Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases


Summary

Background: Therapeutic drug monitoring (TDM) in inflammatory bowel disease (IBD) patients receiving anti-tumour necrosis factor (TNF) agents can help optimise outcomes. Consensus statements based on current evidence will help the development of treatment guidelines.

Aim: To develop evidence-based consensus statements for TDM-guided anti-TNF therapy in IBD.

Methods: A committee of 25 Australian and international experts was assembled. The initial draft statements were produced following a systematic literature search. A modified Delphi technique was used with 3 iterations. Statements were modified according to anonymous voting and feedback at each iteration. Statements with 80% agreement without or with minor reservation were accepted.

Results: 22/24 statements met criteria for consensus. For anti-TNF agents, TDM should be performed upon treatment failure, following successful induction, when contemplating a drug holiday and periodically in clinical remission only when results would change management. To achieve clinical remission in luminal IBD, infliximab and adalimumab trough concentrations in the range of 3-8 and 5-12 μg/mL, respectively, were deemed appropriate. The range may differ for different disease phenotypes or treatment endpoints—such as fistulising disease or to achieve mucosal healing. In treatment failure, TDM may identify mechanisms to guide subsequent decision-making. In stable clinical response, TDM-guided dosing may avoid future relapse. Data indicate drug-tolerant anti-drug antibody assays do not offer an advantage over drug-sensitive assays. Further data are required prior to recommending TDM for non-anti-TNF biological agents.

Conclusion: Consensus statements support the role of TDM in optimising anti-TNF agents to treat IBD, especially in situations of treatment failure.
1 | INTRODUCTION

Currently available biological drugs are large proteins, often monoclonal antibodies, which bind and inhibit a target molecule. Anti-tumour necrosis factor (TNF) agents, including infliximab and adalimumab, were the first biological agents effective in inducing and maintain remission in inflammatory bowel disease (IBD). More recently developed biological agents effective in IBD include vedolizumab, an α4β7-integrin inhibitor, and ustekinumab, an inhibitor of the inflammatory cytokines interleukin-12/23.5-7

Although biological agents have revolutionised IBD treatment, primary nonresponse and secondary loss-of-response are common with resulting adverse outcomes. Among infliximab- and adalimumab-treated patients, primary nonresponse occurs in 10%-30% of patients, and secondary loss-of-response in 23%-46% by 12 months. Treatment with biological agents is expensive and there are limited biological drug choices for IBD, highlighting a need to optimally use each agent. Therapeutic drug monitoring (TDM)-guided anti-TNF dosing has emerged as a strategy to optimise treatment and maximise benefits from these drugs. TDM for anti-TNF agents involves measurement of drug levels and anti-drug antibodies. Reactive TDM is performed in patients failing treatment in order to guide decision-making. Proactive TDM is performed in responding patients to optimise therapy and potentially prevent future flare and loss-of-response. Data for TDM-guided dosing are emerging for other biological agents.10-13

We employed a modified Delphi method to reach a consensus for incorporating TDM for anti-TNF agents into modern IBD management. Points addressed included scenarios for performing TDM, interpretation of results and when/how to act on them. We focused on TDM for anti-TNF agents as this has the largest evidence base to date.

2 | METHODS

A modified Delphi process with 3 iterations was employed in developing these guidelines as previously described. A steering committee (RWL, JMA, SJC, GM, NM) was formed and invited a wide-ranging expert panel comprising adult and paediatric gastroenterologists, clinical pharmacologists/pharmacists and an immunologist. Nominated gastroenterologists were experts in IBD based on publications, clinical experience through high-volume dedicated IBD clinics and leadership within the field. Nominees from other disciplines had expertise in the field of TDM.

A systematic literature search was performed (NM) from inception to 1 June 2016 using PubMed and Medline databases with search terms: inflammatory bowel disease OR Crohn’s disease OR ulcerative colitis AND therapeutic drug monitoring AND infliximab OR adalimumab OR anti-tumour necrosis factor (Figure S1). Articles relevant to the consensus statements were selected. Additional articles were obtained by searching the bibliography of selected articles, via searching abstracts from major international conferences and from committee members. The steering committee drafted an initial set of consensus statements that were subsequently revised through focus groups.

The first voting survey was distributed online. Panellists rated their level of agreement for individual statements as: (A) agree without reservation, (B) agree with minor reservation, (C) agree with major reservation, (D) disagree with some reservation, (E) disagree without reservation or (F) reserved. Draft statements were refined based on anonymous voting results and feedback. Articles from the literature search, an evidence summary and a de-identified summary of the first-round voting results were distributed to panellists prior to the second round of online voting. Following the second voting round, a summary of voting results was again distributed and statements were refined. The third voting round was a face-to-face meeting held in January 2017 in Sydney, Australia. Each statement was presented, discussed, refined and voted on. Statements with 80% agreement without reservation or with minor reservation were accepted as consensus. Failure to achieve consensus allowed the statement to be revised and revoted once only. The reason/s behind the failure to achieve consensus was recorded. For each statement, panellists agreed on the level of evidence and grade of recommendation according to the Australian National Health and Medical Research Council (NHMRC) guidelines. A manuscript committee (NM, RWL, CS, NV, JMA, MS, MB, MW) was formed to draft the manuscript assisted by each delegate. The final draft was approved by all members of the delegation prior to submission for publication.

