



Putting TDM knowledge into practice

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'Knowledge is of no value unless you put it into practice' is a quote usually attributed to Anton Chekov. It is advice particularly relevant to therapeutic drug monitoring (TDM) of infliximab (IFX) in patients with inflammatory bowel disease (IBD). Several observational studies have identified low IFX trough levels, or antibodies to IFX, or both, as a factor in the loss of response to this drug in patients with IBD.¹ In addition, intervention studies to prospectively adjust IFX dosing to maintain a range of trough levels have shown some impact on long-term outcomes (IBD).² Collectively, these data implied that using TDM routinely in the clinic could improve outcomes, and minimise risk of adverse events, for patients. Whether this assumption is correct can only be answered with longitudinal studies from the 'real world'. Recent guidelines have recommended that TDM be performed routinely in patients losing response to IFX, but is of uncertain value in routine monitoring of patients in remission.³

A paper by Kamperidis shares their experience using TDM of IFX levels in an IBD clinic.⁴ They collected data on 238 patients with Crohn's disease, who received IFX, and had TDM testing during therapy. Since this was a retrospective data collection, there was no prespecified timing or indication for TDM in this cohort. Most of the samples (70%) were taken for 'routine monitoring', and the remainder (27%) due to loss of response. The variability of drug levels in practice is highlighted by the fact that IFX trough levels were undetectable in 23% of samples, between 1 and 3 µg/mL in 24%, and greater than 3 µg/mL in 53%. Their primary goal was to quantify the impact of TDM results on clinical management. They report that no action was taken in response to 78% of the results, although this is not surprising, since most patients had detectable trough levels (the majority being ≥ 3 µg/mL). However, the authors interpreted this as a negative outcome, as it cost £28 000 to perform all the assays, and only led to a change in patient management in 22%.

Such an outcome is always challenging to interpret as, depending on your perspective, these results could be seen as either a waste of resources (short-term costs) or confirmation that their dosing schedules were appropriate to achieve better long-term outcomes (long-term costs). Data from several studies have indicated that the minimal trough level of IFX to achieve remission or mucosal healing is >3 µg/mL, so if this threshold was applied to this cohort, at least 48% of patients should have had their dosing adjusted.^{1–5} Cost-effectiveness analyses have reported that TDM had a net cost-saving effect, due to de-escalation in patients with very high levels, and reduction in costly clinical outcomes like relapse.⁶ Although there are upfront costs for the assays, maintaining a greater proportion of patients in clinical remission would seem to be less expensive to a healthcare system than treating the episodes of relapse in 40% of a cohort of 200+ patients. Several other secondary outcomes were examined in this paper; notable among these was that patients who did not have TDM during follow-up were eight times more likely to stop IFX due to loss of response or adverse events, a similar finding to other retrospective studies. I would caution on the clinical implications of this, given the limitations of such a retrospective study.

The take-home message from this cohort is that routine use of TDM in clinical practice may only change management decisions in a subset of patients, if you use a conservative threshold for 'adequate trough levels' of 1 µg/mL. There is also an upfront cost to providing this measure in the clinic. On the flip side, routine TDM can identify underdosed and potentially overdosed patients, and confirm that the dosing schedule used leads to trough levels that have been associated with optimal long-term outcomes. In an era of personalised medicine, this would appear to be a beneficial adaptation to the standardised dosing schedules approved by regulatory bodies.

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REFERENCES

- Moore C, Corbett G, Moss AC. Systematic review and meta-analysis: serum infliximab levels during maintenance therapy and outcomes in inflammatory bowel disease. *J Crohns Colitis* 2016;10:619–25.
- Vande Casteele N, Ferrante M, Van Assche G, *et al.* Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology* 2015;148:1320–9.
- Feuerstein JD, Nguyen GC, Kupfer SS, *et al.* American Gastroenterological Association Institute Guideline on Therapeutic Drug Monitoring in Inflammatory Bowel Disease. *Gastroenterology* 2017;153:827–34.
- Kamperidis V. The impact of therapeutic drug level monitoring on outcomes of patients with Crohn's disease treated with Infliximab: real world data from a retrospective single centre cohort study. *Frontline Gastroenterology* 2019. doi: 10.1136/flgastro-2018-101024.
- Vaughn BP, Martinez-Vazquez M, Patwardhan VR, *et al.* Proactive therapeutic concentration monitoring of infliximab may improve outcomes for patients with inflammatory bowel disease: results from a pilot observational study. *Inflamm Bowel Dis* 2014;20:1996–2003.
- Guidi L, Pugliese D, Panici Tonucci T, *et al.* Therapeutic drug monitoring is more cost-effective than a clinically-based approach in the management of loss of response to infliximab in inflammatory bowel disease: an observational multicentre study. *J Crohns Colitis* 2018 [Epub ahead of print 31 May 2018].