Digestive Diseases and Sciences (2024) 69:5–6
https://doi.org/10.1007/s10620-023-08140-8

INVITED COMMENTARY

Point-of-Care Assays for Infliximab Therapeutic Drug Monitoring in Patients with IBD: Is Quicker Better?

Steven Levitte[1]

Received: 18 September 2023 / Accepted: 2 October 2023 / Published online: 9 November 2023

It has been 25 years since the FDA approved infliximab, the first tumor necrosis factor-a (TNF) inhibitor, for treatment of inflammatory bowel disease (IBD). Despite the subsequent introduction of multiple new therapies, treatment failure remains a major cause of morbidity for patients with IBD. Over the last decade, as experience with biologic medications has advanced, therapeutic drug monitoring (TDM) has emerged as a technique for measuring the serum concentration of biologic medications and detecting anti-drug antibodies that are associated with treatment failure [1] with the intent to reduce the risk of primary and secondary non-response. Several studies have investigated different monitoring strategies for biologic treatment of IBD, broadly falling into reactive (in response to clinical deterioration) vs. proactive (TDM regardless of clinical condition) approaches, with conflicting results in many cases as to utility and cost-effectiveness [2–4]. Though in theory, proactive TDM could prevent loss of response to therapy (vs. reactive TDM which would aim to rescue response in a patient who had relapsed disease), several factors have hindered the wider adoption and analysis of this strategy. Perhaps one of the largest barriers is the infliximab drug concentration is typically measured using an enzyme-linked immunosorbent assay (ELISA) assay that can be time-consuming in some laboratories. To address this, point-of-care (POC) assays were developed to address this issue, with successful use in the detection of anti-drug antibodies, [5] and in a few instances in the measurement of infliximab serum levels, albeit with varying accuracy [6]. Unfortunately, many of the available POC assays rely upon serum input, necessitating additional laboratory equipment over those that can use capillary blood for detection. Valdés-Delgado and colleagues, in an article published in this issue of *Digestive Diseases and Sciences* [7], assessed two capillary blood-based POC tests (one for anti-drug antibodies, the other for drug concentration) for performance against reference ELISA tests in adult patients with IBD both during induction and maintenance phases of treatment. They performed a prospective observational study in which they assessed a total of 135 blood samples using a POC test that could detect drug levels from capillary blood (Promonitor Quick IFX) with excellent correlation between POC and ELISA ($r = 0.84$). Consistent with prior work, the POC assay has slightly lower sensitivity than ELISA for anti-drug antibodies [5]. The overall concordance with regard to therapeutic range between ELISA and POC assays was 87.4%, indicating that for the most part clinical decision-making would have been the same when informed by either assay.

A recent study compared proactive TDM including the use of a POC assay to guide infliximab dosing vs. a standard reactive treatment strategy [2]. In that study, more aggressive TDM was not associated with improved sustained clinical remission or a lower risk of infliximab failure, although the conclusions were limited by the inclusion of subjects only in the maintenance phase of treatment, with assessment of mucosal remission during the study period by endoscopy and/or fecal calprotectin measurement in only a minority of patients.

Approaches that integrate TDM as part of a treat-to-target strategy are increasingly used clinically to optimize long-term disease control and strategies that prioritize mucosal healing may be more cost-effective than approaches that solely optimize clinical response [8]. Valdés-Delgado and colleagues provide valuable insight into this issue by looking at how the POC assay performs at low and high infliximab concentrations, finding that concordance was superior at levels < 8 µg/mL, whereas the POC assay underestimates levels > 8 µg/mL. This is an important limitation of the clinical usefulness of this POC assay, since higher levels of infliximab are associated with improved likelihood of

✉ Steven Levitte
slevitte@stanford.edu

[1] Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Stanford University, 750 Welch Rd Ste 116, Palo Alto, CA 94304, USA

mucosal healing and are often needed to achieve remission in pediatric patients and patients with complicated disease, such as perianal fistulizing Crohn's disease [9]. Although having a reliable POC assay that can inform the decision to use standard or accelerated loading regimens in patients with severe colitis (particularly those with low albumin levels who sometimes require very high doses) would be especially useful in the clinical setting, this is precisely the area where Promonitor Quick IFX seems to fall short. Though future studies will need to clarify the utility and cost-effectiveness of POC assay-based TDM in IBD maintenance therapy, these results should spur further investigation into optimizing POC assays for use during induction therapy when dose escalation informed by rapid POC assessment is perhaps most valuable.