3 | RESULTS

3.1 | Consensus panel and voting sessions

Of the 26 nominees, 25 accepted the invitation, including: 19 gastroenterologists (RWL, SJC, GM, JMA, CS, SG, MG, DL, VK, CC, MGW, MS, DVL, PL, JB, GRS, RB, RM and KV), 1 IBD fellow (NM), 1 gastroenterologist/clinical pharmacologist (MB), 2 clinical pharmacologists (NVC, JM), 1 investigational pharmacist (PS) and 1 immunologist (CT). All 25 voting panellists took part in the first 2 voting rounds. The final face-to-face voting meeting was attended by 22 of the panellists. Four nonvoting panellists comprised of a patient (patient support organisation and consumer representative), 2 IBD fellows and the Chief Executive Officer of the Gastroenterological Society of Australia (GESA, funding body). Consensus was reached on 22/24 statements (Tables 1-3). There was significant correlation between NHMRC evidence level and grade of recommendation (Spearman’s correlation co-efficient = 0.544, P = .006).

3.2 | Scenarios when TDM of anti-TNF agents should be performed

The following statements are scenarios that benefit from TDM. An additional indication to a previous consensus, TDM might identify immunogenicity on re-introduction of a biological agent after previous
TABLE 1  Scenarios for performing TDM of anti-TNF agents and general approach to patients with symptoms of active disease on anti-TNF therapy (Statements 1-6). Acceptance was defined by percentage agreement with no- or only minor reservation. Statements that did not meet criteria for consensus are marked with “*”. The NHMRC evidence levels (EL) and recommendation grades (RG) are described.

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<tr>
<th>Statement</th>
<th>Acceptance (%)</th>
<th>EL</th>
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<tbody>
<tr>
<td>1. In patients in clinical remission following anti-TNF therapy induction, TDM should be considered to guide management</td>
<td>100</td>
<td>II</td>
<td>C</td>
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<tr>
<td>2. TDM can inform clinical decision-making in patients with primary nonresponse</td>
<td>100</td>
<td>II</td>
<td>C</td>
</tr>
<tr>
<td>3. TDM should be performed in patients with secondary loss-of-response to guide clinical decision-making</td>
<td>100</td>
<td>I</td>
<td>B</td>
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<tr>
<td>4. TDM should be considered periodically in patients in clinical remission if the results are likely to impact management</td>
<td>90</td>
<td>IV</td>
<td>D</td>
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<tr>
<td>5. Patients maintained in clinical remission in whom a drug holiday is contemplated, are suggested to have TDM along with other investigations to help guide this decision</td>
<td>100</td>
<td>II</td>
<td>C</td>
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General approach to patients with symptoms of active disease on anti-TNF therapy

<table>
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<th>Statement</th>
<th>Acceptance (%)</th>
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<tr>
<td>6. Patients with symptoms of active disease on anti-TNF therapy should have active inflammatory disease confirmed via objective measures (endoscopy, imaging, serum/taecal biomarkers) and investigations to exclude alternative/concomitant causes of symptoms, prior to change in therapy</td>
<td>100</td>
<td>III</td>
<td>C</td>
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Achieve therapeutic drug levels may reduce the risk of developing anti-drug antibodies and secondary loss-of-response, particularly as most anti-drug antibodies develop in the first 12 months from starting therapy. During the lead-in optimisation phase of the Trough level Adapted infliximab Treatment (TAXIT) trial, patients with Crohn’s disease (CD) who had sub-therapeutic drug levels underwent dose intensification to achieve a target range (3-7 μg/mL). This was associated with a decrease in mean C-reactive protein (CRP) and increase in the proportion of patients in clinical remission. No statistically significant difference was found for UC patients. The median time from first infliximab exposure to recruitment to the TAXIT trial was 4.5 years, and potentially there may be more to gain from earlier dose optimisation. Alternatively, a longer duration of follow-up might have detected a divergence in loss-of-response.

2. TDM can inform clinical decision-making in patients with primary nonresponse (EL-III2, RG-C).

There is good evidence supporting the role of TDM in secondary loss-of-response. Relatively few studies have assessed TDM-guided therapy in primary nonresponse. TDM can indicate if primary nonresponse is driven by pharmacokinetic issues, from inadequate drug levels, or by pharmacodynamic issues, from anti-TNF refractory disease.

3. TDM should be performed in patients with secondary loss-of-response to guide clinical decision-making (EL-I, RG-B).

Therapeutic drug monitoring testing for secondary loss-of-response may guide appropriate intervention that might include dose intensification, change within class or change out-of-class. A cohort study found that TDM-guided treatment following secondary loss-of-response to infliximab resulted in significant cost saving (34% at 12 weeks, 31% at 20 weeks and 24% at 1 year) compared to empiric trial of dose escalation, despite equivalent clinical outcomes.

4. TDM should be considered periodically in patients in clinical remission if the results are likely to impact management (EL-IV, RG-D).

