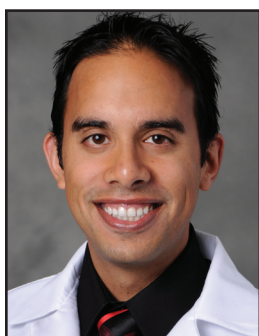
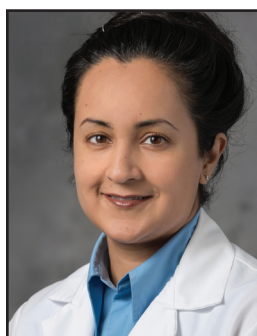


Seymour Katz, M.D., Series Editor

Therapeutic Drug Monitoring in Inflammatory Bowel Disease: A Practical Guide



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Tumor necrosis factor – alpha (TNF- α) antagonist therapy is highly effective for the treatment of Crohn’s disease and ulcerative colitis, broadly termed inflammatory bowel disease (IBD). While this class of medication has revolutionized the field of IBD therapy, 40% of patients lose response within one year of treatment. Therapeutic drug monitoring has emerged as a method to optimize treatment with TNF- α antagonists by guiding treatment decisions, increasing the long term durability of the medications, and maximize the likelihood of a sustained clinical benefit when performed appropriately. Therapeutic drug monitoring with TNF- α antagonists involves measuring serum drug levels and anti-drug antibodies, and maintaining drug levels within a specific therapeutic window. The aim of this review is to provide a comprehensive and practical approach for performing therapeutic drug monitoring for infliximab and adalimumab in patients with IBD.

BACKGROUND

Tumor necrosis factor – alpha (TNF- α) antagonist therapy is highly effective for the treatment of Crohn’s disease and ulcerative colitis, broadly termed inflammatory bowel disease (IBD). While this class of medication has revolutionized the field of IBD therapy, up to 30% of patients show no benefit when treated with a TNF- α antagonist, and another 40%

lose response over time within one year of treatment.¹ Therapeutic drug monitoring has emerged as a method to optimize treatment with TNF- α antagonists by guiding treatment decisions, increasing the long term durability of the medications, and maximizing the likelihood of a sustained clinical benefit with significantly fewer occurrences of secondary loss of response.²

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Therapeutic drug monitoring with TNF- α antagonists involves measuring serum drug levels and anti-drug antibodies, and maintaining drug levels within a specific therapeutic window. The concept of therapeutic drug monitoring is not new, and is applied to solid organ transplant patients receiving immunosuppression with medications such as cyclosporine or tacrolimus, and to septic patients receiving antibiotics such as vancomycin and gentamycin.^{3,4} The main principle of therapeutic

drug monitoring is to maintain patients within a specific therapeutic window, as high concentrations of drug may result in increased toxicity, low concentrations will be ineffective, and for TNF- α antagonists, low concentrations risk resulting in drug antibody formation as well.²

The TNF- α antagonists for which multiple studies have demonstrated the benefit of therapeutic drug monitoring in IBD include infliximab and adalimumab. Studies date back to 2003, and delineate that higher serum concentrations of infliximab and adalimumab are associated with more durable response, sustained clinical outcomes, decreased need for colectomy, and improved patient outcomes.⁵⁻⁸

Numerous studies have shown that higher serum drug concentrations of TNF- α antagonists are associated with improved patient outcomes.² Furthermore, studies have also demonstrated that low or undetectable drug concentrations are linked to anti-drug antibody formation and are ineffective for achieving clinical remission.⁹⁻¹²

