Therapeutic Drug Monitoring of Tumor Necrosis Factor Antagonists in Inflammatory Bowel Disease

INGRID ORDÁS,* BRIAN G. FEAGAN,‡ and WILLIAM J. SANDBORN§

*Gastroenterology Department, Hospital Clinic of Barcelona, CIBER-EHD, IDIBAPS, University of Barcelona, Barcelona, Spain; ‡Robarts Research Institute, University of Western Ontario, London, Ontario, Canada; §Division of Gastroenterology, University of California, San Diego, La Jolla, California

This article has an accompanying continuing medical education activity on page e86. Learning Objective—At the end of this activity, the successful learner will be able to recognize the factors related to an increased clearance of TNF antagonist agents and to select the most appropriate strategy for treatment optimization in case of loss of response based on the assessment of drug and antidrug antibodies concentrations.

Although tumor necrosis factor (TNF) antagonists have shown clear benefits over conventional treatments for inducing and maintaining clinical remission in both Crohn's disease and ulcerative colitis, a high proportion of patients lose response over time. Given the scarce alternative of treatments when treatment failure occurs, it is highly desirable to optimize both initial response and long-term continuation of TNF antagonists. One of the most well-characterized factors associated with loss of response to these agents is the development of immunogenicity, whereby the production of neutralizing antidrug antibodies accelerates drug clearance, leading to subtherapeutic drug concentrations and, ultimately, to treatment failure. However, other patient-related factors, such as sex and/or body size, and disease severity, including TNF burden and serum albumin concentration among others, also may influence the pharmacokinetics of these agents. Nevertheless, the evidence generated to date about these complex interactions is scarce, and further prospective studies evaluating their influence on the pharmacokinetics of TNF antagonists are needed. Drug adjustment empirically based on clinical symptoms often is inaccurate and may lead to suboptimal outcomes. Recent evidence shows that maintenance of an optimal therapeutic drug concentration is associated with improved clinical outcomes. Therefore, incorporation of therapeutic drug monitoring into clinical practice may allow clinicians to optimize treatment by maintaining effective drug concentrations over time.

Keywords: Inflammatory Bowel Disease; Crohn's Disease; Ulcerative Colitis; Tumor Necrosis Factor Antagonists; Therapeutic Monitoring.

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Over the past decade, therapy with monoclonal antibodies targeting tumor necrosis factor (TNF) has transformed the management of patients with inflammatory bowel disease (IBD). These agents have shown clear benefits over conventional treatments for inducing and maintaining clinical remission, reducing corticosteroid requirements, and rates of hospitalization and surgery in both Crohn's disease (CD) and ulcerative colitis (UC).[1–8] Given these benefits, it is highly desirable to ensure both their optimal initial use and long-term continuation. Extensive empiric data have shown that response to TNF antagonists is highly heterogeneous. Approximately 30% of patients either fail initial induction therapy (primary failure) or lose response over time (up to 50%).[9] Therefore, the development of new strategies that minimize these problems and optimize the efficacy of TNF antagonists in clinical practice has relevant potential to improve patient outcomes.

Although TNF antagonists have been used in clinical practice for more than a decade, little is known about their exposure–response relationship. The pharmacology of these agents is complex and depends not only on their structure (monoclonal antibodies), but also on the properties of the target antigen and on patient- and disease-related factors. Identification of the factors that influence the disposition and clearance of TNF antagonists is essential to understand their pharmacokinetic (PK)/pharmacodynamic (PD) relationship, and to inform their use in clinical practice. Although the reasons for treatment failure are multifactorial, interindividual and intraindividual differences in PK are important contributors.[10]

The current approach for managing loss of response to TNF antagonist agents is based on clinical symptoms, and consists of empirically increasing the dose or shortening the treatment interval, in distinction to tailoring therapeutic drug concentrations in

Abbreviations used in this paper: ADAs, antidrug antibodies; ADL, adalimumab; ATI, antibodies to infliximab; AZA, azathioprine; BMI, body mass index; CD, Crohn's disease; CRP, C-reactive protein; CZP, certolizumab; ELISA, enzyme-linked immunosorbent assay; FcRn, neonatal Fc receptor; IBD, inflammatory bowel disease; IFX, infliximab; IQR, interquartile range; PD, pharmacodynamic; PK, pharmacokinetics; RA, rheumatoid arthritis; RES, reticuloendothelial system; RIA, radioimmunoassay; TNF, tumor necrosis factor; UC, ulcerative colitis.

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2012.06.032

Table 1. Factors That Influence the PK of TNF Antagonists

	Impact on TNF antagonist PK
Presence of ADAs	Decreases drug concentration Increases clearance Worse clinical outcomes
Concomitant use of immunosuppressives	Reduces ADA formation Increases drug concentration Decreases drug clearance Better clinical outcomes
Low serum albumin concentration	Increases drug clearance Worse clinical outcome
High baseline CRP concentration	Increases drug clearance
High baseline TNF concentration	May decrease drug concentration by increasing clearance
High body size	May increase drug clearance
Sex	Males have higher clearance

NOTE. Adapted from Ordás et al.[49]

an individual patient. We believe that this empiric strategy is inherently inefficient and results in inferior efficacy outcomes.

