.org/10.1136/gutjnl-2012-304094.
30.• Adedokun OJ, Sandborn WJ, Feagan BG, Rutgeerts P, Xu Z, Marano CW, et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. Gastroenterology. 2014;147(6):1296–307 e5. https://doi.org/10.1053/j.gastro.2014.08.035

This analysis of data from the ACT-1 and ACT-2 trials demonstrated that serum infliximab concentrations are associated with treatment efficacy.

31. Mazor Y, Almog R, Kopylov U, Ben Hur D, Blatt A, Dahan A, et al. Adalimumab drug and antibody levels as predictors of clinical and laboratory response in patients with Crohn's disease. Aliment Pharmacol Ther. 2014;40(6):620–8. https://doi.org/10.1111/apt.12869.
32. Zittan E, Kabakchiev B, Milgrom R, Nguyen GC, Croitoru K, Steinhart AH, et al. Higher adalimumab drug levels are associated with mucosal healing in patients with Crohn's disease. J Crohns Colitis. 2016;10(5):510–5. https://doi.org/10.1093/ecco-jcc/jjw014.
33. Vande Casteele N, Feagan BG, Vermeire S, Yassine M, Coarse J, Kosutic G, et al. Exposure-response relationship of certolizumab pegol induction and maintenance therapy in patients with Crohn's disease. Aliment Pharmacol Ther. 2018;47(2):229–37. https://doi.org/10.1111/apt.14421.
34. Adedokun OJ, Xu Z, Marano CW, Strauss R, Zhang H, Johanns J, et al. Pharmacokinetics and exposure-response relationship of golimumab in patients with moderately-to-severely active ulcerative colitis: results from phase 2/3 PURSUIT induction and maintenance studies. J Crohns Colitis. 2017;11(1):35–46. https://doi.org/10.1093/ecco-jcc/jjw133.
35. Brandse JF, Mould D, Smeekes O, Ashruf Y, Kuin S, Strik A, 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(4):650–60. https://doi.org/10.1097/MIB.0000000000001043.
36. Steenholdt C, Frederiksen MT, Bendtzen K, Ainsworth MA, Thomsen OO, Brynskov J. Time course and clinical implications of development of antibodies against adalimumab in patients with inflammatory bowel disease. J Clin Gastroenterol. 2016;50(6):483–9. https://doi.org/10.1097/MCG.0000000000000375.
37. O'Toole A, Moss AC. Optimizing biologic agents in ulcerative colitis and Crohn's disease. Curr Gastroenterol Rep. 2015;17(8):32. https://doi.org/10.1007/s11894-015-0453-1.
38. Peyrin-Biroulet L, Sandborn W, Sands BE, Reinisch W, Bemelman W, Bryant RV, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. Am J Gastroenterol. 2015;110(9):1324–38. https://doi.org/10.1038/ajg.2015.233.
39. Ungar B, Levy I, Yavne Y, Yavzori M, Picard O, Fudim E, et al. Optimizing anti-TNF-alpha therapy: serum levels of infliximab and adalimumab are associated with mucosal healing in patients with inflammatory bowel diseases. Clin Gastroenterol Hepatol. 2016;14(4):550–7. https://doi.org/10.1016/j.cgh.2015.10.025.
40. Yarur AJ, Jain A, Hauenstein SI, Quintero MA, Barkin JS, Deshpande AR, et al. Higher adalimumab levels are associated with histologic and endoscopic remission in patients with Crohn's disease and ulcerative colitis. Inflamm Bowel Dis. 2016;22(2):409–15. https://doi.org/10.1097/MIB.0000000000000689.
41. Plevris N, Lyons M, Jenkinson PW, Chuah CS, Merchant LM, Pattenden RJ, Watson EF, Ho GT, Noble CL, Shand AG, Din S, Arnott ID, Jones GR, Lees CW Higher adalimumab drug levels during maintenance therapy for Crohn's disease are associated with biologic remission. Inflamm Bowel Dis 2018. https://doi.org/10.1093/ibd/izy320.
42. Juncadella A, Papamichael K, Vaughn BP, Cheifetz AS. Maintenance adalimumab concentrations are associated with biochemical, endoscopic, and histologic

remission in inflammatory bowel disease. Dig Dis Sci. 2018;63:3067–73. https://doi.org/10.1007/s10620-018-5202-5.