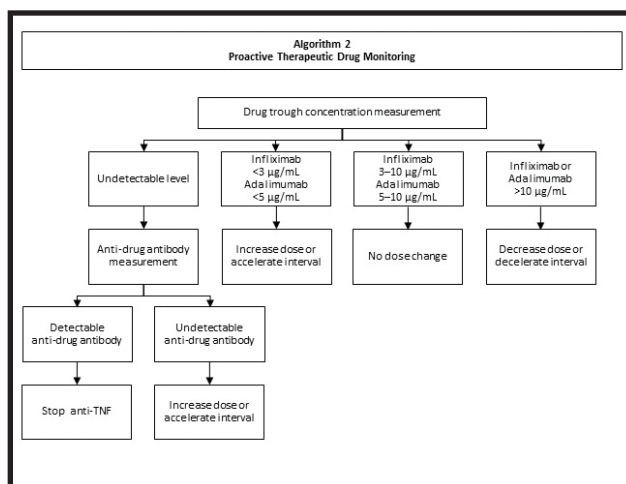
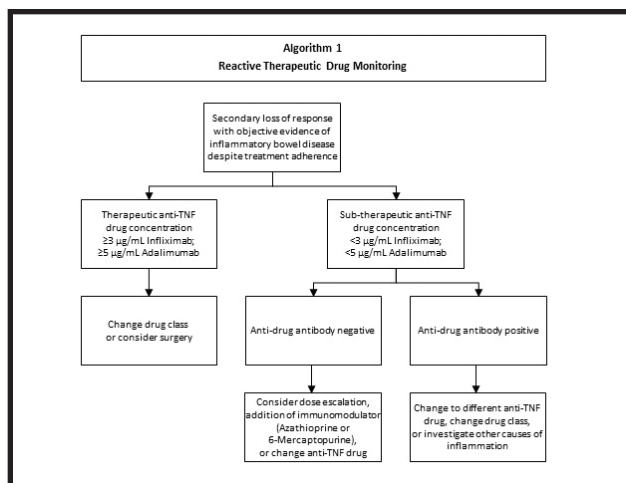
Types of Assays

Many different anti-drug antibody assays are available, and the detection of these antibodies is more variable than serum laboratory assays for drug concentrations. The available types of assays include the Enzyme-Linked Immunosorbent Assay (ELISA), Radioimmunoassay (RIA), Homogeneous Mobility Shift Assay (HMSA), Electro-chemi-luminescence immunoassay (ECLISA), and Functional assay. The ELISA and RIA anti-drug antibody assays are affected by the presence of drug, and these assays can give inaccurate results if there are drug concentrations present in the serum. The antibody assays that are not affected by the drug levels, termed drug-tolerant assays, are more expensive.¹³

How is Drug Monitoring Utilized in Clinical Practice?

Therapeutic drug monitoring can be performed reactively or proactively. Reactive testing involves testing the patient at the time of disease relapse or after a drug reaction has occurred. Proactive testing involves optimizing the dose of the drug within a therapeutic window to achieve clinical efficacy.¹

Serum drug levels are measured as trough levels, as most studies of anti-TNF- α drug levels have tested trough levels, and as drug trough levels roughly correlate with activity of most drugs. The drug trough level is



measured prior to intravenous infusion of infliximab, or prior to subcutaneous injection of adalimumab. Serum drug levels (non-trough) are generally measured during the maintenance phase of treatment for patients, after the induction phase.¹

Algorithm 1 is a reactive testing algorithm, and this algorithm delineates steps to take if faced with a patient with worsening inflammatory bowel disease while on maintenance dosing of infliximab or adalimumab. These patients have demonstrated objective evidence of continued inflammation with elevated C-reactive protein (CRP) levels, fecal calprotectin levels, abnormal imaging studies, and/or endoscopy corroborating persistent inflammation secondary to inflammatory bowel disease despite adherence to infliximab or adalimumab.

