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LETTER TO THE EDITOR

Therapeutic drug monitoring in inflammatory bowel disease: At the right time in the right place

Brindusa Truta

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Abstract

Therapeutic drug monitoring (TDM) was one of most sought-after objective tools to determine therapeutic efficiency of different biologics and its role in the management of patients with inflammatory bowel disease (IBD) was regarded with great anticipation. But implementation of the TDM in clinical practice was challenged by several factors including uncertainty of the optimal cut-off values, assay variable sensitivity in detecting drug levels and antibodies and, most importantly, individual pharmacokinetics. While reactive TDM was embraced in clinical practice as a useful tool in assessing lack of response to therapy, the utility of proactive TDM in managing IBD therapy is still challenged by the lack of consistency between evidence. Described here, there are four groups of IBD patients for whom proactive TDM has the potential to greatly impact their therapeutic outcomes: Patients with perianal Crohn's disease, patients with severe ulcerative colitis, pregnant women with IBD and children. As the future of IBD management moves towards personalizing treatment, TDM will be an important decision node in a machine learning based algorithm predicting the best strategy to maximize treatment results while minimizing the loss of response to therapy.

Key Words: Therapeutic drug monitoring; Inflammatory bowel disease; Biologics; Crohn's disease

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Core Tip: While reactive therapeutic drug monitoring (TDM) was embraced in clinical practice as an important tool for assessing lack of response to biologics, existent evidence inconsistently supports the proactive use of TDM in managing inflammatory bowel disease (IBD) therapy. Exceptions are made for patients with severe ulcerative colitis and perianal Crohn's disease (fistula) for whom TDM has consistently shown to improve clinical outcome, pregnant women with IBD for whom TDM has the potential to play a decisive role in withholding therapy and for children, for whom proactive TDM was found to increase steroid free clinical remission. Future studies are needed to define the real value of TDM in management of IBD.

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TO THE EDITOR

The article presented by Albader *et al*[1] titled "Therapeutic drug monitoring in inflammatory bowel disease: The dawn of reactive monitoring" addresses a controversial topic in clinical practice: The role of therapeutic drug management in patients with inflammatory bowel disease (IBD).

Therapeutic drug monitoring (TDM) was as one of most sought-after objective tools to determine therapeutic efficiency of different biologics. Around one third of patients are primary non-responders and 25%-50% who respond, lose response over time [secondary loss of response (sLOR)][2,3]. Clinicians investigated different techniques to early detect, prevent and overcome sLOR in their patients including serologic and fecal biomarkers, capsule endoscopy and imaging. TDM was regarded with great hope. But, as recognized by Albader *et al*[1], implementation of TDM in clinical practice was challenged by few factors including uncertainty of the optimal cut-off values, assay variable sensitivity in detecting drug levels and antibodies and, most importantly, individual pharmacokinetics influenced by severity of the disease and body weight[4-6].

The studies presented in this review, of which the majority are retrospective and targeting anti-tumor necrosis factors (TNFs), have controversial results regarding the utility of TDM in management of IBD. This controversy arises in part due to the differences in study design including different outcomes: Clinical, endoscopic, histologic response and/or cost efficiency but also due to timing of TDM implementation proactive *vs* reactive to sLOR. The author concluded that it is "difficult to prove that proactive TDM is associated with better therapeutic outcomes" but it should be considered an addition to the other tools already routinely used in practice including biomarkers (calprotectine), imaging, capsule endoscopy[1].

There are few situations that should be discussed as exempt from this conclusion.

In patients with perianal Crohn's disease (CD), closure of the fistula have been consistently shown to require higher trough level of infliximab (≥ 10 μg/mL) (IFX) than the level considered optimal for luminal CD disease (3–7 μg/mL)[6]. This finding seems to be true for both induction and maintenance phase[7,8]. It needs to be recognized that most of the studies reporting on the anti-TNF levels in perianal CD are retrospective in design[7-9]. The results of the prospective randomized controlled trial of adults with perianal fistulizing CD and optimized therapeutic IFX levels (PROACTIVE Trial) currently evaluates the benefit on clinical, radiological, patient-reported outcomes and economic costs of a higher than standard IFX[10].

In patients with moderate to severe ulcerative colitis, a higher than 30 μg/mL IFX level after the induction phase and a detectable drug level at 54 wk has been associated with greater clinical and endoscopy improvement in the post-hoc analysis of 728 patients who participated to ACT-1 and ACT-2 clinical trials[11]. This higher level is also associated with lower colectomy rates and hospitalization (OR: 9.3, $P < 0.001$)[12] when compared with patients with standard IFX level. Patients with severe inflammation have lower tissue anti-TNF levels than those in remission[13] likely due to increased clearance, although drug clearance depends on other additional factors such as albumin level, body mass and gender[14,15]. For these patients, proactive TDM may represent the rescue technique for clinical improvement and colectomy sparing.

TDM may be useful in managing anti-TNF therapy in IBD pregnancy where concerns of intrauterine fetal exposure has been raised, as the data showed higher than therapeutic levels for children of mothers who continue biologics beyond second trimester than for those of mothers who stopped biologics early in pregnancy[16]. Since mother's IFX trough levels increased during pregnancy by 4.2 μg/mL *per* trimester ($P = 0.02$), it has been suggested that late second trimester trough level of biologic may determine timing and dose of biologic agent in the third trimester[17,18].

Although withholding biologic therapy in the third trimester has been associated with increased risk of flaring in pregnancy[19], this approach may be considered safe with TDM in a well-defined group of patients once there is a clear understanding of drug pharmacokinetics and determinants of flaring in pregnancy. TDM may be considered in children with intrauterine drug exposure to decide the timing of safe administration of life virus vaccines. Current guidelines recommend avoiding any live vaccinations for at least 6 mo following delivery unless serum levels in the infant are undetectable[20].

Pediatric IBD represents a special group of patients, where the limited therapeutic armamentarium and challenges in balancing drug safety and efficiency created a critical need for drug monitoring[21]. Pro-active TDM showed to increase corticoid-free clinical remission in children with CD treated with Adalimumab (ADL) compared with reactive monitoring (PAILOT study)[22] and sustained clinical remission in children with CD, ulcerative colitis or IBD-unclassified treated with either IFX or ADL therapy[23]. In addition, model outcomes indicated that proactive TDM *vs* reactive TDM for ADL may provide higher quality-adjusted life-years at lower cost in pediatric CD patients[24].

In comparison with proactive TDM, the utility of reactive TDM has received a greater consensus in guiding therapy for those patients who lost response and where either dose intensification or change to an alternative therapy may be necessary. The utility of reactive TDM have been extended to recently introduced biologics and oral small molecules[25].

As the future of IBD management moves towards personalizing treatment, TDM will play an important role in the algorithm of machine learning based models that predict best strategy to optimize treatment outcomes while minimizing the sLOR to therapy.

FOOTNOTES

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