Therapeutic Drug Monitoring in Inflammatory Bowel Disease

History and Future Directions

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KEYWORDS

- Inflammatory bowel disease • Therapeutic drug monitoring
- Thiopurine metabolite monitoring • Biologics

KEY POINTS

- The roots of therapeutic drug monitoring (TDM) in IBD lie in thiopurines and the tenet of titrating metabolite levels to achieve 6-TGN>235 and 6-MMP<5700.
- TDM for biologic drugs involves measuring drug concentrations and anti-drug antibodies with a subsequent change in therapy to achieve desired levels and prevent antibody formation.
- Proactive TDM with biologics is gaining popularity given its ability to reduce drug costs and improve patient outcomes, but this still requires further validation.
- There is still debate over ideal trough concentrations for each biologic given that patient-specific factors can influence the concentration required for desired end-points, like mucosal or fistula healing.
- Drug concentrations and anti-drug antibody levels should be carefully interpreted given the variability between types of assays.

Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under the abnormal conditions which we know as disease.

—Sir William Osler in 1903

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INTRODUCTION

Inflammatory bowel disease (IBD), comprising mainly the 2 entities Crohn disease (CD) and ulcerative colitis (UC), is a chronic inflammatory disease of the digestive tract. Pharmacotherapy for IBD has focused on dampening this inflammation with agents to both induce remission and then provide durable maintenance, all while avoiding the use of steroids. However, the steroid-sparing regimens are still limited in number and do not lead to adequate disease control in all patients. Clinical trials in IBD have, in general, shown only a 50% to 60% response, and this decreases to 30% in the maintenance phase as patients start to lose response.[1–4] These trials are limited by the use of label dosing, which is either fixed or based on simple weight cutoffs. Label dosing does not take into account individual variability in metabolism and clearance and can be suboptimal, leading to lack of clinical response and development of antidrug antibodies (ADAs). Current clinical practice is designed to optimize response to available medications via tailored dosing regimens, which can be achieved through therapeutic drug monitoring (TDM).

TDM is based on the assumption that the response of a drug is tied to a clinical laboratory measure, such as the unbound concentration of drug in plasma at the end of a dosing interval. This measurement ideally reflects the influence of patient-specific factors such as demographics, disease activity, and drug interactions. The goal of TDM is to then optimize this measure within a target range for each unique individual to maximize benefit while avoiding toxicity. It can also be used to monitor compliance and elucidate the root cause of treatment failures.[5,6]

TDM started its evolution in the IBD space with thiopurines, 6-mercaptopurine (6-MP) and azathioprine (AZA), which were the cornerstone of steroid-sparing maintenance regimens until the advent of monoclonal antibodies (mAbs).[7–9] Despite their prominence in the 1990s and 2000s, there were several concerns over thiopurines' safety profile, leading to the first application of TDM in IBD to achieve a better balance between reaping thiopurines' therapeutic effects without the concomitant adverse effects of severe leukopenia and hepatotoxicity.

IBD specialists were then able to turn their knowledge of TDM to biologics as they increased in prominence with the introduction of infliximab (IFX). TDM is now commonplace in clinical practice, and there has been a compendium of research showing that careful monitoring to achieve sufficient mAb concentrations and to avoid ADA leads to better outcomes.

Although TDM is widely recognized as beneficial to maximize response to, and minimize cost from, mAbs, it is debated whether it should be practiced in a reactive way when a patient is symptomatic and a loss of response is suspected or if it should be practiced in a proactive way to stay abreast of this loss of response. This debate is driving ongoing research in the utility of proactive monitoring with more and more sophisticated systems of dose adjustment under development, such as dashboard-driven dosing systems. This article reviews TDM in IBD from its inception with thiopurines to its active evolution with biologics.

THIOPURINES

Thiopurine Metabolism and Thiopurine Methyltransferase

The origin of TDM with thiopurines is rooted in their unique metabolism. After absorption, AZA is converted quickly and nonenzymatically to 6-MP and S-methyl-4-nitro-5-thioimidazole. 6-MP is then further processed via competing catabolic and anabolic pathways with extensive first-pass metabolism via xanthine oxidase, which is found in the intestine as well as the liver. It subsequently undergoes further catabolism by thiopurine methyltransferase (TPMT) before eventually being anabolized to the active metabolites, 6-