The steps are as follows: first, a drug trough level is measured. If the patient has a therapeutic trough level as defined by a serum infliximab concentration > 3

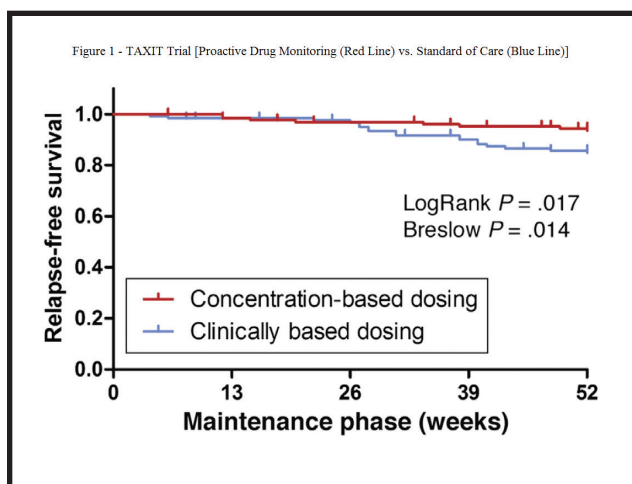


Figure 1. Red Line – Proactive Concentration Based Dosing
Blue Line – Clinically Based Dosing

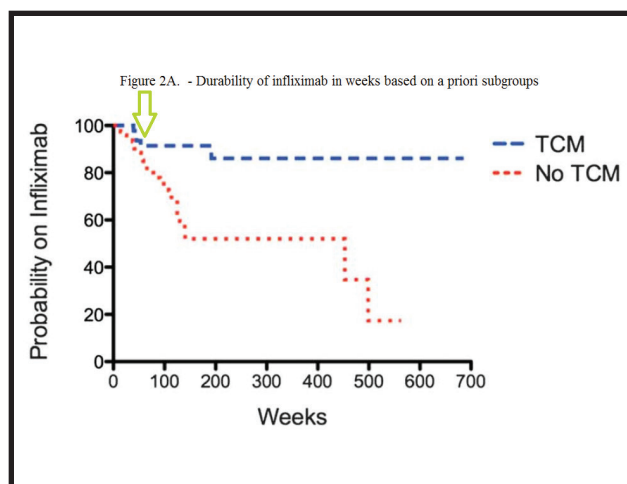


Figure 2a. TCM (Therapeutic Concentration Monitoring)
Blue Line – Patients with proactive therapeutic concentration monitoring.
Red Line – Patients without therapeutic concentration monitoring.
Green Arrow – Time point 1 year.

$\mu\text{g/mL}$ or adalimumab concentrations $> 5 \mu\text{g/mL}$, this patient should be switched to a different drug class with a separate mechanism of action or surgical intervention should be considered. If the patient has a sub-therapeutic drug trough concentration as defined by a serum infliximab concentration $< 3 \mu\text{g/mL}$ or adalimumab concentration $< 5 \mu\text{g/mL}$, this patient should have an anti-drug antibody level measured, and most assays will perform this testing. If the anti-drug antibody level is negative, the patient will benefit from an increase in the dose of drug, acceleration of the interval between infusions, addition of an immunomodulatory medication, or transition to a different anti-TNF- α agent. If the patient has an anti-drug antibody level that is positive, the patient should be switched to a different anti-TNF- α agent or a different drug class; other causes of persistent inflammation should be investigated as well.

Reactive testing has been shown to be more cost effective than empiric dose adjustments, and it allows clinicians to understand if a patient is likely to benefit from dose escalation, or if the patient should be switched to another drug class altogether.

Currently, there are no guidelines when therapeutic drug monitoring should be performed, but the BRIDGE group (Building Research in IBD Globally) has issued the following recommendations: therapeutic drug monitoring should be conducted at the end of induction

in patients with primary non-response, for patients with secondary loss of response, for patients who are on maintenance therapy and who are responding, and for patients restarting treatment after a drug holiday. The utility of testing at the end of induction in patients who are already responding to anti-TNF- α therapy is uncertain.^{14,15}

Proactive Drug Monitoring

Proactive therapeutic drug monitoring entails optimization of drug to a specific therapeutic window. Proactive testing has been demonstrated to improve patient outcomes, and the available medical literature demonstrates benefits of proactive testing in the maintenance phase of treatment for patients.² A pilot observational study of 48 patients demonstrated that a proactive approach more frequently identified patients with low trough concentrations, and resulted in a greater probability of remaining on infliximab, increasing the long term durability of the medication. Proactive therapeutic monitoring has also been shown to improve symptom scores, CRP levels, and decreases the need for rescue therapy.¹⁶