Determinants of the Pharmacokinetics of Tumor Necrosis Factor Antagonists

A growing body of evidence suggests that both short- and long-term treatment outcomes are improved by achieving and maintaining adequate serum drug concentrations.[10–16] One dominant factor that adversely affects the PK of TNF antagonists is the formation of antidrug antibodies (ADAs). These antibodies directly neutralize the biological activity of TNF antagonists by either binding specific drug idiotypes and/or accelerating drug clearance by the reticuloendothelial system (RES) through formation of immune complexes. However, emerging evidence indicates that factors other than ADAs may strongly influence drug clearance. A review of these factors is discussed later and is summarized in Table 1.

Factors Leading to Interpatient Variability

Conventional wisdom holds that therapeutic failure of TNF antagonists is caused by either the existence of non–TNF-mediated inflammatory pathways or the formation of neutralizing ADAs. However, other factors that affect the PK of TNF antagonist agents have been poorly investigated until recently. These factors include body mass index (BMI), the serum albumin concentration, concomitant immunosuppressive therapy, the degree of systemic inflammation (TNF burden), and disease type (CD vs UC). Emerging data indicate that an important relationship exists between serum drug concentration (PK) and clinical efficacy. Studies conducted in both rheumatoid arthritis (RA) and IBD have shown that patients with higher trough drug concentrations have better outcomes.[12,13,15,17] Conversely, the development of ADAs has been linked to lower response rates and a shortened duration of response.[18–20] The development of ADAs to infliximab (IFX) is associated with increased drug clearance and lower serum drug concentrations, resulting in higher rates of treatment failure.[10,18,21] However, undetectable trough serum concentrations of IFX also have been reported in the absence of ADAs in 16% to 39% of patients.[2,12,13,19] These findings indicate that factors other than ADAs may influence the PK profile (and efficacy) of TNF antagonists.

Role of Antidrug Antibodies

Multiple studies have linked the presence of ADAs to inferior outcomes.[16,18,21,22] Development of ADAs reduces drug exposure through formation of immune complexes that accelerate drug clearance by the RES. Baert et al[18] showed, in a cohort of patients with CD, that patients with a high titer of ADAs had a reduced duration of response in comparison with nonsensitized patients (35 vs 71 d, respectively; $P < .001$).[18] Likewise, formation of ADAs was associated with lower rates of prednisone-free remission (57.1% vs 70.6%, respectively) in a large multicenter trial of IFX in early CD.[14] However, it is noteworthy that all of the published data are based on the use of solid-phase drug assays in which the presence of circulating drug masks the presence of ADAs, rendering the test relatively insensitive. Thus, the current literature may underestimate the impact of ADA formation on clinical efficacy. In this regard, the development of a new highly sensitive, liquid-phase assay that can measure ADAs independently of the presence of circulating drug may allow a more accurate assessment of the importance of immunogenicity.[23] Specifically, the rate and intensity of the sensitization process now can be more fully evaluated early in the course of treatment.

Assays for assessment of drug and antidrug antibody concentrations. Over the past years, multiple first-generation assays have been developed for measurement of serum concentrations of TNF antagonist agents and ADAs. The most commonly used method is a solid-phase, double-antigen, enzyme-linked immunosorbent assay (ELISA) using drug for ligand and detection of antibodies (Figure 1). As previously mentioned, this

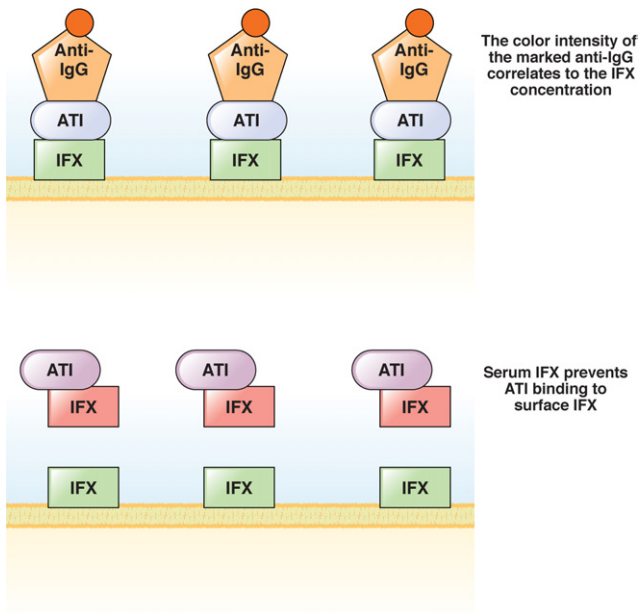

Figure 1. Detection of infliximab antibodies (ATIs) by ELISA. The presence of serum IFX lowers detected ATIs or makes them undetectable, thus a negative test with detectable drug is inconclusive. Because this alters the accuracy of the ATI positive test as well, any sample with detectable drug is deemed inconclusive.