Data on benefits of proactive TDM over empiric dosing or reactive TDM are mixed, making recommending a regular interval for repeating TDM among patients who maintain response difficult. The TAXIT study compared TDM-guided dosing to maintain infliximab levels within a therapeutic range, to dosing based on clinical symptoms and CRP, among infliximab responders following an initial dose optimisation phase. Despite failing to meet its primary endpoint (improvement in clinical and biochemical remission at 12 months), the TDM-guided group had fewer flares necessitating steroid rescue (7 vs 17% at 12 months, P = .018). While the subsequent Tailored Treatment With Infliximab for Active Luminal Crohn’s Disease (TAILORIX) study found no additional benefit of proactive TDM-guided dose intensification after induction therapy compared with usual care for the combined primary endpoint of steroid-free clinical and endoscopic remission. However, a retrospective observational study found significantly lower rates of discontinuing infliximab in IBD patients who had proactive TDM.
TABLE 2  Interpreting TDM results (Statements 7-16). Acceptance was defined by percentage agreement with no or only minor reservation. Statements that did not meet criteria for consensus are marked with “*”. The NHMRC evidence levels (EL) and recommendation grades (RG) are described.²¹

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<th>Statement</th>
<th>Acceptance (%)</th>
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<tr>
<td><strong>Interpreting TDM results in patients with confirmed active inflammatory disease on anti-TNF therapy</strong></td>
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<tr>
<td>7. Patients with confirmed active inflammatory disease and therapeutic drug trough levels (suggests pharmacodynamic failure) should be switched out-of-class</td>
<td>91</td>
<td>III2</td>
<td>C</td>
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<tr>
<td>8. Patients with confirmed active inflammatory disease and sub-therapeutic drug trough levels and no detectable anti-drug antibodies (suggests non-immune mediated pharmacokinetic failure) should have adherence checked first followed by dose escalation of the anti-TNF agent. Optimisation/introduction of an immunomodulator should be considered</td>
<td>100</td>
<td>III3</td>
<td>B</td>
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<tr>
<td>9. Patients with confirmed active inflammatory disease and sub-therapeutic drug trough levels and low titres of anti-drug antibodies (suggests immune mediated pharmacokinetic failure) should have an immunomodulatory added/optimised and/or anti-TNF dose escalation</td>
<td>100</td>
<td>III3</td>
<td>C</td>
</tr>
<tr>
<td>10. Patients with confirmed active inflammatory disease and sub-therapeutic drug trough levels and high titres of anti-drug antibodies (suggests immune mediated pharmacokinetic failure) should be: (1) switched within class for secondary loss-of-response, or (2) switched within class or switched out-of-class for primary nonresponse</td>
<td>100</td>
<td>III2</td>
<td>B</td>
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<tr>
<td><strong>Interpreting TDM results among patients in clinical remission on anti-TNF therapy</strong></td>
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<tr>
<td>11. Patients in clinical remission and therapeutic drug trough levels should be continued on the same dose</td>
<td>100</td>
<td>II</td>
<td>B</td>
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<tr>
<td>12. Patients in clinical remission and with supra-therapeutic drug trough levels should be considered for dose reduction</td>
<td>100</td>
<td>III1</td>
<td>B</td>
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<tr>
<td>13. Patients in clinical remission and with sub-therapeutic drug trough levels should be individually assessed for suitability for a drug holiday</td>
<td>24*</td>
<td>III3</td>
<td>B</td>
</tr>
<tr>
<td>14. Patients in clinical remission who have high-risk features, and sub-therapeutic drug trough levels and undetectable anti-drug antibodies should have an immunomodulatory added/optimised and/or dose escalation</td>
<td>95</td>
<td>III3</td>
<td>C</td>
</tr>
<tr>
<td>15. Patients in clinical remission who have high-risk features, and with sub-therapeutic drug trough levels and low titres of anti-drug antibodies should have an immunomodulatory added/optimised and/or dose escalation</td>
<td>100</td>
<td>III1</td>
<td>B</td>
</tr>
<tr>
<td>16. Patients in clinical remission who have high-risk features with undetectable trough drug levels and persistently high titres of anti-drug antibodies, should be considered for switching within or out-of-class</td>
<td>86</td>
<td>III2</td>
<td>C</td>
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compared to those who had reactive TDM (10% vs 31%, \( P = .009 \)).⁴⁴-⁴⁷ There was, however, potential for confounders in this study. Another retrospective observational study found significantly lower likelihood of treatment failure (HR 0.16, \( P < .001 \)), hospitalisation (HR 0.16, \( P < .001 \)), surgery (HR 0.30, \( P = .017 \)), development of anti-drug antibodies (HR 0.25, \( P = .025 \)) and serious infusion reactions (HR 0.17, \( P = .023 \)) with proactive vs reactive TDM-guided infliximab dosing.⁴⁹

5. Patients maintained in clinical remission in whom a drug holiday is contemplated, are suggested to have TDM along with other investigations to help guide this decision (EL-III2, RG-C).

Suitability for an anti-TNF drug holiday should take into consideration the risk of relapse and the potential consequences of relapse. TDM prior to anti-TNF cessation can help stratify the subsequent risk of relapse. Clinical remission despite sub-therapeutic anti-TNF drug trough levels may be explained by adequate anti-TNF drug exposure at other points of the dosing cycle, an individual with lower drug need, impending loss-of-clinical response or disease remission no longer dependent on anti-TNF drug exposure. The first 2 reasons may be supported by levels being slightly below the therapeutic range. The latter 2 reasons, however, are more likely if drug levels are either very low or undetectable. Patients in clinical remission with persistently undetectable anti-TNF drug trough levels on repeat measurements likely are no longer reliant on anti-TNF drug exposure to maintain remission.⁴⁷ Indeed, sub-therapeutic or undetectable trough levels is associated with lack of relapse following anti-TNF cessation in carefully selected cohorts.⁵⁰-⁵³ Additional predictors for maintaining clinical remission during an anti-TNF drug holiday should also be considered in deciding suitability for an anti-TNF drug holiday. These include the absence of recent corticosteroid use, no prior bowel resections, nonsmoking status, female gender, haemoglobin >145 g/L, endoscopic mucosal healing and normalisation of inflammatory biomarkers (white cell count, CRP and faecal calprotectin).⁵²,⁵⁴-⁵⁷ Given that the consequences of disease relapse are high in patients with aggressive disease phenotypes (such as following multiple surgeries, prior disease refractory to multiple therapeutic classes), the decision to undertake a drug holiday must be carefully considered and individualised.

