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Review article: a clinician's guide for therapeutic drug monitoring of infliximab in inflammatory bowel disease

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SUMMARY

Background
Tumour necrosis factor (TNF)-antagonists have an established role in the treatment of inflammatory bowel diseases (IBDs), however, subtherapeutic drug levels and the formation of anti-drug antibodies (ADAs) may decrease their efficacy.

Aim
The evidence supporting the use of therapeutic drug monitoring (TDM) based clinical algorithms for infliximab (IFX) and their role in clinical practice will be discussed.

Methods
The literature was reviewed to identify relevant articles on the measurement of IFX levels and antibodies-to-infliximab.

Results
Treatment algorithms for IBD have evolved from episodic monotherapy used in patients refractory to all other treatments, to long-term combination therapy initiated early in the disease course. Improved remission rates have been observed with this paradigm shift, nevertheless many patients ultimately lose response to therapy. Although empiric dose optimization or switching agents constitute the current standard of care for secondary failure, these interventions have not been applied in an evidence-based manner and are probably not cost-effective. Multiple TDM-based algorithms have been developed to identify patients that may benefit from measurement of IFX and ADA levels to guide adjustments to therapy.

Conclusions
Therapeutic drug monitoring offers a rational approach to the management of secondary failure to IFX. This concept has gained momentum based on evidence from case series, cohort studies and *post-hoc* analyses of randomised controlled trials.

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INTRODUCTION

Over the past 15 years, tumour necrosis factor (TNF)-antagonists have revolutionised therapy for inflammatory bowel disease (IBD).[1] Treatment algorithms have evolved from episodic monotherapy in refractory cases, to long-term combination therapy earlier in the disease course.[2, 3] As a result, outcomes have improved. For example, a corticosteroid-free remission rate of 29% was observed at week-54 in the ACCENT I trial of infliximab (IFX) monotherapy,[4] compared to a week-50 rate of 55.6% in the SONIC trial of early combined azathioprine (AZA) and IFX therapy.[5] This difference underscores the benefit of administering the optimum treatment at the correct time in the disease course.

Despite these advances, challenges remain. Approximately 40% of patients who initially benefit from TNF-antagonists ultimately lose response.[6] While empiric dose optimisation or switching agents are pragmatic remedies to this problem,[7, 8] these interventions have not been applied in an evidence-based manner and are unlikely to be cost-effective.[9] This issue is of critical importance as several promising alternatives to TNF-antagonists have failed in late-stage development.[10–13] In most of Europe and Canada, the only TNF-antagonists accessible are adalimumab and IFX, while certolizumab is also available in the US. In the setting of secondary failure, out of class options apart from natalizumab, which is encumbered by the risk of progressive multifocal leukoencephalopathy, do not exist. Accordingly, the need for sound decision-making is imperative.

Therapeutic drug monitoring (TDM) offers a rational approach to the management of secondary failure.[14–20] This concept has gained momentum based primarily on data from observational studies.[5, 21–29] The evidence behind TDM-based clinical algorithms, and its role in clinical practice will be discussed. For a more detailed review of the pharmacokinetics (PK) of TNF-antagonists readers are referred to the article by Ordas *et al.*[30]

IMMUNOLOGY REVISITED: HUMORAL IMMUNE RESPONSES TO BIOLOGIC DRUGS

The immune system has developed, to perform a very specific and vital function-recognition of self from non-self. Generation of neutralising antibodies is essential to human survival. However, the creation of biologic drugs, such as monoclonal antibodies, is tasked with circumventing this paradigm, as these agents are foreign proteins.

During embryogenesis, the humoral immune response is programmed, based on environmental and genetic determinants, to sensitise or tolerize. B cell receptors bind to foreign soluble or cell-surface antigens.[31] Antigen recognition drives clonal selection; cells with the greatest binding affinity to foreign antigens proliferate.[32] This process is followed by production of high-affinity antibody that has the capacity to reduce efficacy of bioengineered drugs. Sensitization is a limitation to biologic therapy and is a process that is not easily reversed. Antibodies to recombinant insulin, growth hormone, granulocyte-macrophage colony-stimulating factor, factor VIII, erythropoietin and interferon develop, even though these molecules are 'fully human'.[33] Anti-drug antibodies (ADAs) are associated with increased drug clearance and secondary failure.[33] Consequently, in many clinical settings, measurement of ADAs and drug concentrations are now used to guide therapy.[33]

TNF-antagonists are recombinant proteins that can induce humoral immune responses. It is well established that ADAs negatively affect both the PK and clinical efficacy of these agents.[34, 35] Patients with low drug concentrations due to either PK factors or sensitisation have worse outcomes than those with adequate drug levels.[22, 24] Based on this reality, the role of TDM has potential for the management of TNF-antagonist therapy.