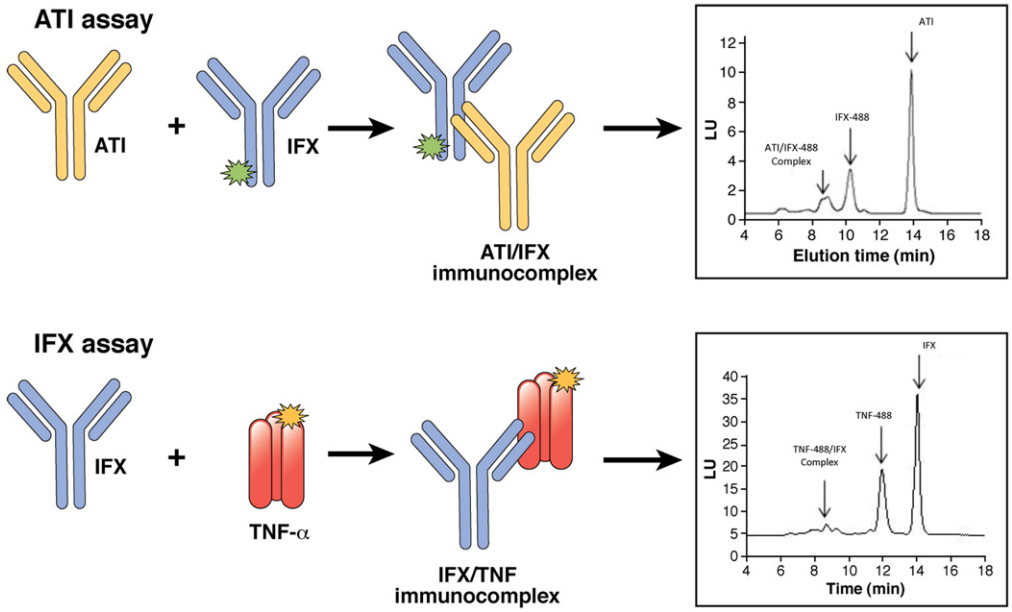

Figure 2. Mobility shift assay principle (Prometheus Laboratories). ATI assay: fluorescent-labeled IFX (IFX-488) with a molecular weight of approximately 150 kilodaltons is incubated with serum containing ATI (molecular weight, ~150–900 kilodaltons). The ATI/IFX immune complexes have a significantly higher molecular weight than the free IFX and can be separated and quantified by size-exclusion high performance liquid chromatography (SE-HPLC) with fluorescent detection. IFX assay: fluorescent-labeled TNF-α (TNF-488, ~51 kilodaltons) is bound to IFX in the serum. The resulting immune complex has a much higher molecular weight (~200 kilodaltons) and can be separated by SE-HPLC and monitored by fluorescent detection.

approach is limited by the inability to measure ADAs in the presence of circulating drug. Radioimmunoassay (RIA) is a more sensitive and specific method than ELISA but has the burden of requiring radioisotopes. In addition, there is scarce information regarding the performance of RIA in the evaluation of drug and ADA concentrations in patients with IBD.[21,24]

Recently, a liquid-phase mobility shift assay for measurement of drug (IFX and adalimumab [ADL]) and ADAs in the presence of drug was developed by Prometheus Laboratories (San Diego, CA). This new assay eliminates many of the limitations of current methodologies (ELISA, RIA), enabling accurate detection of both drug and ADAs in the same serum sample, thus avoiding interference from serum drug concentration for measurement of ADAs. The mobility shift assay (Figure 2) is based on the shift in retention time of the antigen–antibody immunocomplex vs free antigen on size-exclusion chromatography.[23] This new technology may facilitate a more complete understanding of the process of sensitization, which in turn may lead to more effective management strategies.

Concomitant Immunosuppressive Therapy

Antimetabolites such as azathioprine (AZA) and methotrexate can increase the serum concentration of TNF antagonists by either reducing the formation of ADAs or by reducing RES-mediated drug clearance. Post hoc analysis of 4 randomized controlled trials showed that concomitant use of immunosuppressives with IFX was associated with higher serum IFX concentrations.[25] In the Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC) trial, patients with active CD who received combined therapy (IFX plus AZA) had higher trough IFX concentrations compared with those assigned to IFX monotherapy (3.5 vs 1.6 μg/mL, respectively; $P < .001$), and a higher rate of corticosteroid-free remission rate was observed in the combination therapy arm.[14] Although it is apparent that co-administration of AZA decreased drug clearance in patients in the SONIC trial, the mechanisms responsible for this effect are unclear. One likely cause is the reduction in ADA formation (0.9% in patients receiving combination therapy vs 14.6% in patients receiving IFX monotherapy). In contrast, a recent study that evaluated patients with UC reported similar rates of ADA formation irrespective of immunosuppressive use (40% vs 41%; $P = .88$),[12] and another study performed in a similar patient population also showed that IFX clearance was not affected by co-administration of thiopurines.[26] These disparate results are likely due to the differential presence within study populations of other powerful nonimmune determinants of PK.

