Fact sheet

Version 1 – September 2021

Facilitating the translation of evidence into best practice:

Therapeutic drug monitoring in inflammatory bowel disease

Key points

- Therapeutic drug monitoring (TDM) including drug trough concentrations and anti-drug antibodies is indicated in inflammatory bowel disease (IBD) after primary and secondary loss of response:
  - After primary non-response: TDM in this circumstance can help to decide if the primary non-response is a result of pharmacokinetic issues, from inadequate drug trough concentrations, or due to pharmacodynamic issues, from disease refractory to the specific monoclonal antibody.
  - After secondary loss of response: TDM in this setting may guide appropriate intervention that might include dose intensification, change within class or change out-of-class.
- Proactive therapeutic drug monitoring may be indicated in IBD when considering step down therapy and drug holidays.
- There is lack of consensus on ideal trough concentrations for ustekinumab and vedolizumab in IBD after induction and during maintenance.

Background

- TDM of biologic therapy in IBD is being increasingly utilised as a helpful tool to optimize remission rates and prevent relapse.[1]
- Biologic TDM involves the measurement of serum drug concentrations and anti-drug antibody titres.[2]
- TDM is intended to measure drug trough concentrations and therefore is usually performed immediately prior to the next scheduled biologic treatment dose, although for medicines used subcutaneously this may be less important.
- TDM comprises just one aspect of patient monitoring and should be interpreted alongside other relevant clinical, endoscopic, imaging and biomarker findings to aid clinical decision making. Evidence for changing clinical management based on TDM results alone has not been established.[2]
- Dosing regimen modifications should be tailored to the individual.[3]
- Current evidence does not support the superiority of a proactive TDM strategy over a reactive strategy for improving clinical remission rates. It may be useful to guide clinical decision making.

For more information, please contact:

CATAG
Council of Australian Therapeutic Advisory Groups

Phone: (02) 8382 2852
Fax: (02) 8382 3529
Email: catag@stvincents.com.au
Web: www.catag.org.au

Purpose

CATAG has developed this document to facilitate and support the translation of best available evidence into practice for the management of patients with inflammatory bowel disease. The document summarises the evidence on the use of therapeutic drug monitoring of biologics as of May 2021. This will assist good governance and decision-making for health service organisations, medicines governance committees and health professionals. It can be used in conjunction with formulary decisions and recommendations.

Latest evidence

1. Therapeutic drug monitoring including drug trough concentrations and anti-drug antibodies is indicated after primary and secondary loss of response

There is strong evidence for reactive TDM (if treatment failure is developing) of tumour necrosis factor (TNF) inhibitors to support decision making in certain circumstances.[4–6] Much of the data has been extrapolated from trials with infliximab. The use of reactive TDM to guide dose adjustment compared with clinical decision-making alone is associated with better clinical responses.[7] There is limited data suggesting superior cost efficacy with a reactive TDM based treatment algorithm compared to treatment escalation without TDM.[8] See **Table 1** for recommended threshold trough concentrations.

Table 1: Threshold trough concentrations

DRUG	THRESHOLD TROUGH CONCENTRATIONS
Infliximab	>3 µg/mL[4,9]
Adalimumab	>5 µg/mL[4]
Golimumab	≥1 µg/mL[4,9]

It is recommended that any therapeutic range used, should be based on achieving mucosal healing rather than clinical remission.

Interpretation of the target trough concentration depends on the context in which the TDM is being performed. In people with either active disease[10], complicating features such as fistulising Crohn disease[11] or considering down-titration of biologics, higher therapeutic concentrations may be required.

After primary non-response

TDM in this circumstance can help to decide if the primary non-response is a result of pharmacokinetic issues, which is indicated by inadequate drug trough concentrations, or due to pharmacodynamic issues, such as disease refractory to the specific monoclonal antibody.[4,5]

After secondary loss of response

TDM in the setting of secondary loss-of response may guide appropriate intervention that might include dose intensification, change within class or change out-of-class.

In active IBD, TDM can assist in explaining three types of failure to biologics: mechanistic failure (therapeutic drug trough concentrations and absence of anti-drug antibodies), immune-mediated drug failure (low or undetectable drug trough concentrations and high titres of anti-drug antibodies), and non-immune-mediated failure (subtherapeutic drug trough concentrations and absent anti-drug antibodies).[12] See **Table 2** on algorithms for the use of therapeutic drug monitoring in patients with IBD for further interpretation and action on these results.

Which TDM test to undertake

- Drug trough concentrations to ascertain whether they are within recommended target range and the need for dose escalation
- Anti-drug antibody titres when drug trough concentrations are undetectable or very low (the threshold or 'trigger' concentrations for each drug vary between centres and laboratories).[4,5]

Table 2: Algorithms

ALGORITHM	LINK
Reactive and proactive algorithm	Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68(Suppl 3):s1–s106.
	Papamichael K, Cheifetz AS. Use of anti-TNF drug levels to optimise patient management. Frontline Gastroenterology 2016;7:289–300.
Reactive following secondary loss of response	Ciara Egan & Glen A. Doherty Why do we need to improve monitoring of patients with inflammatory bowel disease (IBD) on biologic treatment?, Expert Opinion on Biological Therapy 2019;19:9, 907–18.
	GESA. Clinical Update for General Practitioners and Physicians, Inflammatory Bowel Disease, Updated 2018.
	Mitrev N, Vande Casteele N, Seow CH, Andrews JM, Connor SJ, Moore GT, et al. Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases. Aliment Pharmacol Ther. 2017;46(11–12):1037–53.