DRUG AND ANTIBODY TO INFLIXIMAB ASSAYS

Several methods are available for measuring IFX and antibodies to infliximab (ATIs). The most common is an enzyme-linked immunosorbent assay (ELISA) in which a plate-bound 'capture antigen' is used to detect either IFX or ATIs. However, this approach is insensitive for measuring ATIs since IFX in the serum competes with the detection moiety. Hence, ELISA ATI assay results are reported as 'inconclusive' when IFX is detected in the serum sample.[5, 24] In contrast, the high pressure liquid chromatography (HPLC)-based mobility-shift-assay (HMSA) incorporates an acid dissociation step that separates serum drug/ATI complexes and then quantifies drug and ATI concentrations independently.[36] This process eliminates inconclusive test results. A third method uses a liquid phase radio-immune assay in which serum is incubated with soluble radiolabelled capture antigen. Following the addition of an anti-Fc antibody and centrifugation, the IFX-TNF-anti-Fc complexes precipitate. The IFX concentration is estimated by measuring radioactivity in the precipitant.[37] Although high concentrations of IFX can interfere with ATI detection, the

IFX-ATI complex can be separated from the capture moiety using chromatography columns coated with anti-lambda light chains.[37]

Although these assays measure the same parameters, correlations between tests have not been reported. Variability is presumably greater for measurement of ATIs than for drug concentrations as ATIs consist of a group of similar but not identical proteins.

For a more detailed review of these methodologies, see the supplementary materials section.

USE OF TDM IN PRACTICE

The use of TDM has the potential to revolutionise patient management. However, before TDM becomes widely established in practice, several fundamental questions must be answered.

WHAT IS THE RELEVANCE OF AN ADEQUATE DRUG CONCENTRATION?

Baert et al.'s pivotal observation that higher IFX concentrations are associated with greater efficacy[25] in patients receiving induction therapy for Crohn's disease (CD) laid the foundation for understanding the relationship between the PK of TNF-antagonists and clinical efficacy. Since then, corroborating evidence for this concept has steadily accumulated from retrospective analyses of multiple clinical trials[4, 5, 29, 38] and case series of patients with both ulcerative colitis (UC) and CD.[22, 24]

Maser et al. evaluated the relationship between IFX trough concentrations, ATIs and clinical efficacy in a retrospective cohort study of CD patients who were treated with either scheduled or episodic maintenance therapy.[22] They observed that clinical remission was maintained over 100% of the postinfusion interval in patients with an inconclusive ATI status, (meaning that IFX was present in the sample); 66% of the interval in patients with detectable antibody; and 67% of the postinfusion period for antibody-negative patients with undetectable trough levels ($P < 0.01$). Similarly, in the SONIC trial[5] patients with inconclusive antibody results were more likely to be in corticosteroid-free remission at week 26 and 50 than patients who tested either positive or negative for ATIs. A *post hoc* analysis of the week-14 IFX serum concentrations from ACCENT I reported higher IFX trough concentrations in patients with sustained response compared with nonresponders (4.0 μg/mL and 1.9 μg/mL respectively, $P = 0.03$).[39] Collectively, these findings, which strongly indicate that detectable drug at trough is associated with greater clinical efficacy, have important clinical implications for IFX therapy. Specifically, patients with low IFX trough concentrations may experience loss of efficacy as a result of insufficient drug exposure due to causes other than sensitization.

A similar relationship has been observed in patients with UC.[24] In a retrospective cohort study, clinical outcomes were independent of ATI status in patients who received scheduled maintenance therapy (Figure 1a).[24] Importantly, the presence of detectable drug at trough was associated with higher clinical and endoscopic remission rates and lower colectomy rates (Figure 1b). Using the more sensitive HPLC based HMSA, a trough IFX concentration of 2 μg/mL was more discriminant for predicting efficacy than the previous ELISA-based criterion of any detectable drug.[40] Similarly, a *post hoc* analysis of the ACT 1 and ACT 2 trials that evaluated patients with moderate to severe UC, revealed that higher serum IFX levels were associated with greater rates of remission, response and mucosal healing.[27]

One cautionary note should be expressed regarding the strong associations between higher drug trough concentrations and better clinical outcomes. Causation cannot be inferred from observational data as other confounding factors may be responsible. Nevertheless, these observations suggest that measurement and optimization of serum drug concentrations might result in greater efficacy.

WHEN IS THE OPTIMUM TIME TO MEASURE DRUG CONCENTRATIONS?

A validated PK model should allow accurate prediction of drug concentrations throughout treatment. Unfortunately, the existing models predict the PK of IFX for populations of patients,[41–43] not individuals. For predictive models to be robust determinants of PK must be precisely defined. Fasanmade et al. reported a larger volume of IFX distribution with increased body weight, while low serum albumin and ATIs correlated with greater IFX clearance.[42] Although the authors generated a model that explained 37.7% of the variability in IFX clearance,[41] it is not sufficiently predictive for clinical use. Intensive PK sampling in a large cohort of patients is necessary to further develop such a model.

Serum samples have usually been drawn at one of two time points. Most commonly trough concentrations, taken immediately before the next treatment (generally 8 weeks post-infusion), have been evaluated. However, data based on week-4 samples have also been reported[25] in trials of episodic dosing, in which trough sampling is not easily predefined.[17] Recently, Yamada et al. reported that patients with secondary failure had lower serum IFX