The Reticuloendothelial System and Disease Severity

Because of their high molecular weight, monoclonal antibodies do not undergo renal elimination or metabolism by hepatocytes. Proteolytic catabolism within the RES is believed to be the primary route of clearance.[27] Antibody salvage and recirculation is mediated by the Brambell receptor (neonatal Fc receptor [FcRn]), which is essential for maintaining immunoglobulin and albumin homeostasis. FcRn protects IgG antibodies and albumin from catabolism, thus prolonging their half-life. However, this protective system is saturable at high IgG concentrations, resulting in an inverse relationship between IgG concentration and half-life (the higher the IgG concentration, the shorter the half-life).[28]

Disease severity may influence the clearance of TNF antagonists through multiple mechanisms. The presence of systemic inflammation increases protein catabolism in the RES and an increased serum concentration of C-reactive protein (CRP) has been associated with increased drug clearance.[11,26] Furthermore, patients with severe IBD often have a low serum albumin concentration. The serum albumin concentration has been shown to correlate positively with the trough IFX concentration, potentially as a result of the previously described FcRn mechanism or alternatively as a marker for severe inflammation or even as a result of protein/drug loss through the gut.[29] These observations hold out the possibility that patients with more severe inflammation require higher than average drug doses to obtain the necessary degree of drug exposure and optimum

clinical results. Notably, a very low or undetectable concentration of IFX has been observed in severely ill hospitalized UC patients undergoing IFX induction therapy, with an accelerated clearance to induction therapy of 2.8 days (range, 1.3–6.2 days).[29,30] Interestingly, this accelerated clearance has not been linked to immune complex formation but rather to serum albumin concentrations below the normal range (<35 g/dL).[30] This relationship between baseline serum albumin concentration and serum IFX concentration has been reported for both UC and CD.[29,31] The percentage of UC patient responders to IFX has been shown to be significantly higher among those patients with serum albumin concentrations higher than 35 g/dL compared with those with serum albumin concentrations below the normal range (70% vs 38%; $P = .0021$; respectively).[29] In CD patients, it also recently was shown that IFX clearance increases as serum albumin concentration decreases.[31]

Another potential explanation for an inadequate response to TNF antagonist therapy is incomplete suppression of TNF-α.[32] A high inflammatory burden before treatment is associated with a higher concentration of TNF in both tissue and serum.[33] Therefore, it is logical to hypothesize that patients with greater disease activity may require, in a stoichiometric fashion, more drug to neutralize this excess of TNF. In turn, this state could result in a lower TNF antagonist serum concentration and less functional drug (the antigen sink). In this paradigm, the higher the baseline TNF concentration, the higher the dose of TNF antagonist required to achieve a given PD effect. Moreover, TNF-α serum concentrations may predict the need for dose escalation in patients who are losing response.[32] In support of this notion, Ainsworth et al[21] found that patients who were primary nonresponders to IFX had significantly lower serum TNF concentrations than patients with a secondary loss of response, presumably because primary nonresponders are more likely to have disease mediated by alternative inflammatory pathways. In contrast, secondary nonresponders were TNF-antagonist sensitive but lost response due to an inadequate serum drug concentration. The investigators concluded that measurement of TNF in serum in conjunction with ADAs may provide new insights into the causes of treatment failure (sensitization vs non-TNF inflammatory pathways vs inadequate drug concentration in the absence of sensitization). In line with this concept, the results of a large prospective cohort study of patients with RA highlight the potential importance of determining immunogenicity in the setting of treatment failure.[34] In this study, which prospectively evaluated 292 patients, individuals who were sensitized to a TNF antagonist (either IFX or ADL) had a high rate of success to subsequent therapy with etanercept compared with patients who did not develop ADAs. Conversely, patients with therapeutic drug concentrations who were not sensitized responded poorly to treatment with the second TNF antagonist. These data highlight that a more rational approach to the problem of loss of response to TNF antagonist agents is needed.

Body Mass Index and Mesenteric Fat

Ternant et al[35] confirmed in a population of IBD patients that the systemic clearance of IFX was almost 3-fold higher in the presence of ADAs. However, notwithstanding the presence of such a strong relationship, both sex and weight independently influenced the PK of IFX. Recently, a study conducted in patients with RA showed that a high BMI negatively influenced clinical response to IFX.[36] In a real-life prospective cohort of patients with IBD, 38% of patients needed dose optimization with ADL within 5 months after treatment initiation, BMI being the only predictive factor for dose escalation in the multivariate analysis.[37] A high BMI could be related to an altered bioavailability of TNF antagonist agents or a higher TNF burden in obese patients, although no experimental or observational data exist to evaluate the relative contributions of these factors to this effect. Based on these observations, it is noteworthy that mesenteric adipose tissue plays an important role as a source of proinflammatory cytokines in patients with CD.[38] The potential interactions between PK, TNF burden, BMI, and clinical outcomes have not been investigated adequately. However, we speculate that patients with a higher BMI (obese patients) may have an increased production of proinflammatory cytokines, such as TNF, resulting in a higher inflammatory burden, therefore requiring higher doses of TNF antagonists to neutralize these excess of TNF. However, this hypothesis requires further study.

