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Therapeutic Drug Monitoring of Biologics in Inflammatory Bowel Disease: What, When and Why?

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Therapeutic drug monitoring (TDM) of biologics in inflammatory bowel disease (IBD) is useful in various arenas of clinical practice. It involves the measurement of drug concentrations and anti-drug antibody levels to help optimize therapy. The most popular strategy now considered to be standard of care is 'reactive drug monitoring' which is done when the patient is symptomatic from their disease. Reactive TDM is both efficacious and cost effective when compared to empiric therapy changes. 'Proactive drug monitoring' is an emerging strategy that utilizes a target drug level, often early during an induction period, with adjustments in dosing prior to any development of symptoms. Additional uses of TDM include during de-escalation from combination therapy to biologic monotherapy and re-initiation of biologic therapy after a drug holiday. Prudent use of these assays is essential to reduce costs and avoid unnecessary testing.

INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal tract and has two subtypes, namely Crohn's disease (CD) and ulcerative colitis (UC). Immunosuppressive agents used in the treatment of IBD include corticosteroids, immunomodulators [thiopurines or methotrexate], biologic agents [anti-tumor necrosis factor alpha (anti-TNFs), anti-integrin therapies, anti-IL-12/23 inhibitors] and janus kinase inhibitors.

Biologic therapies in IBD are genetically engineered monoclonal antibodies targeted against inflammatory antigens. They have revolutionized IBD treatment and are considered as first-line therapy in moderate-severe IBD patients.[1,2] Despite their proven efficacy, almost 50% of biologics require discontinuation due to failure to respond to induction therapy (primary non-response), loss of response over time (secondary non-response) or serious adverse events.[3] The concept of therapeutic drug monitoring (TDM) refers to the practice of measuring drug concentrations and anti-drug

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antibodies to help guide treatment changes and optimize the use of biologics. This article will review recommendations from current guidelines and recent evidence on therapeutic drug monitoring of biologics in IBD.

Drug Assays in Practice

At present, therapeutic classes of biologics we can monitor in IBD include anti-TNFs biologics (infliximab, adalimumab, certolizumab pegol and golimumab) and other biologics (vedolizumab, ustekinumab). Drug assays measure drug concentrations and anti-drug antibody levels for individual biologics.[4] Drug concentrations show good correlation amongst assays when measured as trough levels, that is, as close to the next dose as possible within 24 hours.[5] Multiple factors both drug-related (route of administration, dose, inherent immunogenicity, presence of anti-drug antibodies, use of concomitant immunomodulators) and patient-related (such as sex, body mass index, albumin levels, CRP levels) affect the drug concentrations of biologics.[6] Low drug concentrations are associated with antibody development, loss of response and overall poor outcomes.[5] Higher drug concentrations have been associated with better outcomes and do not necessarily increase the risk of side effects. Anti-drug antibody levels are produced as an immune response to the biologic protein and is one of the major causes for loss of response to biologic therapy. Anti-TNFs are considered to be more immunogenic than other biologics.[7] Unlike drug trough levels, there is low agreement across assays on the levels of anti-drug antibody levels.[5] It is, therefore, important to check the reference ranges for the assay being used. There are a variety of commercially available assays for measurement of biologics. The choice of assay typically depends on what is available in the area of practice and insurance coverage. Trying to use of the same assay in practice allows one to become familiar with the reference ranges. Costs vary across various commercial assays and should be taken into consideration when these assays are being ordered.

Strategies for TDM in biologics

Over the years, the indications for TDM in biologics have evolved. Its two main uses are in reactive drug monitoring and proactive drug monitoring. Other indications for TDM are in de-escalation and re-initiation of therapy.

Reactive Drug Monitoring

Reactive TDM with biologic use in IBD is now well-established and is considered standard of care.[3,5,8,9] It refers to drug monitoring in a patient who is symptomatic from their IBD. This is done by checking drug level and anti-drug antibodies in a patient who is losing response to therapy, as defined by clinical symptoms or by an increase in biomarkers, and allows appropriate therapeutic intervention by either salvaging or switching of therapies.

- If drug trough levels are undetectable or low with no antibodies, intensification of therapy by increasing the dose or decreasing the interval would be appropriate. Adding an immunomodulator would also be beneficial in reducing immunogenicity and increasing drug levels. Low drug levels are often in the setting of a high inflammatory burden resulting in rapid drug clearance.

- If drug trough levels are adequate with or without presence of antibodies, it suggests a mechanistic failure of the drug. In other words, the biologic in use is not targeting the appropriate inflammatory pathway for this particular patient. Switching to another drug class of drug with a different mechanism would be the next step.

- If drug levels are undetectable or low with presence of antibodies, treatment options would be based on whether the antibody levels are low or high. Low antibody titers can be a transient phenomenon, and response may be recaptured with dose escalation or addition of an immunomodulator. If antibody titers are high, then either switching to another biologic within the same class or switching class altogether would be appropriate.