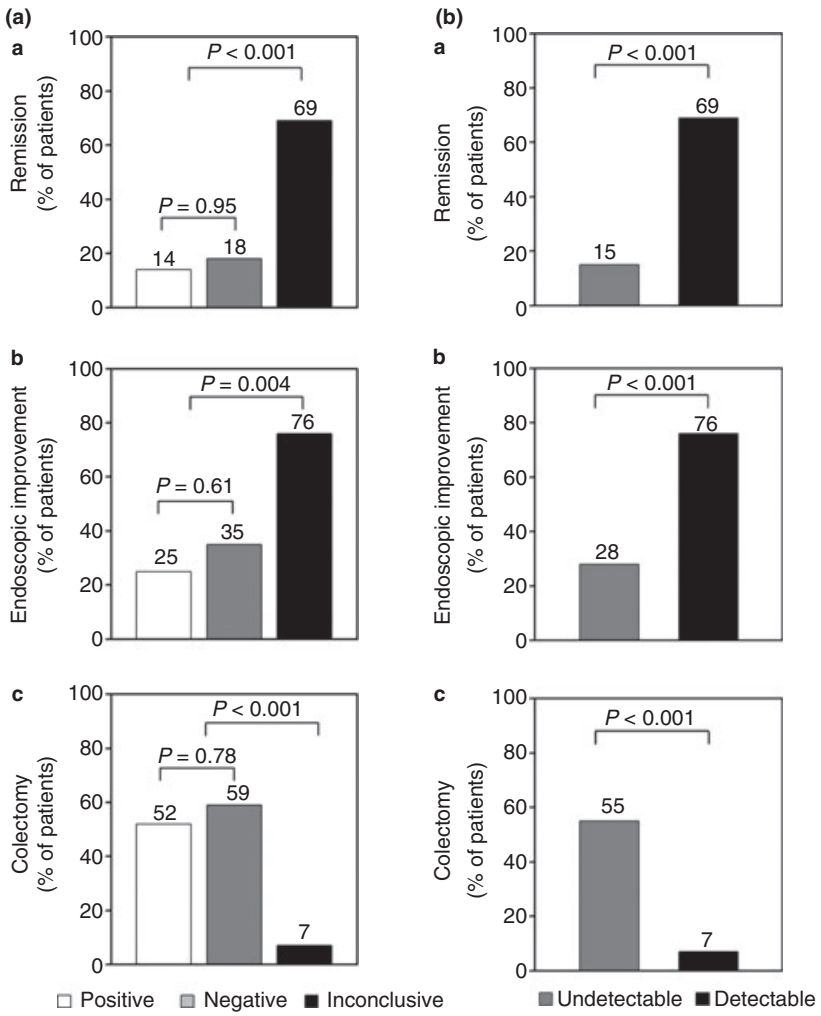

Figure 1 | (a) Clinical outcomes according to antibody to infliximab status.[24] In patients with inconclusive antibody status, clinical remission and endoscopic improvement occurred more frequently, while colectomy occurred less frequently than in patients with positive or negative antibodies. (b) Clinical outcomes according to the presence and absence of detectable trough serum infliximab concentration.[24] Clinical remission and endoscopic improvement occurred more frequently, while colectomy occurred less frequently in patients with detectable antibodies compared to patients with undetectable antibodies. Reprinted with permission from *Gut*.

concentrations immediately following an infusion than continuous responders (126.3 vs. 149.5 μg/mL, $P = 0.04$). This difference was attributed to antibody-mediated drug clearance, and suggesting that post-infusion IFX concentrations may be useful for dose optimization.[44] This approach has not been used consistently in trials or practice. The relative merits of these approaches to sampling have not been evaluated.

WHAT IS THE RELEVANCE OF IMMUNOGENICITY?

In 2003, Baert et al. reported the results of an open-label cohort study of 125 consecutive patients with either luminal or fistulizing CD.[25] After single-dose (luminal CD) or three-dose (fistulizing CD) IFX induction therapy, patients were followed until relapse, at which time a 5 mg/kg dose of IFX could be re-administered. Three key observations came from this study. First, the presence of high-titre ATIs inversely correlated with time to relapse (Figure 2a). Patients with low concentrations of ATIs (<8 μg/mL) had significantly longer median time to relapse than those with high (≥8 μg/mL) concentrations (71 days and 35 days respectively, $P < 0.001$). Second, the serum IFX concentration 4 weeks post infusion predicted time to relapse. Patients with IFX concentration ≥12 μg/mL had significantly longer median times to relapse than those with lower concentrations (81.5 days

