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LETTER TO THE EDITOR

Therapeutic drug monitoring in inflammatory bowel disease treatments

Meng-Yao Wang, Jing-Wen Zhao, Chang-Qing Zheng, Li-Xuan Sang

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Abstract

Recently, biological drugs have played a leading role in the treatment of inflammatory bowel disease, and therapeutic drug monitoring (TDM) may be useful in maximizing their effectiveness. TDM involves the measurement of serum drug and anti-drug antibodies concentrations as the basis for dosage adjustments or drug conversions to achieve a higher response rate. We believe that concentration thresholds should be individualized based on patients' disease severity, extent and phenotype, and therapeutic purposes should also be considered, with higher cut-offs mainly needed for endoscopic and fistula healing than for symptomatic remission. Proactive and reactive TDM can help optimize treatment, especially in patients receiving anti-tumour necrosis factor, and guide dose adjustment or drug conversion with lower cost. TDM is a promising approach to achieve precision medicine and targeted medicine in the future.

Key Words: Therapeutic drug monitoring; Inflammatory bowel disease; Biologic therapies; Reactive; Proactive; Cost-effective

Core Tip: Therapeutic drug monitoring (TDM) has proven to be useful in the management of patients with inflammatory bowel disease (IBD). The therapeutic value, feasibility and application prospect of TDM in the treatment of IBD were discussed.

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TO THE EDITOR

We read with interest the review by Albader *et al*[1] on the application of therapeutic drug monitoring (TDM) in patients with inflammatory bowel disease (IBD). The authors provided a comprehensive overview of the relationship between proactive or reactive TDM and clinical outcomes.

The treatment of IBD has progressed from the original mesalamine to glucocorticoids and immunosuppressants to biologics. Currently, biologic therapy is required by many patients to achieve and maintain clinical and endoscopic remission. However, up to one-third of patients receiving this treatment are primary non-responders, and some patients who show an initial response can also lose response over time[2]. TDM is a useful tool for managing patients on biologic therapy, especially those receiving anti-tumor necrosis factor (anti-TNF) therapy, and it can be used to monitor dose escalation, de-escalation or drug conversion by measuring serum drug concentrations and anti-drug antibodies (ADAs).

However, there does not seem to be a universal optimal cut-off for drug serum concentrations, and the majority of studies have shown that higher serum concentrations are associated with an increased likelihood of clinical response. In 2021, a prospective study of 32 pediatric patients demonstrated that children who achieved endoscopic remission at six months had significantly higher infliximab (IFX) concentrations at different time points during induction (at weeks 4, 6, and 12 as the start of maintenance therapy), and the IFX concentration ≥ 5.0 μg/mL at week 12 was a minimal target to achieve endoscopic remission at six months (area under the receiver operating characteristic curve: 0.796)[3]. A retrospective observational case–control study found that IFX levels below 6.8 μg/mL and antibodies to IFX levels above 4.3 μg/mL before the second infusion were associated with primary nonresponse, especially among patients with Crohn's disease (CD)[4]. A prospective observational study by Kennedy *et al*[5]showed that in multivariable analysis, the only factor independently associated with primary nonresponse was low drug concentration at week 14 [IFX: OR 0.35, $P = 0.00038$; adalimumab (ADA): OR 0.13, $P < 0.0001$], the optimal week 14 drug concentrations associated with remission at both week 14 and week 54 were 7 mg/L for IFX and 12 mg/L for ADA. Importantly, we believe that concentration thresholds should be individualized based on patients' disease severity, extent and phenotype, and therapeutic purposes should also be considered, with higher cut-offs mainly needed for endoscopic and fistula healing than for symptomatic remission.

TDM has not been widely recommended for non-anti-TNF biologicals. A study published in 2018 concluded that potential target vedolizumab (VDZ) concentrations at weeks 6 and 14 and steady state during treatment were proposed to be > 37.1, > 18.4 and > 12.7 μg/mL, respectively[6]. There are no definitive conclusions to guide practitioners regarding the target VDZ concentration for achieving endoscopic remission. A review published in 2020 noted that data from registration trials and real-world cohorts suggested an exposure-efficacy relationship of VDZ in patients with IBD, but future studies need to define an upper limit beyond which dose optimization is very unlikely to further increase response rates[7]. Ustekinumab (UST) is a monoclonal antibody against IgG that affects the immunity of IBD patients by binding to the P40 subunit common to interleukin 12 and interleukin 23. According to a review published in 2021, serum UST concentrations are associated with clinical, biochemical, and histological remissions in most clinical trials[8]. A multicenter crosssectional observational trial based on 110 CD patients concluded that there was no association between short-term clinical outcomes and UST concentrations[9]. We can assume that there is an exposure-efficacy association with UST based on current studies. Further study is required to identify the threshold below which dose optimization may be useful. The Janus kinase inhibitor tofacitinib is not impacted by enzyme polymorphisms or disease activity and is not expected to stimulate the formation of neutralizing ADAs. In addition, the drug concentration is not a meaningful determinant of efficacy, and no loss of efficacy due to low plasma concentration was identified in clinical trials; therefore, TDM is unlikely to be provided during treatment with tofacitinib, according to a review published in 2021[10].

TDM can be implemented in two forms, "Proactive" TDM refers to routine monitoring of serum concentrations, whereas "Reactive" TDM is defined as a measurement taken following treatment failure. This allows doctors to then choose to adjust the dose or change to another drug. Cost-effectiveness is an important factor in the choice of proactive and reactive TDM. According to Assa *et al*[11], proactive monitoring and ADA dose intensification to serum concentrations > 5 μg/mL resulted in a higher rate of clinical remission than reactive monitoring in cases of "loss of response". Fernandes *et al*[12] and Papamichael *et al*[13] concluded that patients in the proactive TDM group had greater clinical outcomes than those in the control group. However, guidelines or consensus in different countries and regions differ on the application of TDM. Guidelines published in 2020 by the European Colitis & Crohn's Organization pointed out that there is insufficient evidence to recommend for or against TDM [14]. The 2017 guidelines of the American Gastroenterology Association only recommend reactive TDM [15]. McNeill *et al*[16] found that reactive TDM of IFX optimizes dosing and reduces expenditure by over 50%, without affecting clinical outcomes. Proactive IFX TDM may confer long-term clinical benefit but is only modestly cost-effective. A systematic review published in 2020 noted that compared with standard treatment without TDM, TDM-guided strategies were consistently reported to be cost saving or cost effective, with no emphasis on proactive or reactive TDM[17]. There are no high-quality studies comparing the cost-effectiveness of proactive and reactive TDM; however, TDM is cost-effective

compared to empirical treatment. The problems to be solved in the implementation of TDM include high price, delivery and transportation difficulties. A survey of over 242 participants in India suggested that significant barriers to TDM use were availability, cost and time lag for results. If these barriers were removed, almost all clinicians would use TDM at least reactively, and 25% would use it proactively[18].

It should be emphasized that the therapeutic goal is to achieve clinical and endoscopic remission and not to target TDM to specific drug concentration levels. Different guidelines recommend different trough concentrations, different departments have different measurement methods, and individuals have different systems, so even if the same threshold is reached, some people will respond and some will not; thus, we recommend dynamic detection of blood drug concentrations. The future medical trend is precision medicine and targeted medicine. We hope that in the future, there will be a tool as convenient and fast as a glucose meter that can measure blood drug concentrations, perform real-time monitoring, combine clinical symptoms and endoscopic manifestations, and then adjust drugs to achieve targeted treatment. We wish to draw readers' attention to the fact that TDM is a promising approach for clinicians to optimize treatment.

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