43. 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(10):2266–71. https://doi.org/10.1093/ibd/izy132.
44. Vande Casteele N, Jeyarajah J, Jairath V, Feagan BG, Sandborn WJ. Infliximab exposure-response relationship and thresholds associated with endoscopic healing in patients with ulcerative colitis. Clin Gastroenterol Hepatol 2018. https://doi.org/10.1016/j.cgh.2018.10.036.
45.• Yarur AJ, Kanagala V, Stein DJ, Czul F, Quintero MA, Agrawal D, et al. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. Aliment Pharmacol Ther. 2017;45(7):933–40. https://doi.org/10.1111/apt.13970

This cross-sectional study suggests that higher trough levels may be required for patients with fistulizing CD.

46. Papamichael K, Vande Casteele N, Ferrante M, Gils A, Cheifetz AS. Therapeutic drug monitoring during induction of anti-tumor necrosis factor therapy in inflammatory bowel disease: defining a therapeutic drug window. Inflamm Bowel Dis. 2017;23(9):1510–5. https://doi.org/10.1097/MIB.0000000000001231.
47. Baert F, Vande Casteele N, Tops S, Noman M, Van Assche G, Rutgeerts P, et al. Prior response to infliximab and early serum drug concentrations predict effects of adalimumab in ulcerative colitis. Aliment Pharmacol Ther. 2014;40(11–12):1324–32. https://doi.org/10.1111/apt.12968.
48. Papamichael K, Van Stappen T, Vande Casteele N, Gils A, Billiet T, Tops S, et al. Infliximab concentration thresholds during induction therapy are associated with short-term mucosal healing in patients with ulcerative colitis. Clin Gastroenterol Hepatol. 2016;14(4):543–9. https://doi.org/10.1016/j.cgh.2015.11.014.
49. Papamichael K, Rivals-Lerebours O, Billiet T, Vande Casteele N, Gils A, Ferrante M, et al. Long-term outcome of patients with ulcerative colitis and primary non-response to infliximab. J Crohns Colitis. 2016;10(9):1015–23. https://doi.org/10.1093/ecco-jcc/jjw067.
50. Bar-Yoseph H, Levhar N, Selinger L, Manor U, Yavzori M, Picard O, et al. Early drug and anti-infliximab antibody levels for prediction of primary nonresponse to infliximab therapy. Aliment Pharmacol Ther. 2018;47(2):212–8. https://doi.org/10.1111/apt.14410.
51. Brandse JF, van den Brink GR, Wildenberg ME, van der Kleij D, Rispens T, Jansen JM, et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. Gastroenterology. 2015;149(2):350–.

e2. https://doi.org/10.1053/j.gastro.2015.04.016.

52. Brandse JF, Mathot RA, van der Kleij D, Rispens T, Ashruf Y, Jansen JM, et al. Pharmacokinetic features and presence of antidrug antibodies associate with response to infliximab induction therapy in patients with moderate to severe ulcerative colitis. Clin Gastroenterol Hepatol. 2016;14(2):251–8. https://doi.org/10.1016/j.cgh.2015.10.029.
53. Afif W, Loftus EV Jr, Faubion WA, Kane SV, Bruining DH, Hanson KA, et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. Am J Gastroenterol. 2010;105(5):1133–9. https://doi.org/10.1038/ajg.2010.9.
54. Steenholdt C, Brynskov J, Thomsen OO, Munck LK, Fallingborg J, Christensen LA, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. Gut. 2014;63(6):919–27. https://doi.org/10.1136/gutjnl-2013-305279.
55. Guidi L, Pugliese D, Panici Tonucci T, Berrino A, Tolusso B, Basile M et al. Therapeutic drug monitoring is more cost-effective than a clinically-based approach in the management of loss of response to infliximab in inflammatory bowel disease: an observational multicentre study. J Crohns Colitis. 2018. https://doi.org/10.1093/ecco-jcc/jjy076.
56. Yanai H, Lichtenstein L, Assa A, Mazor Y, Weiss B, Levine 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(3):522–3.

e2. https://doi.org/10.1016/j.cgh.2014.07.029.