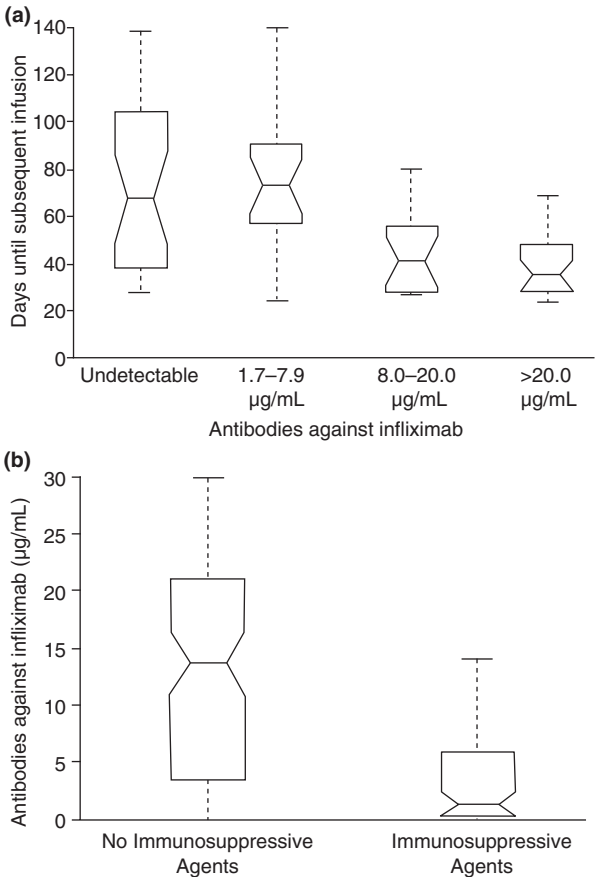

Figure 2 | (a) Duration of response according to the concentration of antibodies against infliximab before an infusion.[25] The median duration of response differed significantly ($P < 0.001$) between patients with infliximab titres greater and less than 8.0 μg/mL. (b) Relationship between concentration of antibodies against infliximab and the use of immunosuppressive therapy.[25] Concentrations of antibodies to infliximab were significantly lower ($P < 0.001$) among patients who were taking immunosuppressive therapy. Reprinted with permission from the *New England Journal of Medicine*.

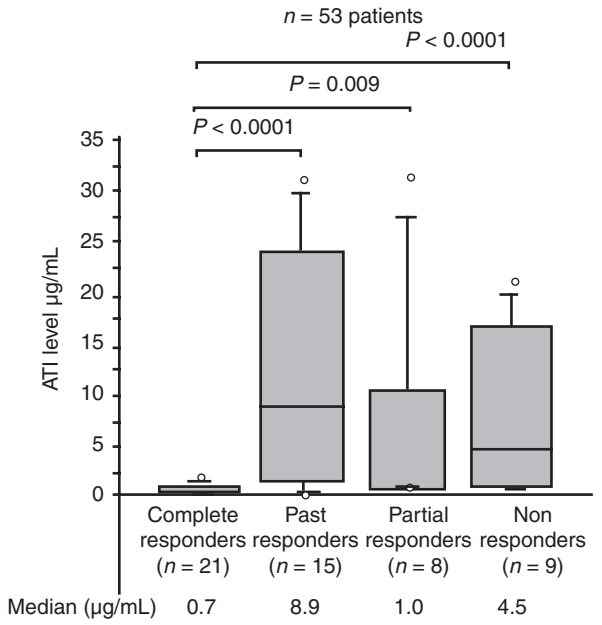

Figure 3 | Antibody concentration and response.[45] ATI, antibody to infliximab. The antibody to infliximab levels were significantly higher in past responders (8.9 μg/mL, $P < 0.0001$), partial responders (1.0 μg/mL, $P = 0.009$) and nonresponders (4.5 μg/mL, $P < 0.0001$), compared to continuous responders (0.7 μg/mL). Reprinted with permission from *Gastroenterology*.

and 68.5 days respectively, $P < 0.01$). Third, in episodically dosed patients, concomitant immunosuppression with AZA independently increased the likelihood of week-4 drug concentrations of ≥12 μg/mL (Figure 2b).[25]

Subsequently, Farrell et al.[45] examined the relationship between ATIs and clinical efficacy in a retrospective analysis of 53 patients treated episodically with IFX (Figure 3). Continuous responders had lower median trough ATI concentrations than patients with secondary failure (0.7 and 8.9 μg/mL respectively, $P < 0.0001$). In multivariate analyses, scheduled maintenance dosing (<8 weeks between infusions) and concomitant immunosuppression independently protected against the development of ATIs. A follow-up, double-blind, placebo controlled, single centre randomised controlled trial, demonstrated that pre-infusion administration of 200 mg of hydrocortisone reduced the proportion of patients with ATIs (26% and 42%, respectively, $P = 0.06$) and the median ATI concentration (1.6 and 3.4 μg/mL, $P = 0.02$) compared with placebo. Notably, in Baert et al.[25] and Farrell et al.[45] studies, most patients received single dose induction therapy, in contrast to a three-dose regimen, and were treated episodically rather than with scheduled maintenance therapy.

A *post hoc* analysis of the ACCENT I study,[28] in which continuous maintenance therapy was administered, found no relationship between clinical efficacy and ATIs. Response and remission rates were similar with detectable antibodies and with negative tests (64% vs. 62%, $P = 0.35$ for response and 41% vs. 39%, $P = 0.76$ for remission). Although the proportion of patients with detectable antibodies in this trial was only 16% by week-72, the dose escalation design resulted in many inconclusive tests attributable to the presence of detectable serum drug levels. Again, concomitant immunosuppression was

associated with lower rates of ATI formation. As ACCENT I patients assigned to placebo who failed therapy were allowed retreatment with IFX, a valuable observational comparison between scheduled and episodic dosing was possible. Patients in the scheduled maintenance therapy group were considerably less likely to develop ATIs than those who received intermittent therapy (8% vs. 30%; odds ratio, 0.21; 95% confidence interval, 0.13–0.36; $P < 0.0001$).[28] Although these results provided evidence that scheduled treatment is associated with lower rates of sensitization, aggressive dose intensification may have obscured the negative effects of antibody formation.