The Role of Disease Type: Crohn's Disease vs Ulcerative Colitis

Potential PK differences between CD and UC exist that may or may not be explained by systematic differences in the previously described factors. Based on existing data, the clearance of IFX is similar among CD, RA, and psoriasis.[39] In distinction, potentially important PK differences exist between CD and UC.[12,13] Seow et al[12] showed that patients with moderately active UC had higher rates of clinical response (70% vs 41%; $P = .004$), clinical remission (41% vs 17%; $P = .015$), and endoscopic remission (26% vs 4%; $P = .046$) after IFX induction therapy than those with severe disease. An undetectable trough serum IFX concentration was associated with less favorable outcomes irrespective of antibody status. In this study, the proportion of patients with an undetectable IFX trough concentration was substantially higher than that observed in a

Table 2. Proportions of Patients Achieving Clinical Remission by Serum IFX Concentration in Ulcerative Colitis[41]

	Serum IFX concentration, μg/mL/proportion of patients, %				
Clinical remission	1st quartile	2nd quartile	3rd quartile	4th quartile	*P* values
Week 8	<21.3 (26.3)	≥21.3 to <33.0 (37.9)	≥33.0 to <47.9 (43.9)	>47.9 (43.1)	.05
Week 30	<0.11 (14.6)	≥0.11 to <2.4 (25.5)	≥2.4 to <6.8 (59.6)	>6.8 (52.1)	<.001
Week 54	<1.4 (21.1)	≥1.4 to <3.6 (55)	≥3.6 to <8.1 (79.0)	>8.1 (60)	.001

NOTE. Patients in the lowest quartile of the IFX trough concentration distribution had remission rates at week 54 that were 40% lower than those in the highest quartile.

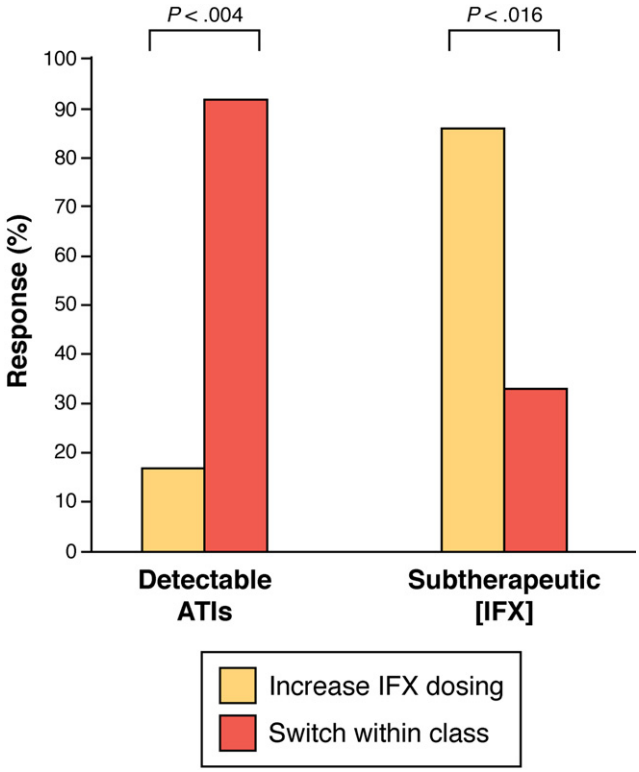

Figure 3. Clinical outcomes to IFX according to serum drug concentration and ATIs.

previous study performed by the same investigators in patients with CD.[13] A potential explanation for these findings is that patients with UC have a more rapid clearance of IFX than patients with CD due to a higher inflammatory burden and/or a lower serum albumin concentration. Nevertheless, this hypothesis needs confirmation.

Two additional observations support the concept that important PK differences exist between UC and CD. First, 2 large randomized controlled trials performed in patients with UC have shown that rates of remission with ADL induction therapy might be lower than those observed with IFX[2] using an ADL dosing regimen that is highly effective for CD,[5,6] whereas intravenously administered IFX and subcutaneously administered ADL have similar efficacy in CD.[1,40] Second, a post hoc analysis of data from the Active Ulcerative Colitis Trial 1 (ACT1) and ACT2 that evaluated IFX therapy in ambulatory patients with UC (Table 2) showed a striking relationship between PK and clinical outcomes that was not observed to the same degree in similar CD trials.[41]

Collectively, all of these factors (immunogenicity, disease burden, serum albumin concentration, BMI, etc) likely contribute to the large interindividual differences in concentration time profiles (PK) observed among equally dosed patients and similarly contribute to treatment failure in many patients.[10] Therefore, a re-examination of the determinants of the PK/PD relationship of TNF antagonist agents is clearly needed. An improved understanding of this relationship has great potential to improve the care of patients with IBD, resulting in better clinical outcomes.

The Potential of Therapeutic Drug Monitoring

Historically, in clinical practice when a responding patient becomes refractory to a TNF antagonist, the following approach is used. First, the presence of active inflammation is evaluated by objective tools, either endoscopy or imaging and surrogate biomarkers of disease activity (CRP and fecal calprotectin). If inflammation is not confirmed, then other disease processes should be excluded by appropriate investigations (eg, bacterial overgrowth; bile salt deficiency; steatorrhea; infection, especially *Clostridium difficile*; irritable bowel syndrome). If objective evidence of inflammation exists, 3 strategies of treatment adjustment are apparent: (1) empirically increase the dose or shorten the interval between doses of the existing drug; (2) switch to another TNF antagonist agent (switch within class; eg, from IFX to ADL, from ADL to certolizumab [CZP]), or (3) switch to another agent with a different mechanism of action (switch out of class). The latter option becomes particularly constrained in IBD patients (in distinction to those with RA) due to the limited availability of alternative drugs (natalizumab, ustekinumab, tofacitinib, or vedolizumab; some of which remain under clinical investigation).