3.3  General approach to patients with symptoms of active disease on anti-TNF therapy

6. Patients with symptoms of active disease on anti-TNF therapy should have active inflammation confirmed via objective measures (endoscopy, imaging, serum/faecal biomarkers) and investigations to exclude alternative/concomitant causes of symptoms, prior to change in therapy (EL-III3, RG-C).
TABLE 3  Therapeutic drug levels, anti-drug antibodies and TDM for non-anti-TNF biological agents (Statements 17-24). Acceptance was defined by percentage agreement with no or only minor reservation. Statements that did not meet criteria for consensus are marked with **. The NHMRC evidence levels (EL) and recommendation grades (RG) are described.

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<th>Statement</th>
<th>Acceptance (%)</th>
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<tr>
<td>Target drug trough levels</td>
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<tr>
<td>17. In IBD patients with luminal disease a steady state trough infliximab level between 3 and 8 μg/mL is generally recommended</td>
<td>96</td>
<td>II</td>
<td>B</td>
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<tr>
<td>18. In IBD patients with luminal disease a steady state adalimumab trough level between 5 and 12 μg/mL is generally recommended</td>
<td>95</td>
<td>II</td>
<td>C</td>
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<tr>
<td>19. In certain situations higher or lower trough levels than the above ranges may be appropriate</td>
<td>100</td>
<td>III</td>
<td>B</td>
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<tr>
<td>Anti-drug antibodies</td>
<td></td>
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<tr>
<td>20. When interpreting anti-drug antibodies, quantifying titres is clinically more useful than positive/negative status</td>
<td>100</td>
<td>II</td>
<td>B</td>
</tr>
<tr>
<td>21. When interpreting anti-drug antibodies, repeat testing is useful to determine if antibodies are transient or persistent</td>
<td>100</td>
<td>II</td>
<td>B</td>
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<tr>
<td>22. There is insufficient evidence to recommend a drug-tolerant assay for anti-drug antibody detection</td>
<td>95</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>TDM for non-anti-TNF biological agents and future therapies</td>
<td></td>
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<tr>
<td>23. There is emerging evidence that drug levels of non-anti-TNF biological agents may be relevant to clinical endpoints. However, more data are required before the routine use of TDM to guide therapy with these agents can be recommended</td>
<td>96</td>
<td>IV</td>
<td>D</td>
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<tr>
<td>24. Data on TDM should be available at time of registration for all future therapies</td>
<td>77*</td>
<td>III</td>
<td>B</td>
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3.4 Interpreting TDM results in patients with confirmed active inflammatory disease on anti-TNF therapy

The recommendations for interpreting TDM results among patients with active disease on anti-TNF therapy were summarised in an algorithm (Figure 1).

7. Patients with confirmed active inflammatory disease and therapeutic drug trough levels (suggests pharmacodynamic failure) should be switched out-of-class (EL-III2, RG-C).

Patients with confirmed active inflammatory disease with therapeutic levels of anti-TNF drug are likely to have pharmacodynamic failure, provided the therapeutic range is appropriate for the chosen endpoint. Molecular polymorphisms in apoptosis genes or other pathways can cause anti-TNF-resistance manifested as primary non-response and prolonged anti-TNF therapy may paradoxically promote TNF-independent inflammatory pathways resulting in secondary loss-of-response. Continuing anti-TNF therapy or within-class switching is unlikely to be effective. Yanai et al found that among patients with secondary loss-of-response to infliximab or adalimumab with therapeutic drug levels, response rates were no different in those who underwent dose intensification compared to switching within class to an alternate anti-TNF agent or had anti-TNF withdrawal and symptomatic treatment. However, switching out-of-class was associated with significantly improved outcomes.

8. Patients with confirmed active inflammatory disease and sub-therapeutic drug trough levels and no detectable anti-drug antibodies (suggests non-immune-mediated pharmacokinetic failure) should have adherence checked first followed by dose escalation of the anti-TNF agent. Optimisation/introduction of an immunomodulator should also be considered (EL-III2, RG-B).

Among patients with sub-therapeutic anti-TNF drug levels, measurement of anti-drug antibodies may help identify the cause of pharmacokinetic failure. In immune-mediated pharmacokinetic failure, anti-drug antibodies increase anti-TNF drug clearance. In non-immune-mediated pharmacokinetic failure, drug clearance may be increased due to genetic polymorphisms, higher body mass index (BMI), male sex or high inflammatory burden.
patients with sub-therapeutic infliximab or adalimumab drug levels, absence of anti-drug antibodies is associated with response to dose escalation. Addition of an immunomodulator has also been shown to increase drug levels. This may result from direct suppression of anti-drug antibody production, reduction of monoclonal antibody clearance by the reticuloendothelial system or by reducing inflammatory burden and circulating and tissue TNF levels.

9. Patients with confirmed active inflammatory disease and sub-therapeutic drug trough levels and low titres of anti-drug antibodies (suggests immune-mediated pharmacokinetic failure) should have an immunomodulatory added/optimised and/or anti-TNF dose escalation (EL-III3, RG-C).

Anti-drug antibody titre can influence the response to a change in management. Low-titre anti-drug antibodies may be overcome with dose escalation to restore therapeutic drug levels and response. The addition of methotrexate or a thiopurine can also overcome anti-drug antibodies.