57. Papamichael K, Chachu KA, Vajravelu RK, Vaughn BP, Ni J, Osterman MT, 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(10):1580–.

e3. https://doi.org/10.1016/j.cgh.2017.03.031.

58. Colombel JF, Sandborn WJ, Reinisch W, Mantzaris GJ, Kornbluth A, Rachmilewitz D, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med. 2010;362(15):1383–95. https://doi.org/10.1056/NEJMoa0904492.
59. Panaccione R, Ghosh S, Middleton S, Marquez JR, Scott BB, Flint L, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology. 2014;146(2):392–400. https://doi.org/10.1053/j.gastro.2013.10.052.
60. Beaugerie L, Brousse N, Bouvier AM, Colombel JF, Lemann M, Cosnes J, et al. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. Lancet. 2009;374(9701):1617–25. https://doi.org/10.1016/S0140-6736(09)61302-7.
61. Lega S, Phan BL, Rosenthal CJ, Gordon J, Haddad N, Pittman N, et al. Proactively optimized infliximab

monotherapy is as effective as combination therapy in IBD. Inflamm Bowel Dis. 2018;25:134–41. https://doi.org/10.1093/ibd/izy203.

62. Colombel JF, Adedokun OJ, Gasink C, Tang KL, Cornillie F, D'Haens GR, et al. Higher levels of infliximab may alleviate the need of azathioprine comedication in the treatment of patients with Crohn's disease: a sonic post HOC analysis. Gastroenterology. 2017;152(5):S37–S8. https://doi.org/10.1016/S0016-5085(17)30490-0.

63.•• Vande Casteele N, Ferrante M, Van Assche G, Ballet V, Compernolle G, Van Steen K, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. Gastroenterology. 2015;148(7):1320–9. https://doi.org/10.1053/j.gastro.2015.02.031

TAXIT Trial: this prospective randomized trial did not demonstrate that concentration-based dosing of infliximab to trough concentrations of 3-7 μg/mL was associated with improved 1-year clinical remission.

64. Pouillon L, Ferrante M, Van Assche G, Rutgeerts P, Noman M, Sabino J, et al. Mucosal healing and long-term outcomes of patients with inflammatory bowel diseases receiving clinic-based vs trough concentration-based dosing of infliximab. Clin Gastroenterol Hepatol. 2018;16(8):1276–8.

e1. https://doi.org/10.1016/j.cgh.2017.11.046.

65.•• D'Haens G, Vermeire S, Lambrecht G, Baert F, Bossuyt P, Pariente B, 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(5):1343–51 e1. https://doi.org/10.1053/j.gastro.2018.01.004

TAILORIX Trial: this double-blind randomized trial of patients with active CD did not demonstrate that increasing infliximab dosing by symptoms, biomarkers, and TDM improved clinical remission.

66. Papamichael K, Osterman MT, Siegel CA, Melmed GY, Dubinsky MC, Colombel JF, et al. Using proactive therapeutic drug monitoring of anti-tumor necrosis factor therapy in inflammatory bowel disease: from an old concept to a future standard of care? Gastroenterology. 2018;154(4):1201–2. https://doi.org/10.1053/j.gastro.2018.01.001.

67.•• Mitrev N, Vande Casteele N, Seow CH, Andrews JM, Connor SJ, Moore GT, et al. Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases. Aliment Pharmacol Ther. 2017;46(11-12):1037–53. https://doi.org/10.1111/apt.14368

Consensus recommendations for use of TDM from the Australian Inflammatory Bowel Diseases Consensus Working Group.