The most common algorithm in clinical practice is to intensify treatment with the existing drug and, if failure occurs, empirically switch to another TNF antagonist. Although this strategy is relatively straightforward, it has several inherent disadvantages. First, patients who have developed high-titer ADAs will be unlikely to respond to dose intensification. Consequently, in these patients, this is a costly and futile intervention that may be associated with adverse effects from allergic reactions with no likely therapeutic gain. Second, although empiric dose intensification may salvage some patients with nonimmune pharmacokinetic mechanisms, this is a relatively cost-inefficient tactic because patients can be either underdosed or overdosed. Third, this empiric approach does not identify patients who have continued inflammation in the presence of therapeutic drug concentrations. Although this clinical circumstance now often is attributed to mechanistic resistance or escape, the etiology currently is unknown. As previously mentioned, reported data from RA support the notion that patients with therapeutic drug concentrations and loss of response are highly unlikely to respond to treatment with a second TNF antagonist in the absence of immunogenicity.[34]

Impact of Therapeutic Monitoring: Review of Recent Evidence

Development of ADAs has been associated clearly with loss of response and hypersensitivity reactions.[18] A growing

Table 3. Median CRP Concentrations and Interquartile Ranges (ng/mL) According to IFX and ATI Concentrations

	ATI negative	ATI positive	*P* value
IFX <3 μg/mL	5.65 (1.68–16.1)	8.40 (3.10–20.1)	<.001
IFX ≥3 μg/mL	1.50 (1.00–4.70)	9.90 (5.82–20.2)	<.01
P value	<.001	NS	

NOTE. Therapeutic IFX concentration in the presence of ATIs had no effect on clinical response measured by CRP.

Table 4. CD Activity Index Remission Rates During the CZP Open-Label Study by CZP Plasma Concentration[46]

	CZP plasma concentration quartile, μg/mL			
Week	1st quartile (<19.3)	2nd quartile (19.3 to <27.5)	3rd quartile (27.5 to <33.8)	4th quartile (≥33.8)
0	26% (12–39)	21% (8–33)	46% (31–62)	48% (32–63)
2	39% (23–54)	31% (16–45)	49% (33–64)	48% (32–63)
4	39% (23–54)	33% (19–48)	56% (41–72)	48% (32–63)
6	41% (26–57)	46% (31–62)	59% (44–74)	43% (27–58)

NOTE. 95% CI is shown in parentheses.

body of evidence shows that clinical monitoring of drug and ADA concentrations may help to optimize treatment with TNF antagonist agents.

In a retrospective study, Afif et al[42] evaluated the clinical utility of measuring ADAs and trough drug concentrations in patients with loss of response to IFX. In patients with ADAs, the strategy of switching within class (ie, from IFX to ADL), led to a complete or partial response in a very high proportion of patients (92%), whereas increasing the dose was associated with very low response rates (17%). Conversely, dose escalation in patients with subtherapeutic IFX concentrations was associated with clinical response in 86% of patients, whereas the rate of clinical response in patients changing to a different TNF antagonist agent was 33% (Figure 3). The results of this study should be interpreted with caution given its retrospective nature and the absence of a control group. Prospective studies are needed to evaluate the added value of tailoring TNF antagonists' dosage according to drug and ADA concentrations in clinical practice.

The Future of Therapeutic Drug Monitoring

Interestingly, recent evidence suggests that ADAs can be either transient or persistent. In a retrospective, single-center study performed by Steenholdt et al,[43] antibodies to infliximab (ATIs) disappeared in up to two thirds of patients during continued treatment. The concept of transient ADAs recently was reproduced in a different cohort of patients with IBD. Vande Casteele et al[44] retrospectively evaluated 52 patients treated with IFX showing that in 27% of patients ATIs disappeared over time, whereas in 73% of patients ATIs persisted. Of those with transient ADAs, in 57% of cases ATIs disappeared after dose optimization and in 43% ATIs disappeared spontaneously. Patients with transient ATIs had significantly lower ATI concentrations (median, 18.7 U/mL; interquartile range [IQR], 10.6–31.5 U/mL) compared with patients with sustained ATIs (median, 22.1 U/mL; IQR, 14.0–45.7 U/mL; $P < .01$). Concomitant use of immunosuppressive therapy was associated with lower ATI concentrations compared with monotherapy (8.8 vs 15.5 U/mL, respectively; $P < .01$). In addition, patients with sustained ATIs more often discontinued IFX therapy due to loss of response and/or hypersensitivity reactions compared with patients with transient ATIs (68% vs 14%, respectively; $P < .001$). However, it remains unclear whether patients with transient ADAs have greater drug clearance, which would imply that although it is possible to overcome transient ADAs in the short term, this strategy ultimately might be unsuccessful in the long term and/or more costly than a within-class switch. More information is needed regarding the optimum management of such patients.