An algorithmic approach helps us to understand the role of reactive TDM and shift gears appropriately based on drug concentration and antibody levels (Figure 1).[10] Target trough

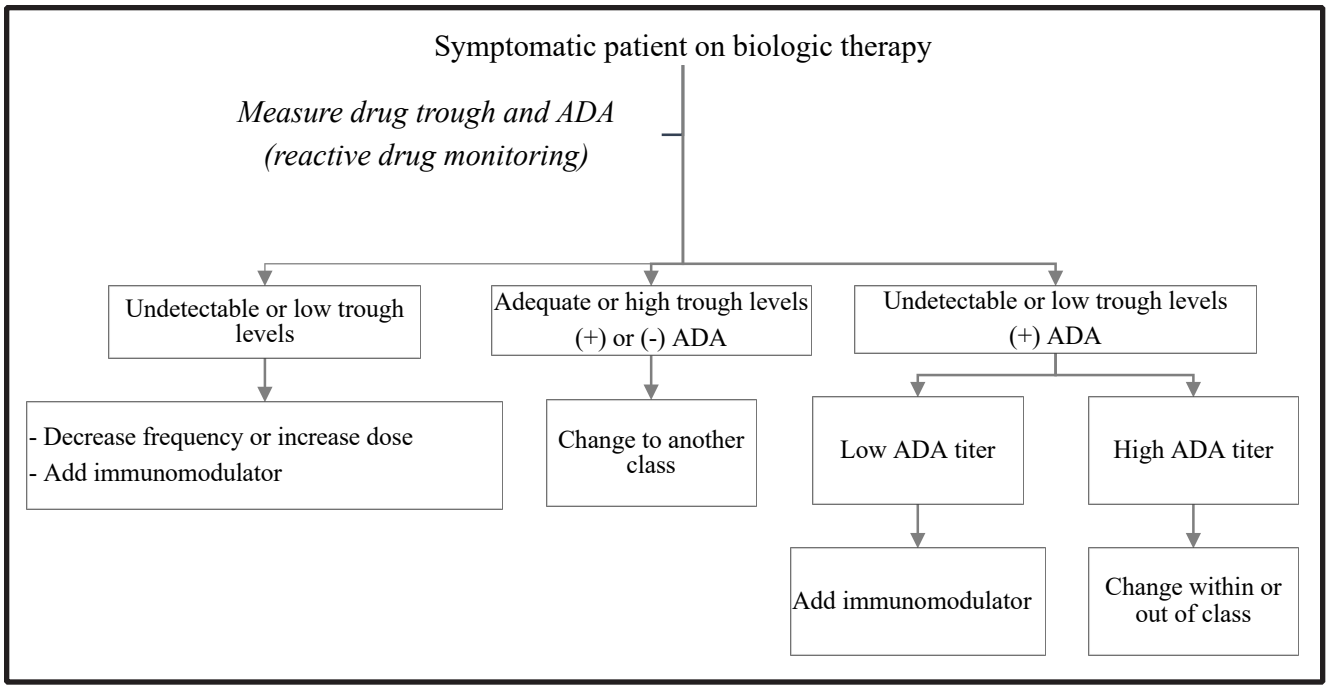

Figure 1. Algorithm for Reactive Therapeutic Drug Monitoring of Biologics
Footnote: Adapted from Sofia MA and Rubin DR.[10] ADA=anti-drug antibodies

concentrations of at least 5 mcg/mL for infliximab and 7.5 mcg/mL for adalimumab have been historically considered to be adequate to achieve mucosal healing.[5,11] More recent prospective data has suggested slightly higher levels are predictive of response (7.5 mcg/mL for infliximab and 12 mcg/mL for adalimumab). For other biologics, such as ustekinumab and vedolizumab, the data is not as robust and the overall drug exposure and efficacy relationship are less clear.[12] Target trough levels of biologics for reactive TDM based on currently available data are summarized in Table 1.[3,5,12] Above these levels, there is a low chance of further improvement with dose titration.

Proactive Drug Monitoring

Proactive TDM refers to drug monitoring in a patient who is clinically doing well on a biologic therapy. Dose adjustments are made preemptively based on drug concentration and antibody levels. The goal is to adjust therapy early on and thereby prevent primary or secondary loss of response. Proactive TDM could be done at specific time-points such as during induction, post induction or during maintenance therapy, though current evidence is most supportive for post induction (post loading) TDM.