Vital data regarding the role of AZA for preventing ATIs in the setting of continuous therapy were provided by the SONIC trial.[5] In this study, which did not allow dose escalation, an inverse relationship was demonstrated between co-administration of AZA and the rate of ATI formation. Median trough IFX levels were higher in patients treated with combination therapy compared with monotherapy (3.5 μg/mL vs. 1.6 μg/mL, $P < 0.001$ at week-30), and the presence of trough IFX was associated with a trend to greater corticosteroid-free remission rates (Figure 4).

Similarly, the role of methotrexate (MTX) in the prevention of ATIs was evaluated in the COMMIT trial[38] in which patients with active CD were treated with IFX and corticosteroid induction therapy. In addition, they were randomly assigned to receive placebo or MTX. Compared to patients who received placebo, those randomised to the use of concomitant MTX were less likely to develop ATI (4.0% vs. 20.4%, $P = 0.01$), had a higher median trough serum IFX concentrations (6.35 mg/mL vs. 3.75 mg/mL, $P = 0.08$), and were more likely to have detectable drug at trough (25.9% vs. 14.0%, $P = 0.13$).

Recent work has expanded our understanding of the importance of ATIs in clinical practice. A multicentre prospective cohort study,[26] demonstrated that week-4 serum IFX concentrations were predictive of the development of high-titre ATI (>8 μg/mL). These investigators generated a clinical prediction rule based on week-4 IFX concentrations: values <4 μg/mL had a positive predictive value of 81% for the subsequent development of high-titre ATIs. Conversely, values >15 μg/mL had an 80% positive predictive value for the future absence of ATIs. These observations have not been prospectively evaluated to confirm a causal relationship. Nevertheless, they suggest drug monitoring with dose intensification for low serum concentrations may protect against sensitization and secondary failure. However, patients with transiently detectable ATIs may have a different prognosis than those with a persistent response. A recent study that evaluated 53 patients with ATIs, reported persistence of ATIs over time in 72% of patients which conferred a twofold risk of infusion reactions. In the 28% of patients with transient ATIs, antibodies resolved following dose optimization in 20% of individuals and spontaneously in the remaining patients. The authors concluded that dose intensification may overcome ATI formation.[46] In a recent analysis of 2021 serum samples using the HPLC assay, detection of any ATIs was associated with a higher likelihood of active disease, as measured by an increase in C-reactive protein (CRP).[47] Conversely, adequate serum IFX concentration were associated with CRP-defined remission.[47] In a multivariate regression analysis, detection of ATIs was independently associated with increased disease activity even in the presence of adequate drug concentrations.[47] These findings suggest that empiric dose escalation may not overcome sensitization.

In summary although regression of ATIs has been observed, both spontaneously and following dose intensification, these antibodies generally persist[46] and are associated with worse outcomes.[26] Although some studies have reported better prognosis with low-titre ATI, these conclusions are generally based on abstracts with a small number of patients. Although further research is required, it does not seem biologically plausible to overcome sensitization in the absence of a formal tolerization regimen. Accordingly, prevention of ATIs is a prudent strategy. Scheduled dosing of IFX, use of hydrocortisone prior to IFX infusions, co-administration of an immunosuppressant,[5, 28, 38, 45] and potentially maintenance of adequate serum IFX concentration, are effective measures for prevention of ATIs.

TDM IN THE CLINIC: CAN THESE OBSERVATIONS BE PUT IN TO PRACTICE?

In 2010, investigators at the Mayo Clinic published their initial experience with TDM.[21] In this retrospective analysis, the majority of patients (82%) received three induction infusions followed by scheduled maintenance therapy. Forty-nine percent of the tests (110 tests in 76 individuals) were performed for secondary failure. In patients with subtherapeutic drug concentrations, dose intensification with IFX was superior to switching to another TNF-antagonist (86% vs. 33% response, $P < 0.02$). However, in patients with detectable ATIs, switching to agents was superior to dose escalation (92% vs. 17% response, $P < 0.004$). Although this study had

