**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 72834

**Manuscript Type:** LETTER TO THE EDITOR

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

Truta B. Therapeutic drug monitoring in IBD

Brindusa Truta

**Brindusa Truta,** Internal Medicine, Johns Hopkins University, Baltimore, MD 21210, United States

**Author contributions:** Truta B performed literature review, analyzed data, wrote the letter.

**Corresponding author: Brindusa Truta, MD, Assistant Professor,** Internal Medicine, Johns Hopkins University, 1830 E Monument Street, Room 426, Baltimore, MD 21210, United States. brindusa\_73@yahoo.com

**Received:** October 30, 2021

**Revised:** January 17, 2022

**Accepted:** February 27, 2022

**Published online:** April 7, 2022

**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

**©The** **Author(s) 2022.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Citation:** Truta B. Therapeutic drug monitoring in inflammatory bowel disease: At the right time in the right place. *World J Gastroenterol* 2022; 28(13): 1380-1383

**URL:** https://www.wjgnet.com/1007-9327/full/v28/i13/1380.htm

**DOI:** https://dx.doi.org/10.3748/wjg.v28.i13.1380

**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.

**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.

**REFERENCES**

1 **Albader F**, Golovics PA, Gonczi L, Bessissow T, Afif W, Lakatos PL. Therapeutic drug monitoring in inflammatory bowel disease: The dawn of reactive monitoring. *World J Gastroenterol* 2021; **27**: 6231-6247 [PMID: 34712029 DOI: 10.3748/wjg.v27.i37.6231]

2 **Ben-Horin S**, Kopylov U, Chowers Y. Optimizing anti-TNF treatments in inflammatory bowel disease. *Autoimmun Rev* 2014; **13**: 24-30 [PMID: 23792214 DOI: 10.1016/j.autrev.2013.06.002]

3 **Papamichael K**, Cheifetz AS. Therapeutic drug monitoring in inflammatory bowel disease: for every patient and every drug? *Curr Opin Gastroenterol* 2019; **35**: 302-310 [PMID: 30973355 DOI: 10.1097/MOG.0000000000000536]

4 **Argollo M**, Kotze PG, Kakkadasam P, D'Haens G. Optimizing biologic therapy in IBD: how essential is therapeutic drug monitoring? *Nat Rev Gastroenterol Hepatol* 2020; **17**: 702-710 [PMID: 32879465 DOI: 10.1038/s41575-020-0352-2]

5 **Kapoor A**, Crowley E. Advances in Therapeutic Drug Monitoring in Biologic Therapies for Pediatric Inflammatory Bowel Disease. *Front Pediatr* 2021; **9**: 661536 [PMID: 34123968 DOI: 10.3389/fped.2021.661536]

6 **Yarur AJ**, Kanagala V, Stein DJ, Czul F, Quintero MA, Agrawal D, Patel A, Best K, Fox C, Idstein K, Abreu MT. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. *Aliment Pharmacol Ther* 2017; **45**: 933-940 [PMID: 28211593 DOI: 10.1111/apt.13970]

7 **Sun XL**, Chen SY, Tao SS, Qiao LC, Chen HJ, Yang BL. Optimized timing of using infliximab in perianal fistulizing Crohn's disease. *World J Gastroenterol* 2020; **26**: 1554-1563 [PMID: 32327905 DOI: 10.3748/wjg.v26.i14.1554]

8 **Plevris N**, Jenkinson PW, Arnott ID, Jones GR, Lees CW. Higher anti-tumor necrosis factor levels are associated with perianal fistula healing and fistula closure in Crohn's disease. *Eur J Gastroenterol Hepatol* 2020; **32**: 32-37 [PMID: 31567638 DOI: 10.1097/MEG.0000000000001561]

9 **Strik AS**, Löwenberg M, Buskens CJ, B Gecse K, I Ponsioen C, Bemelman WA, D'Haens GR. Higher anti-TNF serum levels are associated with perianal fistula closure in Crohn's disease patients. *Scand J Gastroenterol* 2019; **54**: 453-458 [PMID: 31032686 DOI: 10.1080/00365521.2019.1600014]

10 **Gu B**, De Gregorio M, Pipicella JL, Vande Casteele N, Andrews JM, Begun J, Connell W, D'Souza B, Gholamrezaei A, Hart A, Liew D, Radford-Smith G, Rimola J, Sutherland T, Toong C, Woods R, Wu Y, Xuan W, Williams AJ, Ng W, Ding NS, Connor S. Prospective randomised controlled trial of adults with perianal fistulising Crohn's disease and optimised therapeutic infliximab levels: PROACTIVE trial study protocol. *BMJ Open* 2021; **11**: e043921 [PMID: 34210720 DOI: 10.1136/bmjopen-2020-043921]

11 **Adedokun OJ**, Sandborn WJ, Feagan BG, Rutgeerts P, Xu Z, Marano CW, Johanns J, Zhou H, Davis HM, Cornillie F, Reinisch W. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. *Gastroenterology* 2014; **147**: 1296-1307.e5 [PMID: 25173754 DOI: 10.1053/j.gastro.2014.08.035]

12 **Vande Casteele N**, Jeyarajah J, Jairath V, Feagan BG, Sandborn WJ. Infliximab Exposure-Response Relationship and Thresholds Associated With Endoscopic Healing in Patients With Ulcerative Colitis. *Clin Gastroenterol Hepatol* 2019; **17**: 1814-1821.e1 [PMID: 30613004 DOI: 10.1016/j.cgh.2018.10.036]