Central to the proactive strategy for IBD is the TAxIT trial, which was a one year randomized controlled trial at a tertiary referral center including 263 adults. These patients were split into two groups,

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with medication dosing adjusted based upon clinical features (reactive) or trough concentrations of infliximab (proactive). At the start of the trial all patients were dose optimized to a drug concentration of 3-7 $\mu\text{g/mL}$, and then 123 of the patients had dosing adjusted based upon their clinical features and CRP levels, which is the current standard of care, and 128 patients had dosing adjusted during maintenance to a therapeutic window of 3-7 $\mu\text{g/mL}$.¹⁷

The primary outcomes for this trial were measured at one year. At that time, no significant difference was seen in the primary end point for this study (Figure 1), which compared clinical remission between the two groups, likely due to two reasons: (1) at the start of the study, all patients regardless of treatment group were dose optimized, and (2) these patients were only followed for one year. Notably, by the end of one year, the curves begin to separate, and one could infer that they would separate even further over time, with higher relapse-free survival in patients who underwent proactive therapeutic drug monitoring.¹⁷

A number of secondary endpoints in this trial favored proactive drug monitoring for patients receiving infliximab: (1) patients receiving proactive treatment did not need rescue therapy as often as the clinical group (7% vs 17.3%, $p = 0.004$); (2) more patients in the proactive group maintained trough concentrations within the therapeutic window (74% vs. 17.3%, $p < 0.001$); (3) fewer patients had undetectable trough concentrations (OR 3.7; $p < 0.001$); and (4) costs were similar between both groups.¹⁷

A separate study by Cheifetz and colleagues from the BridgeIBD group followed patients being treated with infliximab for more than ten years, with a goal therapeutic window between 5-10 $\mu\text{g/mL}$ (Figure 2A).¹⁶ Over time, proactive therapeutic drug monitoring maintained patients on infliximab for more than ten years, versus the patients undergoing reactive monitoring, many of whom appeared to demonstrate loss of response by ten years. In this same trial (Figure 2B),¹⁶ patients who attained a trough concentration of greater than 5 $\mu\text{g/mL}$ fared much better than those patients who had low levels of drug, or patients receiving the standard of care. Notably, by the end of ten years most of these patients had lost response to infliximab.^{14,16}

In clinical practice, algorithm 2 can be followed to proactively dose-optimize patients to a therapeutic

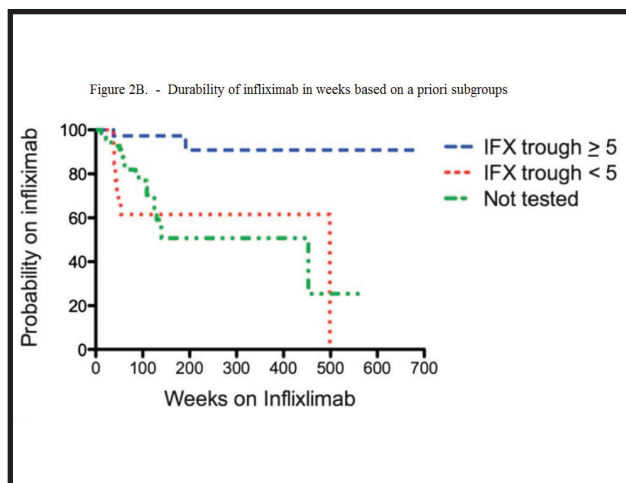


Figure 2b. IFX (Infliximab)

Blue Line – Patients with infliximab troughs proactively maintained $> 5 \text{ mg/mL}$

Red Line – Patients with infliximab troughs $< 5 \text{ mg/mL}$

Green Line – Patients with no therapeutic drug monitoring performed.