Consensus guidelines recommendations on TDM state that proactive drug monitoring could be a consideration during the first year of therapy, though its role was uncertain.[3,5,9] Since then, we have more data looking at proactive TDM. An important study is a large prospective cohort study (PANTS study) of nearly 1500 Crohn's disease patients on infliximab or adalimumab looking at predictors for anti-TNF treatment failure.[13] In multivariable analysis, the only factor independently associated with non-response was low drug concentration at week 14. Optimal week 14 (post loading) drug concentrations associated with remission were 7 mcg/mL for infliximab and 12 mcg/mL for adalimumab. Another randomized control trial (PAILOT trial) in pediatric Crohn's disease patients started on adalimumab showed significantly higher rates of steroid-free clinical remission than reactive monitoring with adalimumab trough concentrations adjusted to achieve trough concentrations of at least 5 mcg/mL.[14] With newly emerging data from the aforementioned studies, there seems to be a role of checking a one time early drug concentration (post loading) as a part of active monitoring and dose intensification if needed, which is associated with improved long-term outcomes. Target drug

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concentrations used for post loading doses should be at least those suggested for reactive TDM monitoring (Table 1) or higher (7 mcg/mL for infliximab and 12 mcg/mL for adalimumab based on the PANTS study). These can be checked at week 12-14 for infliximab and week 6-8 for adalimumab. At present, there is no role for an ultra-proactive approach, that is, measuring drug at every interval and adjusting medications accordingly.

De-Escalation from Combination Therapy

De-escalation from long-term use of combination therapy (biologic with immunomodulator therapy) is often considered in clinical practice because of safety concerns. Discontinuation of infliximab and continuing immunomodulatory monotherapy (azathioprine or methotrexate) has resulted in nearly 50% relapse rates and lack of maintenance of remission.[15] Therefore, once biologic therapy has been initiated, it is important to continue therapy with the biologic unless there is loss of response or an adverse event. On the other hand, de-escalation from combination therapy (biologic with immunomodulator therapy) to biologic monotherapy can be attempted in carefully selected patients.[16,17] It is important to assess risk factors associated with poor prognosis and confirm deep (clinical, endoscopic and histological) remission. TDM of biologics to determine if biologic levels are appropriate can help in decision making prior to de-escalation. Drug trough levels similar to those suggested in Table 1 for reactive TDM are considered appropriate prior to withdrawal of an immunosuppressive agent. It is important to note that withdrawal of immunomodulator therapy can drop in biologic drug levels and increase immunogenicity, especially with anti-TNF therapies and increases the risk of relapse. De-escalation should be a shared decision making process. It is important to have a risk-benefit discussion with the patient. It is also important to have a monitoring and rescue strategy in case of a relapse. Post de-escalation, drug concentrations and antibody levels can be checked at some point, usually in 6-12 months once the effect of discontinuation of the immunomodulator has worn off, to ensure adequate drug levels persist without development of immunogenicity.

Table 1. Recommended Minimal Trough Levels of Various Biologics used in IBD

Drug	Trough Level (mcg/mL)
Anti-TNFs	
Infliximab	≥5 – 7.5
Adalimumab	≥7.5 - 12
Certolizumab pegol	≥20
Golimumab	Unknown
Vedolizumab	1.0–4.5
Ustekinumab	5.1–11.0

Footnote: Threshold levels modified from Feuerstein JD et al. and Restellini S et al.[5,12] Anti-TNFs=anti-tumor necrosis factor antibodies; ADA=anti-drug antibodies

Re-Initiation of Therapy after a Drug Holiday

Reasons for drug holiday or discontinuation of biologic therapy in IBD patients can include elective discontinuation due to infection or surgery, loss of insurance coverage, de-escalation from combination therapy or self-discontinuation by patients. In these situations, the same therapy may need to be restarted. The main concern is of an immunologic reaction to the biologic once it has been withdrawn, especially with the anti-TNF class of drugs that are considered to be highly immunogenic. Studies looking at restarting anti-TNF therapy after a drug holiday (providing no prior significant reaction to the anti-TNF) are promising. Approximately two-thirds of patients are able to recapture response even after a one-year gap.[15,18] TDM has a role in determining efficacy and safety of reintroducing anti-TNFs, and if there is a need to switch therapies based on an immunogenic reaction. Institution specific protocols have been described with strategies to re-capture response after a drug holiday.[19] These include initiation of a concomitant immunomodulator, premedication with steroids, slow infusion rates for the first few doses and checking antibody levels 7-14 days after the first infusion. It is not useful to check drug antibody levels prior to therapy re-initiation as antibody levels will be negative due to lack of drug exposure and will not be informative.

CONCLUSION

The field of therapeutic drug monitoring for biologic therapies in IBD is evolving. It is useful in various arenas of clinical practice. Gastroenterology providers taking care of IBD patients should familiarize themselves with its appropriate application. The most common form of TDM used is reactive TDM: checking serum drug levels and anti-biologic antibodies to modify therapy in the setting of active IBD symptoms or a change in biomarkers. Reactive TDM is considered standard of care and should be implemented in one's practice. This strategy helps avoid empiric therapy changes and decision making is more evidence-based. Trough drug levels (levels checked just before the next dose) are the most interpretable and are consistent amongst different assays. Proactive TDM is emerging as a new therapeutic strategy. Newer prospective data shows the benefit of checking drug levels after completion of induction regimens (post loading) for early adjustment of therapy and improvement in long-term outcomes. Other uses of TDM include in de-escalation from combination to monotherapy and in re-initiation of biologic therapy after a drug holiday. Judicious use of drug assays in the right clinical setting is imperative to improve outcomes, prevent unnecessary testing and to avoid significant out-of-pocket costs to the patient. ■

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