In terms of broader applicability, few studies have been conducted outside of the USA and the UK to understand how POC assays may contribute to TDM strategies in resource-limited settings. One survey of IBD providers in India found that substantial barriers to TDM include cost, availability, and time lag in result reporting [10]. Almost all of the respondents in the survey reported that they would use TDM if these barriers were removed, indicating a substantial opportunity for incorporation of POC assays in these settings. In the USA, insurance reimbursement for TDM remains a major obstacle to broad uptake; this may stem in part from the lack of clear evidence in the literature despite routine use at many IBD centers [11]. Until vigorous long-term TDM studies settle the question of clinical utility, it will be difficult for POC assays to find their optimal clinical niche. Finally, Valdés-Delgado and colleagues acknowledge some of the important shortcomings of their work. Most importantly, this was a unicentric study, although the results are broadly consistent with what has been found by others.

In summary, Valdés-Delgado and colleagues demonstrate reliable POC quantification of infliximab levels in capillary blood from patients with IBD. While it remains to be seen how POC assays will integrate into overall TDM treatment strategies, this work is an important step forward in bringing these tests to the clinic.

Acknowledgments Dorsey Bass for critical review.

Funding This work did not receive any funding.

Declarations

Conflict of interest SL reports scientific grant funding unrelated to this work from Genentech Inc., South San Francisco, USA.

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.
2. Bossuyt P, Pouillon L, Claeys S, D'Haens S, Hoefkens E, Strubbe B et al. Ultra-proactive Therapeutic Drug Monitoring of Infliximab Based on Point of Care Testing in Inflammatory Bowel Disease: Results of a Pragmatic Trial. *J Crohns Colitis.* 2022;16:199–206.
3. Shmais M, Regueiro M, Hashash JG. Proactive versus Reactive Therapeutic Drug Monitoring: Why, When, and How? *Inflamm Intest Dis.* 2022;7:50–58.
4. Sethi S, Dias S, Kumar A, Blackwell J, Brookes MJ, Segal JP. Meta-analysis: The efficacy of therapeutic drug monitoring of anti-TNF-therapy in inflammatory bowel disease. *Aliment Pharmacol Ther.* 2023;57:1362–1374.
5. Facchin S, Buda A, Cardin R, Agbariah N, Zingone F, De Bona M et al. Rapid point-of-care anti-infliximab antibodies detection in clinical practice: comparison with ELISA and potential for improving therapeutic drug monitoring in IBD patients. *Therap Adv Gastroenterol.* 2021;14:1756284821999902.
6. Ruiz-Argüello B, del Agua AR, Torres N, Monasterio A, Martínez A, Nagore D. Comparison study of two commercially available methods for the determination of infliximab, adalimumab, etanercept and anti-drug antibody levels. *Clin Chem Lab Med.* 2013;51:e287–e289.
7. Valdés-Delgado T, Aguado-Paredes, A, Merino-Bohórquez, V, et al. Performance of a new rapid point-of-care test for infliximab levels in patients with inflammatory bowel disease: a comparison to ELISA. *Dig Dis Sci*. https://openaccesspub.org/journal/digestive-disorders-and-diagnosis#:~:text=Journal%20of%20Digestive%20Disorders%20And%20Diagnosis%20is%20a%20comprehensive%2C%20peer,of%20scientists%20around%20the%20globe.
8. Colombel JF, D'haens G, Lee WJ, Petersson J, Panaccione R. Outcomes and Strategies to Support a Treat-to-target Approach in Inflammatory Bowel Disease: A Systematic Review. J Crohns Colitis. 2020 14:254–66.
9. Jongsma MME, Winter DA, Huynh HQ, Norsa L, Hussey S, Kolho KL et al. Infliximab in young paediatric IBD patients: it is all about the dosing. *Eur J Pediatr.* 2020;179:1935–1944.
10. Patel RN, Nigam GB, Jatale RG, Desai D, Makharia G, Ahuja V et al. An Indian national survey of therapeutic drug monitoring with anti-tumor necrosis (TNF) medications in inflammatory bowel disease. *Indian J Gastroenterol.* 2020;39:176–185.
11. Campbell JP, Burton E, Wymer S, Shaw M, Vaughn BP. Out-of-Pocket Cost Is a Barrier to Therapeutic Drug Monitoring in Inflammatory Bowel Disease. *Dig Dis Sci.* 2017;62:3336–3343.