68. Rosario M, Dirks NL, Milch C, Parikh A, Bargfrede M, Wyant T, et al. A review of the clinical pharmacokinetics, pharmacodynamics, and immunogenicity of vedolizumab. Clin Pharmacokinet. 2017;56(11):1287–301. https://doi.org/10.1007/s40262-017-0546-0.

69. Lamb YN, Duggan ST. Ustekinumab: a review in moderate to severe Crohn's disease. Drugs. 2017;77(10):1105–14. https://doi.org/10.1007/s40265-017-0765-6.

70. Feagan BG, Sandborn WJ, Gasink C, Jacobstein D, Lang Y, Friedman JR, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2016;375(20):1946–60. https://doi.org/10.1056/NEJMoa1602773.

71. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, Sandborn WJ, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013;369(8):699–710. https://doi.org/10.1056/NEJMoa1215734.

72. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, Colombel JF, Sands BE, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. N Engl J Med. 2013;369(8):711–21. https://doi.org/10.1056/NEJMoa1215739.

73. Rosario M, Dirks NL, Gastonguay MR, Fasanmade AA, Wyant T, Parikh A, et al. Population pharmacokinetics-pharmacodynamics of vedolizumab in patients with ulcerative colitis and Crohn's disease. Aliment Pharmacol Ther. 2015;42(2):188–202. https://doi.org/10.1111/apt.13243.

74. Kotze PG, Ma C, Almutairdi A, Al-Darmaki A, Devlin SM, Kaplan GG, et al. Real-world clinical, endoscopic and radiographic efficacy of vedolizumab for the treatment of inflammatory bowel disease. Aliment Pharmacol Ther. 2018;48(6):626–37. https://doi.org/10.1111/apt.14919.

75. Adedokun OJ, Xu Z, Gasink C, Jacobstein D, Szapary P, Johanns J, et al. Pharmacokinetics and exposure response relationships of ustekinumab in patients with Crohn's disease. Gastroenterology. 2018;154(6):1660–71. https://doi.org/10.1053/j.gastro.2018.01.043.

76. Battat R, Kopylov U, Bessissow T, Bitton A, Cohen A, Jain A, et al. Association between ustekinumab trough concentrations and clinical, biomarker, and endoscopic outcomes in patients with Crohn's disease. Clin Gastroenterol Hepatol. 2017;15(9):1427–3.

e2. https://doi.org/10.1016/j.cgh.2017.03.032.

77. Yarur AJ, Jain A, Sussman DA, Barkin JS, Quintero MA, Princen F, et al. The association of tissue anti-TNF drug levels with serological and endoscopic disease activity in inflammatory bowel disease: the ATLAS study. Gut. 2016;65(2):249–55. https://doi.org/10.1136/gutjnl-2014-308099.

78. Yoshihara T, Shinzaki S, Kawai S, Fujii H, Iwatani S, Yamaguchi T, et al. Tissue drug concentrations of anti-tumor necrosis factor agents are associated with the long-term outcome of patients with Crohn's disease. Inflamm Bowel Dis. 2017;23(12):2172–9. https://doi.org/10.1097/MIB.0000000000001260.

79. Sandborn WJ, Bressler B, Lee S, Bhandari R, Kanwar B, Tozzi L et al. PTG-100, an oral gut-restricted peptide

α4β7 antagonist, induces clinical and histologic remission in patients with moderate to severely active ulcerative colitis. United Eur Gastroenterol J. Presented at UEG Week 2018 in Vienna, Austria, 2018;6(Supplement 1).
80. Sandborn WJ, Bhandari R, Leighton JA, Ganeshappa R, Nguyen D, Ferslew B et al. The intestinally restricted, orally administered, pan-JAK inhibitor TD-1473 demonstrates favorable safety, tolerability, pharmacokinetics, and signal for clinical activity in subjects with moderately-to-severely active ulcerative colitis. United Eur Gastroenterol J. Presented at UEG Week 2018 in Vienna, Austria, 2018;6(Supplement 1).