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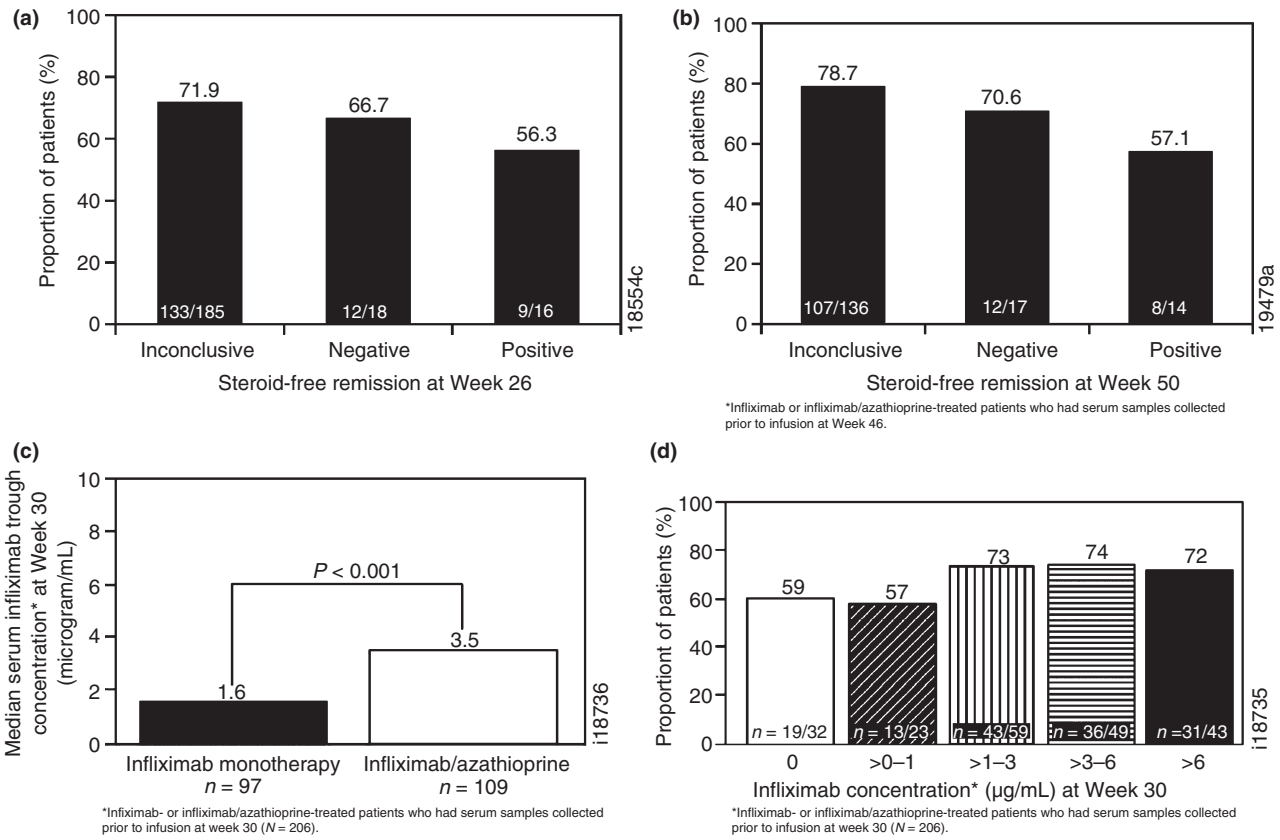

Figure 4 | (a and b) Presence of antibodies and remission.[5] (a) Patients with positive antibodies to infliximab at week 30, were less likely to achieve corticosteroid-free remission (56.3%) at week 26 compared to those with negative (66.7%) and inconclusive (71.9%) antibody status. (b) Patients with positive antibodies to infliximab at week 46, were less likely to achieve corticosteroid-free remission (57.1%) at week 50 compared to those with negative (70.6%) and inconclusive (78.7%) antibody status. (c and d) Presence of infliximab and remission.[5] (c) Median serum infliximab concentrations at week 30 were higher in patients on combination therapy. (d) Proportion of patients achieving corticosteroid-free remission at week 26 stratified by median trough infliximab concentration at week 30. Reprinted with permission from the *New England Journal of Medicine*.

an imprecise definition of response, these results are consistent with the following concepts: (i) Switching to a second TNF-antagonist in patients who have responded but are sensitised to the first TNF-antagonist is highly effective. (ii) Patients with inadequate serum drug levels without sensitization may benefit from dose intensification.

Additional support for this concept came from a cohort study conducted in patients with rheumatoid arthritis.[48] Patients who were sensitised following initial treatment with IFX or adalimumab, had a similar response to etanercept as TNF-antagonist naïve individuals. However, response to the second TNF-antagonist was significantly lower in patients without ADAs, implicating non-ATI mediated mechanisms of increased clearance or possibly non-TNF mediated disease processes.

Table 1 | Clinical management based on therapeutic drug monitoring[48]

	Antibody to IFX negative	Antibody to IFX positive
IFX less than threshold	Increase dose	Switch agent (within class)
IFX greater than threshold	Re-evaluate for active disease	Switch agent (out of class)

IFX, infliximab.

These studies have formed the basis of the management paradigms used in clinical practice (Table 1).

However, another retrospective study that examined the value of TDM-based decision making in 76 patients

reached different conclusions.[23] In this trial, three possible interventions occurred following secondary failure. Patients had no change in therapy, the dose of IFX was increased, or the patient was switched to adalimumab. Patients who underwent changes in therapy had higher response rates than individuals without treatment modification. However, the conclusions of the Mayo Clinic study were not confirmed. Patients who underwent dose intensification improved irrespective of ATI status (6 of 10 ATI-positive compared to 21 of 29 ATI-negative patients, $P = 0.54$). Most surprisingly, ATI concentrations were reduced in three patients, and eliminated, in two individuals, following dose intensification. However, these data need to be interpreted with caution as the number of patients evaluated was relatively small. In addition, patients with secondary failure with therapeutic IFX concentrations did not undergo imaging to confirm disease activity.

EMERGING TREATMENT ALGORITHMS BASED ON THE BEST AVAILABLE EVIDENCE

The current observational data offer clinicians a framework upon which sensible clinical decisions can be made. Presently, the most compelling application of TDM is in the evaluation of secondary failure to IFX.[21] In this situation, many potential underlying causes are possible. Physicians may elect to dose intensify, change TNF-antagonist, or switch to an out-of-class agent. Several algorithms, based on expert opinion, are emerging to guide clinical decision making. These algorithms feature endoscopy, ATI-guided and symptom-guided approaches.