2. Proactive therapeutic drug monitoring may be indicated when considering step down therapy and drug holidays

Recommendations for proactive TDM vary significantly between guideline and other expert groups.

The evidence for recommending proactive TDM (i.e. routine TDM to optimise drug dosing towards a target drug concentration range when patient is clinically well) is less clear with evidence showing mixed results and it is not recommended by the international gastroenterological organisations.[6,10,12–14] Studies supporting a proactive TDM approach are described below:

- The Pediatric Crohn's Disease Adalimumab Level-based Optimization Treatment (PAILOT) trial. Randomised controlled trial, comparing proactive versus reactive TDM of adalimumab in paediatric patients with Crohn disease demonstrated proactive TDM to be superior to reactive monitoring, in the setting of scheduled monitoring of clinical and biologic measures, resulting in higher corticosteroid-free sustained remission.[15]
- The Trough Concentration Adapted Infliximab Treatment (TAXIT) study, a randomised controlled trial, which despite failing to meet its primary endpoint, showed that proactive TDM of infliximab compared with clinically based dosing was associated with fewer flares requiring steroid rescue (7% versus 17% at 12 months, P = 0.018), lower frequency of undetectable drug concentrations and lower risk of relapse.[16]
- The TAILORIX trial was a prospective randomised, double-blinded, multicentre study, in which adult patients with active CD receiving infliximab in combination with an immunosuppressant were randomised to proactive versus reactive TDM. Dose increase of infliximab based on a combination of symptoms, biomarkers, and/or serum drug concentrations was not superior to dose increase based on symptoms alone.[17]

Based on this limited evidence, proactive TDM may be considered under the following circumstances (see **Table 3**).

Table 3: When to consider proactive TDM

SCENARIO	RATIONALE
When stepping down from combination therapy	When ceasing an immunomodulator that has been part of a combination regimen with a biologic, to ensure trough concentrations are within recommended target range.
When reducing the dose from a previously escalated dose above conventional dosing	Before and after de-escalating biologic therapy, which has been dose-escalated previously, to ensure trough concentrations are/remain within recommended target range.
After induction therapy	Drug trough concentrations below the therapeutic range are associated with an increased risk of developing anti-drug antibodies and as a result increased disease activity. The risk of anti-drug antibodies increases with duration of subtherapeutic concentrations. Keeping the TNF inhibitor within the therapeutic range decreases the risk for development of anti-drug antibodies (particularly against TNF inhibitors), and subsequent loss of effectiveness. Proactive TDM following induction, will help identify those patients whose drug concentration is subtherapeutic.[5]
Undertaking drug holidays	To inform decisions on stopping biologics.[5]

3. There is lack of consensus on ideal trough concentrations for ustekinumab and vedolizumab after induction and during maintenance

The evidence for the use of TDM with ustekinumab and vedolizumab is limited, with little guidance available. Further research is required to identify the concentration ranges predictive of clinical and endoscopic remission, and whether TDM of ustekinumab and vedolizumab improves overall outcomes.[18]

Further information

- Scottish Biologic Drug Monitoring Service
- NPS bDMARDs program.

Appendices

APPENDIX 1: Glossary

TERM	DEFINITION
Primary loss of response	Lack of improvement following a course of induction therapy.[19]
Proactive	Routine TDM performed in patients who are clinically well with the aim of optimising drug dosing towards a target drug concentration range to prevent future flares and loss of response.[5]
Reactive	TDM performed in patients who are failing treatment in order to guide decision-making.[5]
Secondary loss of response	A subsequent loss of response during maintenance therapy, in patients who has previously responded to induction therapy.[19]

APPENDIX 2: How this was developed

CATAG has developed this document, based on evidence summaries produced by the Quality Use of Medicines and Pharmacy Research Centre, University of South Australia, to facilitate and support the translation of best available evidence into practice for the management of inflammatory bowel disease. This will assist good governance and decision-making for health service organisations, medicines governance committees and health professionals.

This guidance has been developed by CATAG, as part of the ViP bDMARDs program.

This guidance was developed in consultation with the CATAG member organisations listed below:

- ACT Health
- NSW Therapeutic Advisory Group (NSW TAG)
- Northern Territory Drug and Therapeutics Committee
- Queensland Health Medicines Advisory Committee (QHMAC)
- South Australian Medicines Advisory Committee (SAMAC)
- Tasmanian Medicines Access and Advisory Committee (TMACC)
- Victorian Therapeutics Advisory Group (VicTAG)
- Western Australian Therapeutics Advisory Group (WATAG).

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+TARGETED THERAPIES ALLIANCE

Helping consumers and health professionals make safe and wise therapeutic decisions about biological disease-modifying antirheumatic drugs (bDMARDs) and other specialised medicines. Funded by the Australian Government Department of Health through the Value in Prescribing bDMARDs Program Grant.

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