Therefore, ADA concentration should be evaluated on a dynamic basis (single determinations may yield incorrect interpretation) because the humoral immune response to TNF antagonist agents can be latent, transient, or sustained.[45]

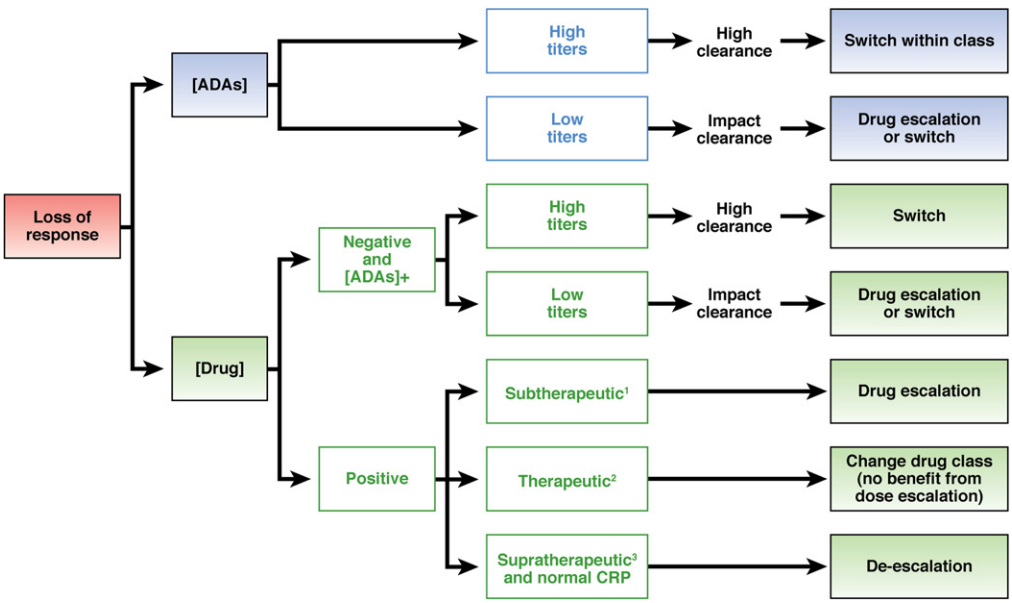

Figure 4. Proposed treatment algorithm in the setting of loss of response. (1) [IFX], <3 μg/mL; [ADL], <8 μg/mL; [CZP], <27.5 μg/mL. (2) [IFX], 3–7 μg/mL; [ADL], ≥8 μg/mL; [CZP], ≥27.5 μg/mL. (3) [IFX], >7 μg/mL. Additional information is required about the optimal cut-off values for ADL and CZP.

A recent study evaluated the samples from 4 patient cohorts and clinical trials of patients with CD under treatment with IFX in a combined analysis using the new liquid-phase mobility shift assay developed by Prometheus Laboratories. The results of this study, in which IFX and ADAs against IFX (ATIs) could be measured simultaneously, showed that in patients developing ADAs, achievement of therapeutic IFX concentration (IFX $\geq$3 μg/mL) had no effect on clinical efficacy, measured by CRP as a surrogate marker of disease activity, suggesting that benefits of IFX are diminished in the presence of ATIs despite the presence of an optimal drug concentration (Table 3).[46] These unexpected findings require confirmation and then further study to understand. One possible explanation is that the presence of ADAs in patients with measurable IFX at trough has a negative impact on the overall PK profile of IFX. On the other hand, in this same study, sustained adequate drug concentrations at trough correlated with better outcomes in terms of clinical remission and decreased CRP.[46]

The therapeutic cut-off threshold for the IFX trough concentration appears to be 3 μg/mL or greater.[46] For ADL and CZP these values are not well defined and need further evaluation. However, preliminary data suggest that trough concentrations of 8 μg/mL or greater and 27.5 μg/mL or greater could be considered therapeutic for ADL[22] and CZP,[47] respectively (Table 4).

With regard to IFX, an ongoing randomized controlled trial (the Trough Level Adapted Infliximab Treatment [TAXIT] trial), including 275 patients, is evaluating the value of individualized treatment with IFX based on therapeutic drug monitoring compared with the conventional strategy (adjustment based on clinical symptoms and CRP level).[48] Before randomization, IFX dosing was optimized to achieve baseline trough IFX concentrations between 3 and 7 μg/mL (considered therapeutic). Note that targeting this rather tight range of concentrations implies that some patients will have their IFX dose reduced. Preliminary results of the optimization phase of the study showed that only 44% of patients under sustained clinical remission had trough IFX concentrations between 3 and 7 μg/mL, therefore needing no dose adjustment before entering the randomized phase of the trial; 26% of patients had trough IFX concentrations greater than 7 μg/mL, which was considered supratherapeutic, and in this subset of patients the interval dosing of IFX was prolonged. Patients with a baseline trough IFX concentration of less than 3 μg/mL had a significantly higher CRP (median, 2.7 mg/L; IQR, 1.1–7.5 mg/L) compared with patients with concentrations between 3 and 7 μg/mL (median, 1.5 mg/L; IQR, 0.60–3.8; $P < .001$) and compared with patients with concentrations greater than 7 μg/mL (median, 1.2 mg/L; IQR, 0.6–4.8 mg/L; $P < .01$). This study further confirms that trough IFX concentrations are correlated inversely with CRP. The current controlled study will discern whether long-term adjustment of treatment based on IFX concentrations is a superior strategy.