10. Patients with confirmed active inflammatory disease and sub-therapeutic drug trough levels and high titres of anti-drug antibodies (suggests immune-mediated pharmacokinetic failure) should be: (1) switched within class for secondary loss-of-response or (2) switched within class or switched out-of-class for primary nonresponse (EL-III2, RG-B).

Detection of ATI does not negatively impact likelihood of response on switching to adalimumab, and similarly, a high proportion of adalimumab-treated patients with ATA recapture response when switched to infliximab. Patients who have previously demonstrated anti-TNF responsive disease, particularly with documented steroid-free mucosal healing, who subsequently develop secondary loss-of-response, will likely also respond to another anti-TNF agent. Patients with primary nonresponse in the setting of sub-therapeutic anti-TNF drug levels and high-titre anti-drug antibodies who have not previously demonstrated anti-TNF responsiveness may switch to another anti-TNF agent or to another biological agent class or nonbiologic immunosuppressant.

**FIGURE 1** Interpreting TDM results in patients with bowel symptoms while on anti-TNF therapy. Evidence for this algorithm is mainly in secondary loss-of-response; however, it may also be used to elicit mechanisms of failure and guide treatment decisions in primary nonresponders. ADA, anti-drug antibodies; TDM, therapeutic drug monitoring; IMM, immunomodulator; IBS, irritable bowel syndrome; TL, trough level.
Commencing or optimising existing immunomodulatory therapy when switching to another biological agent may reduce immunogenicity. Concomitant immunomodulator use reduces the risk of ATI or ATA formation. Antibodies to vedolizumab were found in only 0.4%-1.0% at 52 weeks in the registration trials and concomitant immunomodulation further reduces this rate. Similarly in the IM-UNITI study, week 52 antibodies to ustekinumab (ATU) positivity rates were low (2.3%) but it was not reported if concomitant immunomodulator use reduced this rate.

### 3.5 | Interpreting TDM results among patients in clinical remission on anti-TNF therapy

These statements are relevant for patients with high-risk poor prognostic factors for disease relapse, such as corticosteroid requirement, elevated serum/stool inflammatory biomarkers, active disease at endoscopy, shorter duration of disease remission, prior surgical resection, current smoker status, male sex and those associated with severe consequences in the event of relapse, such as prior bowel resections or short gut syndrome. These subjects should continue on a biological agent. The recommendations for TDM among patients in clinical remission were summarised in an algorithm (Figure 2).

11. Patients in clinical remission and with therapeutic trough drug levels should be continued on the same dose (EL-II, RG-B).

The above statement assumes the therapeutic range chosen is appropriate for the treatment endpoint.

12. Patients in clinical remission and with supra-therapeutic trough drug levels should be considered for dose reduction (EL-III1, RG-B).

Due to limited incremental clinical benefit of targeting anti-TNF trough concentrations above a certain threshold, significant cost saving can be achieved by dose reducing patients with supra-therapeutic levels without worsening clinical outcomes.

14. Patients in clinical remission who have high-risk features, and sub-therapeutic trough drug levels and undetectable anti-drug antibodies should have immunomodulator added/optimised and/or dose escalation (EL-III3, RG-C).

Patients in clinical remission unsuitable for a biological agent drug holiday and who have been found to have sub-therapeutic drug levels, restoration of therapeutic anti-TNF drug levels or switch to another biological agent can be recommended. Absence of anti-drug

![Figure 2](https://example.com/figure2.png)

**FIGURE 2** Interpreting TDM results in patients in clinical remission while on anti-TNF therapy. High-risk features include risk factors for disease relapse as well as risk factors for severe consequences in event of relapse (Statement 6). ADA, anti-drug antibodies; TDM, therapeutic drug monitoring; IMM, immunomodulator; TL, trough level
antibodies is associated with restoration of therapeutic drug levels on dose escalation.\textsuperscript{39,40} Dose escalating patients in remission with sub-therapeutic levels and no anti-drug antibodies, may prevent future anti-drug antibody formation and loss-of-response as previously discussed.\textsuperscript{22,26-31,107} The addition of an immunomodulator also increases anti-TNF drug levels, and this may be effective in patients with undetectable or low titre anti-drug antibodies.\textsuperscript{27,96-98}

15. Patients in clinical remission who have high-risk features, and with sub-therapeutic trough drug levels and low titres of anti-drug antibodies should have an immunomodulator added/optimised and/or dose escalation (EL-III1, RG-B).

As previously discussed, low titre anti-drug antibodies can be overcome with anti-TNF dose escalation or addition of an immunomodulator to restore therapeutic anti-TNF drug levels.\textsuperscript{39,97,98} This has predominantly been demonstrated among patients with loss-of-response but likely still applies for patients in clinical remission.

16. Patients in clinical remission who have high-risk features with undetectable trough drug levels and persistently high titres of anti-drug antibodies should be considered for switching within or out-of-class (EL-II, RG-C).

Anti-TNF dose intensification or immunomodulator addition are unlikely to eliminate persistent high titre anti-drug antibodies to restore therapeutic anti-TNF drug levels.\textsuperscript{39,102} Although high titre anti-drug antibodies are associated with persistence of antibodies, there may be less urgency to change treatment in asymptomatic patients, and repeat testing to exclude anti-drug antibody transiency may still be worthwhile before switching to another biological agent.