These three approaches share several features. Each algorithm begins by evaluating symptomatic patients for objective evidence of active disease and eliminating alternative diagnoses with serum and faecal biomarkers, and selective use of cross-sectional imaging. In addition, trough samples are used to assess drug and ATI concentrations to employ TDM-based decision making.

In TDM-guided decision-making, serum IFX and ATIs concentrations classify patients into three categories. Group 1 consist of patients with high-titre ATIs and low drug levels at trough. These individuals are sensitised to IFX and should be switched to another TNF-antagonist. In jurisdictions with limited access to TNF-antagonists, an argument might be made for arbitrary dose optimisation.[23] Patients with adequate trough concentrations comprise the second group. These individuals are unlikely to respond to dose intensification as their inflammatory process may not be mediated by TNF-related mechanisms. Physicians may consider switching to out-of-class agents, if available. In the absence of such an agent, adding AZA if not already prescribed, switching immunosuppressive agents, adding corticosteroids, or surgery are alternative options. Dose intensification is recommended for a third group of patients with low drug levels without detectable antibodies. The specific dose optimization strategy is dependent on the timing of symptom onset. Patients who initially respond to an infusion with relapse prior to the next dose generally benefit from shortening of the dosing interval. Alternatively, patients with an attenuated response following an infusion may benefit from higher doses of IFX. Treatment intensification should be followed by repeat TDM evaluation to verify that the intervention has resulted in therapeutic drug concentrations. In patients who fail to recapture clinical response, this care path is reapplied.

Despite these similarities, the three algorithms differ substantially in the application of these principles. The endoscopy-guided algorithm is a modification of the proposal by Ben-Horin and Chowers (Figure 5a).[14] According to this model, symptomatic patients routinely undergo endoscopy. The TDM-guided care path is applied based on endoscopic findings in addition to clinical response.

In contrast, the ATI-guided algorithm (Figure 5b) restricts endoscopy to patients with symptoms in the setting of therapeutic IFX levels. In this instance, the TDM-guided care path suggests no benefit from further TNF-antagonist therapy. As there are limited therapeutic options available for these patients, endoscopy serves as a gold standard to establish active disease. The cost-effectiveness of this algorithm was evaluated in a decision analysis made of a hypothetical cohort with secondary failure to IFX. The testing based algorithm resulted in better outcomes, at less cost, than empiric dose intensification and switching within class.[9] Although these findings need confirmation by prospective studies, they strongly suggest that TDM is cost-effective in the management of CD.

Finally, the symptom-guided approach is based on patterns of response to treatment (Figure 5c). Patients are classified into one of three categories: (i) patients with no worsening throughout the entire infusion interval do not require TDM, (ii) patients who initially respond to the infusion but subsequently develop worsening symptoms before the next dose and (iii) patients who are no longer responding to infusions and remain symptomatic throughout the infusion interval. Based on the literature previously reviewed, this algorithm assumes that Group 2 has subtherapeutic drug concentrations at

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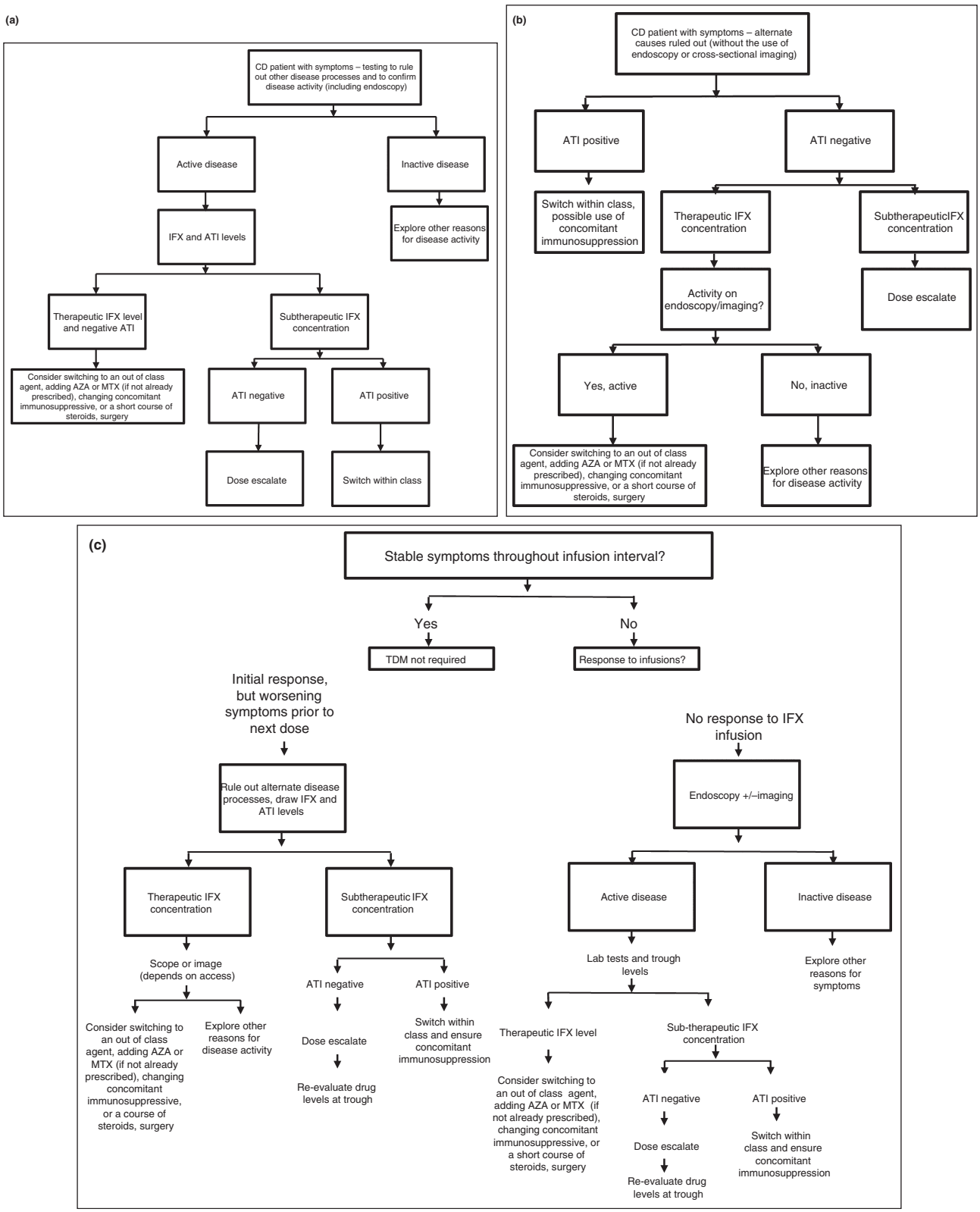