window for infliximab and adalimumab. The steps are as follows: first a trough concentration is measured. If the drug trough concentration is undetectable, and anti-drug antibody level should be measured. If the anti-drug antibody level is detectable, the patient's anti-TNF- α drug should be discontinued. If the anti-drug antibody is undetectable, the patient's dose of anti-TNF- α drug should be increased or the interval between doses should be accelerated. If the patient's drug trough concentration is sub-therapeutic, the patient's dose of drug should be increased or the interval between doses should be accelerated. If the patient has a therapeutic drug concentration of infliximab between 3-10 $\mu\text{g/mL}$ or adalimumab between 5-10 $\mu\text{g/mL}$, no dose adjustments are necessary. And lastly, if the patient has an infliximab or adalimumab concentration greater than 10 $\mu\text{g/mL}$, the dose of drug should be decreased or the interval between doses should be decelerated.¹⁴

The optimal therapeutic window is not completely known. Data exists for a goal trough of 3-7 $\mu\text{g/mL}$, while other data suggests a level of 5-10 $\mu\text{g/mL}$ for infliximab and adalimumab.¹⁴ During the maintenance phase for stable patients, for infliximab, a trough level of 5 $\mu\text{g/mL}$ or higher has been associated with clinical remission. For deep remission, a trough level of greater than 8 $\mu\text{g/mL}$ could provide benefit. For adalimumab, clinical remission was seen at or above a level of

5 µg/mL, and deep remission was seen at or above 8 µg/mL.^{8,17,21-26}

Since guidelines regarding therapeutic drug monitoring are not yet available, the optimal therapeutic windows are unknown; patients with particularly severe disease may warrant a higher therapeutic window than a patient with mild disease.

Contributing Clinical Factors

There are multiple factors that play into the pharmacology of monoclonal antibodies, particularly regarding clearance. The presence of anti-drug antibodies is associated with higher drug clearance and worsened clinical outcomes. Addition of an immune-modulator such as thiopurine or methotrexate has demonstrated benefit, by reducing anti-drug antibody formation and increasing drug concentrations. Factors associated with poor outcomes include severe disease, high CRP levels, low albumin, and higher baseline TNF-α concentrations. Furthermore, patients with severe disease demonstrated a faster rate of drug clearance, via proteolytic catabolism by the reticuloendothelial system.²⁷ Clearance is also increased in patients with higher body mass index and male gender.^{14,18}

Economic Considerations

Data strongly show that reactive drug monitoring is more cost-effective than empiric dose escalation. Reactive testing prevents over-prescribing high doses of biologics. One study calculated associated costs over the course of one year, and reactive testing was found to be approximately \$5,000 less per year than empiric dose escalation for patients. Moreover, the reactive testing in the algorithm previously provided allows for more accurate management for patients with secondary loss of response.²³

Another study that looked at costs of over-prescribing high doses of infliximab without drug monitoring found that costs to patients were reduced by 56% when reactive testing was performed, versus empiric dose escalation. Notably, the drug assay used was inexpensive and thus cost effective.²⁰

CONCLUSIONS

For practical use, the following is recommended: knowledge of the test performed by one's institution, whether the antibody assay is affected by drug concentrations, and the cost of testing would all be prudent. Understanding the therapeutic algorithms would increase the likelihood of improved outcomes and cost-effective care. Utilization of web-based resources to tailor therapy (<http://www.bridgeibd.com/anti-tnf-optimizer>) to optimize outcomes for patients would be ideal as well.

Reactive testing is clearly beneficial as has been shown herein. With more research and time, proactive testing may become more widely utilized. Consider proactive testing after induction and following patients at least once per year during maintenance to ensure they are within the therapeutic window and do not develop a secondary loss of response.

Questions that remain to be answered include: is there a safety benefit to dose-reduction for patients with supra-therapeutic drug levels? Should drug monitoring be individualized to each patient, or should therapeutic windows be generalized to specific patient populations? Should more aggressive disease phenotypes warrant higher therapeutic windows? As many of these assays involve significant cost, determination of appropriate utilization is paramount. And lastly but importantly, will assays be different for other biologic agents including novel therapies such as vedolizumab, ustekinumab and biosimilars? Further research will certainly be warranted to address these questions. ■

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