### 3.6 Target drug trough levels

It is unclear if trough levels are the best predictor of response to anti-TNF agents, compared to peak drug levels, drug levels at other points of the dosing cycle or total drug exposure as defined by area under a concentration-time graph.\textsuperscript{81,108} Few studies have related nontrough drug levels to clinical outcomes.\textsuperscript{42,107} To ensure comparable results, drug levels are typically measured once steady state is established. However, given the long elimination half-life of both infliximab and adalimumab of approximately 7.7-18.5 and 20 days respectively, and the variable dosing during induction therapy, steady state can take months from initiation of treatment.\textsuperscript{110-116} Waiting for steady state before measuring drug levels is not always practical. To further complicate matters, there is inter- and intra-individual variability in the elimination half-life of anti-TNF agents dependent on gender, BMI, immunomodulators co-therapy, serum albumin concentration, inflammatory burden, intestinal drug loss and anti-drug antibodies.\textsuperscript{22,91,96,99-101} Performing TDM at trough is less critical for adalimumab given the smaller fluctuations in drug levels during the dosing cycle.\textsuperscript{117,118}

The committee considered several factors in agreeing on a therapeutic range. Most TDM data, particularly for adalimumab, are for luminal CD patients; however, studies among UC patients have found similar cut-offs.\textsuperscript{47} The defined therapeutic ranges for adalimumab and infliximab should be applied with a degree of caution to UC patients. Anti-TNF drug levels do not correlate with risk of side effects.\textsuperscript{47,85-87,119} Hence, a therapeutic range should focus on optimising clinical efficacy rather than avoiding toxicity.\textsuperscript{47,81} Due to measurement error, the proposed ranges were rounded to whole numbers. A therapeutic range should be specific for a defined endpoint to use TDM-guided anti-TNF therapy in a treat-to-target strategy. The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) group recommended that a combination of patient reported outcomes remission and endoscopic remission should be the endpoint for both CD and UC treatment.\textsuperscript{58} However, the Australian Pharmaceutical Benefits Scheme funding body emphasises clinical scores to assess response to biological agents in IBD.\textsuperscript{120,121} Accordingly, the committee focused on defining a therapeutic range for this endpoint. Certolizumab and golimumab are unavailable in Australia and their TDM data were not considered.\textsuperscript{122,123}

Although drug levels measured by different assays correlate and generally lead to the same therapeutic decision, there are systematic differences between measured levels.\textsuperscript{124-133} These may be overcome to a degree with better calibration against a universal standard, known concentrations of the tested drug. Assay standardisation is required of registered pathology laboratories, while this may not necessarily be the case in the research setting. Testing drug levels in the same laboratory will minimise inter-laboratory variability of results.\textsuperscript{124}

17. In IBD patients with luminal disease, a steady-state trough infliximab level between 3 and 8 μg/mL is generally recommended (EL-II, RG-B).

Studies have found that responders have higher infliximab levels than nonresponders.\textsuperscript{134-138} Several have defined an infliximab therapeutic cut-off or range that is associated with a specific endpoint.\textsuperscript{29,35,39,42,47,106,107,134,135,137,152} In a retrospective study of secondary loss-of-response in IBD, a pre-dose intensification infliximab trough of \( \geq 3.4 \mu g/mL \) was 90% specific for failure to recapture response.\textsuperscript{39} Similarly, prospective studies by Steenholdt et al and Vande Casteele et al demonstrated cost saving and reduced flares respectively targeting a range of 3-7 μg/mL in patients receiving maintenance infliximab.\textsuperscript{25,28,36-38} Post hoc analysis of the Active Ulcerative Colitis Trials (ACT) 1 and 2 trials demonstrated that week 54 clinical remission rates plateau above a week 30 trough of 8.4 μg/mL, based on concentration quartiles.\textsuperscript{134}

18. In IBD patients with luminal disease, a steady-state trough adalimumab level between 5 and 12 μg/mL is generally recommended (EL-II, RG-C).

Data supporting a therapeutic cut-off or range for adalimumab for various endpoints have also been reported.\textsuperscript{27,39,41,47,106,139,153-161} Among patient with secondary loss-of-response, Yanai et al found a pre-dose intensification adalimumab drug level of \( \geq 4.5 \mu g/mL \) to be 90% specific for failure to respond.\textsuperscript{39} Immediately following induction therapy, a cross-sectional study found a week 14 adalimumab trough level of \( \geq 4.5 \mu g/mL \) to be associated with clinical response or
remission.\textsuperscript{28,139} Rheumatological studies show that response plateaus above an adalimumab trough of 7.8 \(\mu\)g/mL.\textsuperscript{162,163} The upper limit of the adalimumab therapeutic range to achieve clinical remission in IBD is poorly defined, but endoscopic remission rates plateau above a trough level of 12 \(\mu\)g/mL.\textsuperscript{106}

19. In certain situations, higher or lower trough levels than the above ranges may be appropriate (EL-II, RG-B).

Therapeutic ranges for infliximab or adalimumab may differ according to treatment targets and/or disease phenotypes. Therapeutic thresholds to achieve endoscopic remission appear to be higher than those required for clinical remission.\textsuperscript{47} Therapeutic ranges of 6-10 \(\mu\)g/mL for infliximab and 8-12 \(\mu\)g/mL for adalimumab were most strongly associated with endoscopic remission.\textsuperscript{106} Perianal CD fistula healing requires higher infliximab trough levels of >10 \(\mu\)g/mL, and even as high as 20 \(\mu\)g/mL.\textsuperscript{164,165}

3.7 Anti-drug antibodies

20. When interpreting anti-drug antibodies, quantifying titres is clinically more useful than positive/negative status (EL-II, RG-B).

