Update on Therapeutic Drug Monitoring in Crohn's Disease

Valérie Heron, MD, FRCPC, Waqqas Afif, MD, MSc, FRCPC*

KEYWORDS

• Therapeutic drug monitoring • Biologics • Anti-tumor necrosis factor
• Drug concentrations • Anti-drug antibodies • Crohn's disease
• Inflammatory bowel disease

KEY POINTS

- Therapeutic drug monitoring involves measuring drug concentrations and anti–drug antibodies, which are associated with clinical and endoscopic outcomes.
- In patients with a loss of response to anti–tumor necrosis factor therapy, therapeutic drug monitoring is clinically useful and likely cost-effective.
- There is evidence for the use of therapeutic drug monitoring in the withdrawal of immunosuppression in combination therapy, dose deescalation, post–drug holiday, and perhaps post-induction monitoring.
- Therapeutic drug monitoring in routine maintenance therapy has not yet been shown to improve treatment efficacy.
- There is interassay variability, and optimal therapeutic drug and antibody thresholds remain to be firmly established.

INTRODUCTION

Therapeutic drug monitoring (TDM) is one of the cornerstones of personalized medicine and has been widely used to improve the treatment of various diseases. In the setting of infectious disease and transplant medicine, measuring serum concentrations of antibiotics and immunosuppressive medications has dramatically improved patient outcomes. The understanding of the pharmacokinetic and pharmacodynamic

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Division of Gastroenterology, McGill University Health Center, Montreal General Hospital, McGill University, 1650 Cedar Avenue, Montreal, Quebec H3G 1A4, Canada
* Corresponding author. McGill University Health Center, Montreal General Hospital, 1650 Cedar Avenue, Room C7-200, Montreal, Quebec H3G 1A4, Canada.
E-mail address: waqqas.afif@mcgill.ca

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properties of these medications has aided in achieving therapeutic targets, thereby optimizing efficacy while limiting potential drug-related toxicity.

The introduction of biologic therapies in the treatment of Crohn's disease (CD) has ushered in a new era of treatment. These drugs have the potential to alter the natural history of this progressive disease. Unfortunately, remission rates with these biologic medications are only approximately 40%,[1] and in those who do achieve remission, the rate of loss of response (LOR) is more than 10% per year.[2] There is evidence to suggest that the use of TDM may help to guide and optimize therapy in CD patients on biologic medications. In clinical practice, measuring drug and anti–drug antibody (ADA) concentrations has already been used to adapt treatment strategies in a variety of situations.

In this review, we examine the available data on TDM, with both anti–tumor necrosis factor (anti-TNF) agents and newer biologic medications, in the treatment of patients with CD.

MEASURING BIOLOGIC CONCENTRATIONS AND ANTI–DRUG ANTIBODIES

Before any discussion on the use of TDM, there must be a clear understanding of the various techniques available to measure drug and ADA concentrations. Depending on the technique used, the thresholds to alter therapy can vary significantly from assay to assay as well as between different laboratories. This lack of a standardized testing method therefore limits the ability to reliably compare drug and antibody thresholds with patient outcomes in clinical studies. Therefore, an understanding of TDM assays is important to help accurately interpret the results of available data. Commercialized assays include various techniques such as enzyme-linked immunosorbent assay (ELISA), electro-chemiluminescence immunoassay (ECLIA), radioimmunoassay (RIA), and a high mobility shift assay (HMSA).

Most studies to date were performed using a conventional solid phase ELISA. In this technique, TNF is plated, which binds anti-TNF from a serum sample. Labeled anti–immunoglobulin G is then added, which binds the anti-TNF to allow for measurement of drug concentration. Drug concentrations generated by ELISA assays are thought to be congruent between different laboratories, as demonstrated by a recent trial comparing 3 European assays.[3] Measurement of ADAs, using ELISA, is performed by plating anti-TNF. However, an important limitation of this method is that it is a drug-sensitive assay. Therefore, ADAs can only be detected in the absence of circulating anti-TNF, because serum anti-TNF renders ADAs undetectable.[4] An alternative "sandwiched" ELISA technique uses a monoclonal antibody in the detection phase, which limits the problem of serum anti-TNF interfering with ADA measurement and is therefore considered a drug-tolerant assay.[5] RIA yields a higher sensitivity and specificity than ELISA and is less prone to drug interference. However, it involves the use of radioisotopes rendering the technique more complex.[6] The homogenous mobility shift assay (Prometheus Laboratories, San Diego, CA, USA) was developed to allow both drug levels and antibodies to be detected simultaneously.[7] This method uses fluorescent-labeled anti-TNF for the detection of ADA and fluorescent-labeled TNF-alpha for the measurement of drug levels. Resulting labeled immune complexes are subsequently detected based on their specific molecular weight.[8] Similarly, ECLIA (LabCorp, Calabasas Hills, CA, USA) detects anti–drug antibodies even in the presence of anti-TNF.[6] Although this technique has been shown to detect IFX with higher sensitivity (lower limit of detection) than ELISA-based assays, its use has not yet been validated in clinical trials.[6] Cost, availability, and accessibility are major factors that influence the routine use of these diagnostic tests. In general, regardless of the assay,