Based on these data we propose an updated algorithm for therapeutic monitoring and decision making in cases of loss of response to TNF antagonist agents (Figure 4).

Future Research Needs

To establish whether therapeutic monitoring is superior to the empiric dose-adjustment approach, randomized controlled trials are needed comparing both strategies. The TAXIT trial is one such study that will begin to provide evidence-based answers to this question.

On the other hand, the use of clinical pharmacology to define the PK profile of TNF antagonist agents, together with clinical, endoscopic, and imaging data, may be useful for the development of single predictive models based on clinical factors that will help to determine the induction dosing regimen that would be required to achieve a target therapeutic drug concentration and consequently achievement of maximal therapeutic benefit for individual patients. Similarly, a single predictive model based on clinical factors and postinduction drug and ADA concentrations could help determine the optimum maintenance dosing regimen for individual patients.

Although multiple factors may influence the PK of TNF antagonist agents (eg, antigen load, BMI, albumin, immunogenicity, concomitant immunosuppressive use, etc), no systematic attempt based on intensive PK sampling has been made to examine the interplay of these factors at the patient level. Elucidation and identification of the critical determinants of the PK of TNF antagonist agents should allow rational dose selection and treatment optimization in individual patients during both the induction and maintenance phases of treatment, resulting in greater efficacy and improved safety. This strategy would allow a personalized approach to therapy that should be more effective and cost efficient. Therapeutic monitoring in patients with IBD under TNF antagonist treatment has the potential for important cost savings and improved cost utility of therapy.

Conclusions

Available evidence suggests that adjustment of drug based only on clinical symptoms is frequently inaccurate and may lead to suboptimal outcomes. Observational data regarding therapeutic monitoring of drug and ADA concentrations suggests that incorporation of this strategy into clinical practice may allow clinicians to optimize treatment by maintaining effective drug concentrations over time.

Because of the high interpatient variability leading to heterogeneous responses to TNF antagonist agents, each clinical scenario (ie, loss of response as a result of immunogenicity, accelerated clearance due to high TNF burden, etc) likely requires different approaches that are guided by knowledge of the presence (or absence) of therapeutic drug concentrations and the corresponding rate of ADAs.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://dx.doi.org/10.1016/j.cgh.2012.06.032.

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Reprint requests

Address requests for reprints to: William J. Sandborn, MD, Division of Gastroenterology, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093-0956. e-mail: wsandborn@ucsd.edu; fax: (858) 657-5022.

Conflicts of interest

The authors disclose the following: Ingrid Ordás has received lecture fees from MSD (previously Schering-Plough), Abbott Laboratories, and Shire Pharmaceuticals. Brian G. Feagan has received research support, consulting, and lecture fees from Janssen (previously Centocor), Merck (previously Schering Plough), Abbott Laboratories, and UCB Pharma. William J. Sandborn has received consulting fees from Abbott, ActoGeniX NV, AGI Therapeutics Inc, Alba Therapeutics Corp, Albireo, Alfa Wasserman, Amgen, AM-Pharma BV, Anaphore, Astellas, Athersys Inc, Atlantic Healthcare Ltd, Aptalis, BioBalance Corp, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Celek Pharmaceuticals, Cellerix SL, Cerimon Pharmaceuticals, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado Biosciences, Cytokine Pharmasciences, Eagle Pharmaceuticals, EnGene Inc, Eli Lilly, Enteromedics, Exagen Diagnostics Inc, Ferring Pharmaceuticals, Flexio Therapeutics Inc, Funxional Therapeutics Ltd, Genzyme Corp, Gilead Sciences, Given Imaging, GSK, Human Genome Sciences, Ironwood Pharmaceuticals, KaloBios Pharmaceuticals, Lexicon Pharmaceuticals, Lycera Corp, Meda Pharmaceuticals, Merck Research Laboratories, Merck Serono, Millenium Pharmaceuticals, Nisshin Kyorin Pharmaceuticals, Novo Nordisk, NPS Pharmaceuticals, Optimer Pharmaceuticals, Orexigen Therapeutics Inc, PDL Biopharma, Pfizer, Procter and Gamble, Prometheus Laboratories, ProtAb Ltd, Purgenesis Technologies Inc, Relypsa Inc, Roche, Salient Pharmaceuticals, Salix Pharmaceuticals, Santarus, Schering Plough, Shire Pharmaceuticals, Sigmoid Pharma Ltd, Sirtris Pharmaceuticals, SLA Pharma UK Ltd, Targacept, Teva Pharmaceuticals, Therakos, Tilliotts Pharma AG, TxCell SA, UCB Pharma, Viamet Pharmaceuticals, Vascular Biogenics Ltd, Warner Chilcott UK Ltd, and Wyeth; research grants from Abbott, Bristol-Myers Squibb, Genentech, GSK, Janssen, Milennium Pharmaceuticals, Novartis, Pfizer, Procter and Gamble, Shire Pharmaceuticals, and UCB Pharma; payments for lectures/speakers bureau from Abbott, Bristol-Myers Squibb, and Janssen; and holds stock/stock options in Enteromedics.