Anti-drug antibodies can interfere with the activity of anti-TNF agents by increasing drug clearance and by direct neutralisation.\textsuperscript{89,90,166,167} Qualitative detection of antibodies to adalimumab (ATA) and ATI is associated with sub-therapeutic drug trough levels, loss-of-response and lack of recapture of response following dose escalation.\textsuperscript{40,168-170} However, quantification of the anti-drug antibody level is a better predictor.\textsuperscript{23,39,154,171} Low-titre anti-drug antibodies can often be overcome with dose intensification, and do not appear to reduce the likelihood of response as compared to patients with undetectable anti-drug antibodies.\textsuperscript{39} Differences in assay methodology result in varying sensitivity to detect various anti-drug antibody subtypes, and adjusting for these differences is difficult due to a wide variation in the relative proportions of anti-drug antibody subtypes between individuals.\textsuperscript{125,126,172,173} Therefore, ATI and ATA cut-offs are assay specific.

21. When interpreting anti-drug antibodies, repeat testing is useful to determine if antibodies are transient or persistent (EL-II, RG-B).

Anti-drug antibodies can be transient and can disappear on repeat testing. Such transient anti-drug antibodies, particularly ATI, are common and not associated with loss-of-response or failure to respond to dose intensification, unlike persistent anti-drug antibodies.\textsuperscript{25,174,175} The presence of ATI on 2 consecutive blood samples ≥2 months apart was associated with subsequent loss-of-response. Initially, high titres of ATI do not consistently predict for antibody persistence.\textsuperscript{102,175} Although ATA tend to occur at lower rates, they appear to have a higher rate of persistence, and, in turn, greater chance of loss-of-response compared with ATI.\textsuperscript{25,34,173} Once ATI or ATA are detected, repeat testing at a later time point to differentiate transient from persistent antibodies is recommended where appropriate. Repeat testing to confirm anti-drug antibody persistence may also be appropriate for patients with high initial titres, particularly for those responding to therapy in whom the next step would be switching therapy. Other scenarios, such as severe active symptoms, may require a prompt change in therapy without delay in repeat testing.

22. There is insufficient evidence to recommend a drug-tolerant assay for anti-drug antibody detection (EL-III, RG-C).

Assays for measuring anti-TNF drug and anti-drug antibody levels can be broadly divided into drug-tolerant or drug-sensitive, depending on their capacity to detect anti-drug antibodies in the presence of drug.\textsuperscript{176-178} Drug-sensitive assays are less expensive, and are commonly enzyme-linked immunosorbent assays (ELISA) or radio-immunoassays (RIA). Drug-tolerant assays include the homogeneous mobility-shift assay (HMSA) and the electrochemiluminescence immunoassay.\textsuperscript{176,177,179} Recently, drug-tolerant ELISAs and RIAs which include an acid-disassociation step to separate free drug from bound anti-drug antibody prior to total anti-drug antibody detection have been reported.\textsuperscript{81,180} Detection of anti-drug antibodies in the presence of therapeutic anti-TNF drug levels does not appear to provide an advantage. Most anti-drug antibodies detected via the HMSA lack neutralising potential when tested via a functional cell-based reporter-gene assay, which infers they may not be clinically significant.\textsuperscript{126} Although detectable ATI in the presence of therapeutic infliximab levels have been associated with higher CRP levels, in another study they were not associated with lack of response to dose intensification.\textsuperscript{140,181} Among patients with treatment failure, presence of anti-drug antibodies with therapeutic drug levels likely indicates pharmacodynamic failure and nonneutralising anti-drug antibodies. Such patients would likely respond best to changing out-of-class.

Consensus voting was impacted by inconsistent benefits of drug-tolerant over drug-sensitive assays. In a recent post hoc analysis of the TAXIT trial, 62% of pre-optimisation blood samples were positive for ATI via a drug-tolerant assay as opposed to 21% via a drug-sensitive assay.\textsuperscript{182} For the drug-tolerant assay, only ATI titres in the highest quartile were associated with a need for higher infliximab doses to achieve therapeutic infliximab concentrations, and all except one of these patients were also detected as ATI positive via the drug-sensitive assay. This is evidence against the benefit of drug-tolerant assays over drug-sensitive assays.

3.8 TDM for non-anti-TNF biological agents and future therapies

23. There is emerging evidence that drug levels of non-anti-TNF biological agents may be relevant to clinical endpoints. However, more data are required before the routine use of TDM to guide therapy with these agents can be recommended (EL-IV, RG-D).

There are limited data for TDM of non-anti-TNF biological agents in IBD. However, there is no reason why the general pharmacokinetic principle of response being related to exposure would not apply. Higher vedolizumab drug levels are associated with higher rates of clinical and endoscopic remission in UC.\textsuperscript{10,11} Rates of mucosal healing were higher with increasing vedolizumab drug level quartiles at week 6 in a small cross-sectional study. A week 6 vedolizumab drug level threshold of <19.0 \(\mu\)g/mL was found to be
predictive of subsequent dose escalation for lack of response, and
doze escalation was successful in inducing clinical remission in this
setting. Of note, vedolizumab completely saturates the \( \alpha_4 \beta_7 \)
receptor at serum levels of 1 \( \mu g/mL \) in vitro. However at such con-
centrations in vivo, efficacy is no different to placebo inferring that
the pharmacokinetic-pharmacodynamic relationship with vedolizu-
mab might be different to that observed with anti-TNF therapy.