13 **Yarur AJ**, Jain A, Sussman DA, Barkin JS, Quintero MA, Princen F, Kirkland R, Deshpande AR, Singh S, Abreu MT. The association of tissue anti-TNF drug levels with serological and endoscopic disease activity in inflammatory bowel disease: the ATLAS study. *Gut* 2016; **65**: 249-255 [PMID: 25670812 DOI: 10.1136/gutjnl-2014-308099]

14 **Khan N**, Patel D, Shah Y, Trivedi C, Yang YX. Albumin as a prognostic marker for ulcerative colitis. *World J Gastroenterol* 2017; **23**: 8008-8016 [PMID: 29259376 DOI: 10.3748/wjg.v23.i45.8008]

15 **Ordás I**, Mould DR, Feagan BG, Sandborn WJ. Anti-TNF monoclonal antibodies in inflammatory bowel disease: pharmacokinetics-based dosing paradigms. *Clin Pharmacol Ther* 2012; **91**: 635-646 [PMID: 22357456 DOI: 10.1038/clpt.2011.328]

16 **Zelinkova Z**, de Haar C, de Ridder L, Pierik MJ, Kuipers EJ, Peppelenbosch MP, van der Woude CJ. High intra-uterine exposure to infliximab following maternal anti-TNF treatment during pregnancy. *Aliment Pharmacol Ther* 2011; **33**: 1053-1058 [PMID: 21366638 DOI: 10.1111/j.1365-2036.2011.04617.x]

17 **Seow CH**, Leung Y, Vande Casteele N, Ehteshami Afshar E, Tanyingoh D, Bindra G, Stewart MJ, Beck PL, Kaplan GG, Ghosh S, Panaccione R. The effects of pregnancy on the pharmacokinetics of infliximab and adalimumab in inflammatory bowel disease. *Aliment Pharmacol Ther* 2017; **45**: 1329-1338 [PMID: 28318043 DOI: 10.1111/apt.14040]

18 **van der Woude CJ**, Ardizzone S, Bengtson MB, Fiorino G, Fraser G, Katsanos K, Kolacek S, Juillerat P, Mulders AG, Pedersen N, Selinger C, Sebastian S, Sturm A, Zelinkova Z, Magro F; European Crohn’s and Colitis Organization. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. *J Crohns Colitis* 2015; **9**: 107-124 [PMID: 25602023 DOI: 10.1093/ecco-jcc/jju006]

19 **Truta B**, Leeds IL, Canner JK, Efron JE, Fang SH, Althumari A, Safar B. Early Discontinuation of Infliximab in Pregnant Women With Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2020; **26**: 1110-1117 [PMID: 31670762 DOI: 10.1093/ibd/izz250]

20 **Mahadevan U**, Cucchiara S, Hyams JS, Steinwurz F, Nuti F, Travis SP, Sandborn WJ, Colombel JF. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organisation: pregnancy and pediatrics. *Am J Gastroenterol* 2011; **106**: 214-23; quiz 224 [PMID: 21157441 DOI: 10.1038/ajg.2010.464]

21 **Wren AA**, Park KT. Targeted Dosing as a Precision Health Approach to Pharmacotherapy in Children with Inflammatory Bowel Disease. *AMA J Ethics* 2018; **20**: E841-E848 [PMID: 30242815 DOI: 10.1001/amajethics.2018.841]

22 **Assa A**, Matar M, Turner D, Broide E, Weiss B, Ledder O, Guz-Mark A, Rinawi F, Cohen S, Topf-Olivestone C, Shaoul R, Yerushalmi B, Shamir R. Proactive Monitoring of Adalimumab Trough Concentration Associated With Increased Clinical Remission in Children With Crohn's Disease Compared With Reactive Monitoring. *Gastroenterology* 2019; **157**: 985-996.e2 [PMID: 31194979 DOI: 10.1053/j.gastro.2019.06.003]

23 **Lyles JL**, Mulgund AA, Bauman LE, Su W, Fei L, Chona DL, Sharma P, Etter RK, Hellmann J, Denson LA, Minar P, Dykes DM, Rosen MJ. Effect of a Practice-wide Anti-TNF Proactive Therapeutic Drug Monitoring Program on Outcomes in Pediatric Patients with Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2021; **27**: 482-492 [PMID: 32448898 DOI: 10.1093/ibd/izaa102]

24 **Yao J**, Jiang X, You JHS. Proactive therapeutic drug monitoring of adalimumab for pediatric Crohn's disease patients: A cost-effectiveness analysis. *J Gastroenterol Hepatol* 2021; **36**: 2397-2407 [PMID: 33326123 DOI: 10.1111/jgh.15373]

25 **Restellini S**, Afif W. Update on TDM (Therapeutic Drug Monitoring) with Ustekinumab, Vedolizumab and Tofacitinib in Inflammatory Bowel Disease. *J Clin Med* 2021; **10** [PMID: 33802816 DOI: 10.3390/jcm10061242]

**Footnotes**

**Conflict-of-interest statement:** No conflict of interest to declare.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review started:** October 30, 2021

**First decision:** December 12, 2021

**Article in press:** February 27, 2022

**Specialty type:** Gastroenterology and hepatology

**Country/Territory of origin:** United States

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B, B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Gazouli M, Greece; Xiao Y, China **S-Editor:** Fan JR **L-Editor:** A **P-Editor:** Fan JR



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2022 Baishideng Publishing Group Inc. All rights reserved.**