Figure 5 | (a) A conventional approach to therapeutic drug monitoring, using endoscopy as the gold standard. (b) Antibodies to infliximab-guided decision. (c) Response-guided decision for secondary failure. CD, Crohn's disease; IFX, infliximab; ATIs, antibodies to infliximab; AZA, azathioprine; MTX, methotrexate; TDM, therapeutic drug monitoring.

trough, and that Group 3 has high-titre ATIs. In Group 2, the TDM care path is applied, and similar to the ATI-guided algorithm, only patients with adequate drug concentrations at trough undergo endoscopy. In Group 3, the order of events is different. A higher probability exists that a process other than active disease is responsible for their worsening symptoms. As such, similar to the endoscopy-guided algorithm, endoscopy is performed upfront. Patients with inactive disease on endoscopy and imaging are investigated for non-IBD processes, whereas patients with active disease are suspected to have high-titre ATIs and TDM is performed.

Each of these algorithms advocates for the use of TDM to direct rational, evidence-based decision making, while optimising health care resources. The endoscopy-based algorithm assesses patients for the presence of mucosal inflammatory lesions, prior to initiating TDM. This algorithm has the advantage of objectively measuring disease activity and response. It rules out alternative diagnoses, and tailors options based on the individual patients' results. However, it is resource intensive, which may make it impracticable in some jurisdictions and has the potential to delay definitive management while testing is completed.

In contrast, the symptom-based algorithm conserves resources by separating patients into three groups. Although this algorithm stratifies patients to isolate those that are most likely to benefit from TDM, it depends on population based assumptions regarding drug response. While this strategy minimises resource utilisation, it also minimises the amount of objective data acquired and does not capitalise on TDM to optimise care at the individual patient level.

The ATI-based algorithm strikes a balance between making decisions on the basis of objective data and the efficient use of resources. Patients with evidence of active disease, based on serum and faecal inflammatory biomarker testing, undergo TDM to determine the most appropriate management option. Only patients with specific indications undergo endoscopic or imaging studies. Each of these strategies has inherent benefits and limitations. While further research is required to determine the optimal strategy, access to resources may dictate the strategy that an individual practitioner employs in the interim.

OTHER INDICATIONS FOR TDM

Potential value for TDM may exist in indications other than secondary failure. These include assessment of adherence, evaluation of patients with infusion reactions and reintroduction of IFX after prolonged interruption of therapy. However, measurement in these situations will seldom be helpful in clinical decision-making and are discussed in the supplementary information.

PREDICTIVE MODELS IN INDIVIDUAL PATIENTS

The large inter-patient heterogeneity in the PK of TNF-antagonists has been attributed to variations in body mass index, serum albumin level, concomitant use of immunosuppressive therapy, severity of inflammation and disease type.[30] Generation of predictive models for individual patients would permit dose optimization. Challenges to the development of such models include defining thresholds for serum IFX and antibody concentrations that are associated with clinical outcomes. Thresholds have been variably defined in studies, and generally reflect the detection level of the assay used.[17] We refer the reader to the supplementary materials for a description of the studies that have attempted to define predictive thresholds.

CONCLUSIONS

Tumour necrosis factor-antagonists have an important role in the management of IBD. As understanding of PK of these agents evolves new therapeutic algorithms for their use will develop. It is now established that the development of ATIs and low serum drug concentrations are associated with worse clinical outcomes. As current treatment options in TNF-antagonist failures remain limited, emphasis has been placed on rational decision-making based on TDM. Although evidence from prospective controlled trials that definitively demonstrate the benefits of TDM in IBD is lacking, acceptance of its value in clinical practice is increasing.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Measurement of antibodies to infliximab (ATI) via enzyme-linked immunosorbent assay (ELISA).

Figure S2. Homogenous Mobility Shift Assay (HMSA).

Figure S3. Radio-immuno assay (RIA) for infliximab.

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