Higher ustekinumab drug levels were also associated with
greater rates of clinical remission. Week 8 ustekinumab trough
levels >4.5 and >5 \( \mu g/mL \) are also associated with endoscopic
response and CRP normalisation respectively. In psoriasis, in con-
trast, ustekinumab levels did not correlate with clinical response.

3.9 Statements that did not reach consensus

13. Patients in clinical remission and with sub-therapeutic drug
trough levels should be individually assessed for suitability for a
drug holiday (EL-III3, RG-C).

Anti-TNF drug holiday should not be considered for a patient
purely based on an unexpected finding of sub-therapeutic drug
trough levels during proactive TDM. This is in agreement with state-
ment 4 that a routine TDM interval for patients in clinical remission
is not recommended and that TDM should only be performed if
results will alter management.

24. Data on TDM should be available at time of registration for all
future therapies (EL-III1, RG-B).

Although the majority of the panel supported the need for TDM
data to accompany pivotal clinical studies, consensus was not
reached. This recommendation is best left to regulatory bodies to
endorse.

4 DISCUSSION

Inappropriate use of biological agents to treat IBD leads to increased
cost burden, toxicity risk and delay rescue strategies. Early discontin-
uation of a biological agent might diminish their subsequent response through development of anti-drug antibodies. Conversely, empiric dose intensification might be appropriate only in given situa-
tions and be futile in others. Appropriate use of TDM is a strategy
that aims to maximise the benefit of anti-TNF therapy, guide switching or dose changes and allow these decisions to be made in a
timely manner. This strategy is especially appropriate in IBD, a life-
long disease affecting a young demographic with a limited choice of
approved biological agents for treatment. These consensus state-
ments address issues around the optimal use of TDM to aid clini-
cians in utilising biological therapy in IBD patients.

The committee recommends TDM of anti-TNF agents upon
treatment failure, following successful treatment induction, and
when contemplating a drug holiday. There is inconsistent evidence
for proactive TDM, and we advise that TDM should be performed
for patients in stable remission only if results are likely to impact
clinical management. The panel delineated an appropriate
therapeutic range for infliximab and adalimumab to make these
guidelines more clinically applicable. The evidence levels of each
statement correlated well with the recommendation grades (Spear-
man's correlation co-efficient = 0.544, \( P = .006 \)).

There are limitations to these statements. Firstly, these therapeu-
tic ranges were for clinical remission as the endpoint, which is
emphasised by the Australian pharmaceutical funding body. There is
emerging evidence that mucosal healing beyond symptoms might
require higher trough drug levels. Secondly, most of the current
evidence stems from uncontrolled retrospective cross-sectional and
observational studies rather than longitudinal or controlled interven-
tional data validating different TDM strategies. Well-powered inter-
ventional studies with long-term follow-up are required to further
support the various roles of TDM. Thirdly, most data currently cover
anti-TNF agents. Other biological agents with different therapeutic
targets require further studies to evaluate exposure-response relations-
ships and applicability of TDM. For this reason, the majority of
the panel supported the need for TDM data to accompany pivotal
clinical studies of all future IBD therapies but this statement did not
achieve consensus (77% of panellists agreed without or only minor
reservation). Finally, most TDM studies on anti-TNF agents are with
infliximab and adalimumab, with few focusing on golimumab and cer-
tolizumab so far. Although a similar TDM-guided decision algo-

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Shire, Takeda. SJC has served as a speaker and advisory board member for Janssen, Abbvie, Pfizer, Ferring, Shire, MSD, Celgene and Takeda and has received research funding from GESA. GM has served as a speaker and an advisory board member for Janssen, AbbVie, Hospira, Takeda, Ferring, Shire, and has received unrestricted research funding from GESA, Ferring, and Abbvie. RB served as a speaker for Shire, Takeda, and Janssen, and has received conference travel support from Ferring and Takeda. WC has no personal interests to declare. CC has served as a consultant for Janssen, and has received research funding from GESA, Abbvie, Ferring, and Shire. DL has served as an advisory board member for Abbvie and Janssen. VK has no personal interests to declare. PL has served as a speaker and advisory board member for Abbvie and Janssen. JM has no personal interests to declare. RM has served as a speaker for Janssen. GRS has served as a consultant for Abbvie, Janssen, Hospira, Ferring, Takeda, MSD, Celgene, Pfizer, Protagonist, and Amgen. PS has no personal interests to declare. MS has served as an advisory board member for Janssen, Abbvie, Takeda, Pfizer, Celgene and MSD and has received speaker fees from Janssen, Abbvie, Ferring, Takeda and Pfizer. CT has no personal interests to declare. DVL has served as a speaker and consultant for Abbvie, Takeda and Janssen, and has received research funding from Abbvie, Takeda and Janssen. MGW has served as a speaker for Janssen, Abbvie, Ferring and Takeda, and has received research funding from Abbvie. RWL has served as an advisory board member for AbbVie, Aspen, Celgene, Ferring, Hospira, MSD, Pfizer, Janssen and Takeda, and has received research funding from Endochoice, Shire and Janssen.

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REFERENCES


76. Wong SH, Tang W, Wu JC, Ng SC. *Clostridium difficile* infections in inflammatory bowel disease patients is associated with increased use of immunosuppressants and higher rates of colectomy: results from a population-based cohort. *Digestive Diseases Week*; 2016.


140. Feagan BG, Singh S, Lockton S, et al. 565 novel infliximab (IFX) and anti-tumor necrosis factor (anti-TNF) assays are predictive of disease activity...


SUPPORTING INFORMATION

Additional Supporting Information will be found online in the supporting information tab for this article.

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APPENDIX 1

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