Received: 9 July 2017 | First decision: 6 August 2017 | Accepted: 19 September 2017

DOI: 10.1111/apt.14368

WILEY AP&T Alimentary Pharmacology & Therapeutics

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

N. Mitrev[1] | N. Vande Casteele[2] | C. H. Seow[3] | J. M. Andrews[4] | S. J. Connor[1] | G. T. Moore[5] | M. Barclay[6] | J. Begun[7] | R. Bryant[4] | W. Chan[1] | C. Corte[1] | S. Ghaly[1] | D. A. Lemberg[1] | V. Kariyawasam[1] | P. Lewindon[7] | J. Martin[8] | R. Mountifield[4] | G. Radford-Smith[7] | P. Slobodian[4] | M. Sparrow[5] | C. Toong[1] | D. van Langenberg[5] | M. G. Ward[5] | R. W. Leong[1] | IBD Sydney Organisation and the Australian Inflammatory Bowel Diseases Consensus Working Group

[1]Sydney, NSW, Australia
[2]San Diego, CA, USA
[3]Calgary, AB, Canada
[4]Adelaide, SA, Australia
[5]Melbourne, Vic., Australia
[6]Christchurch, New Zealand
[7]Brisbane, Qld, Australia
[8]Newcastle, NSW, Australia

Correspondence
Prof. R W Leong, Concord Hospital IBD Service, Sydney, NSW, Australia.
Email: rupertleong@outlook.com

Funding information
This study was funded in full by the Gastroenterological Society of Australia (GESA). GESA has previously received unrestricted educational grants from AbbVie, Janssen, Takeda and Pfizer to aid the development of these guidelines. The funding bodies had no involvement with the consensus process including its membership, design, development of the statements, voting and manuscript writing. NM received a GESA research grant for his work on the development of these consensus statements.

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.

The Handling Editor for this article was Professor Jonathan Rhodes, and this uncommissioned review was accepted for publication after full peer-review.
The authors' complete affiliations are listed in Appendix 1.

 © 2017 John Wiley & Sons Ltd

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).[1-4] 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.[3,4,8,9] 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.[14-19] 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.[20] 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.[21] A manuscript committee (NM, RWL, CS, NVC, 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 reintroduction 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[21]

Statement	Acceptance (%)	EL	RG
Scenarios when TDM of anti-TNF agents should be performed			
1. In patients in clinical remission following anti-TNF therapy induction, TDM should be considered to guide management	100	II	C
2. TDM can inform clinical decision-making in patients with primary nonresponse	100	III2	C
3. TDM should be performed in patients with secondary loss-of-response to guide clinical decision-making	100	I	B
4. TDM should be considered periodically in patients in clinical remission if the results are likely to impact management	90	IV	D
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	100	III2	C
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 inflammatory disease confirmed via objective measures (endoscopy, imaging, serum/faecal biomarkers) and investigations to exclude alternative/concomitant causes of symptoms, prior to change in therapy	100	III3	C

exposure.[22] Detectable antibodies to infliximab (ATI) during infliximab reintroduction, particularly high titres, are associated with an increased risk of subsequent infusion reactions.[23] Transient ATI on infliximab reintroduction, however, are common and not associated with infusion reactions in most patients.[23-25] There is no clear ATI titre cut-off that predicts for reactions with adequate power. Discontinuing patients with anti-drug antibodies following anti-TNF reintroduction who are otherwise responding, may result in more futile treatment changes than prevented drug reactions.

1. In patients in clinical remission following anti-TNF therapy induction, TDM should be considered to guide management (EL-II, RG-C).

Sub-therapeutic adalimumab and infliximab drug levels are associated with increased future risk of developing anti-drug antibodies and increased disease activity.[22,26-31] The risk of ATI increased with the duration of the sub-therapeutic drug levels.[31] TDM shortly following successful induction therapy may identify patients with sub-therapeutic drug levels. Dose intensification to 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.[32-34] 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.[35,36] 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.[28,37-40] Relatively few studies have assessed TDM-guided therapy in primary nonresponse.[41,42] 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.[39,40] 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.[25,28,37,38,43]

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.[36,44-48] 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.[36] 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.[48] 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]

Statement	Acceptance (%)	EL	RG
Interpreting TDM results in patients with confirmed active inflammatory disease on anti-TNF therapy			
7. Patients with confirmed active inflammatory disease and therapeutic drug trough levels (suggests pharmacodynamic failure) should be switched out-of-class	91	III2	C
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	100	III3	B
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	100	III3	C
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	100	III2	B
Interpreting TDM results among patients in clinical remission on anti-TNF therapy			
11. Patients in clinical remission and therapeutic drug trough levels should be continued on the same dose	100	II	B
12. Patients in clinical remission and with supra-therapeutic drug trough levels should be considered for dose reduction	100	III1	B
13. Patients in clinical remission and with sub-therapeutic drug trough levels should be individually assessed for suitability for a drug holiday	24*	III3	C
14. Patients in clinical remission who have high-risk features, and sub-therapeutic trough drug levels and undetectable anti-drug antibodies should have an immunomodulatory added/optimised and/or dose escalation	95	III3	C
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	100	III1	B
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	86	III2	C

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[21]

Statement	Acceptance (%)	EL	RG
Target drug trough levels			
17. In IBD patients with luminal disease a steady state trough infliximab level between 3 and 8 μg/mL is generally recommended	96	II	B
18. In IBD patients with luminal disease a steady state adalimumab trough level between 5 and 12 μg/mL is generally recommended	95	II	C
19. In certain situations higher or lower trough levels than the above ranges may be appropriate	100	III3	B
Anti-drug antibodies			
20. When interpreting anti-drug antibodies, quantifying titres is clinically more useful than positive/negative status	100	II	B
21. When interpreting anti-drug antibodies, repeat testing is useful to determine if antibodies are transient or persistent	100	II	B
22. There is insufficient evidence to recommend a drug-tolerant assay for anti-drug antibody detection	95	III1	C
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	96	IV	D
24. Data on TDM should be available at time of registration for all future therapies	77*	III1	B

Objective assessment of disease activity should be used in addition to symptoms in a "treat-to-target" management approach.[58,59] Only half of CD patients considered to be in clinical remission are found to have mucosal healing, and faecal calprotectin is a more accurate predictor of mucosal healing in CD than clinical assessment using the Crohn's Disease Activity Index (CDAI).[60,61] Bowel symptoms may not correlate with endoscopic—or serum/faecal biomarker—evidence of inflammation.[62-66] As such, non-inflammatory causes of symptoms, such as intestinal stricture, bile salt malabsorption, malignancy, small bowel bacterial overgrowth, dietary intolerances or overlapping irritable bowel syndrome (IBS) need to be considered.[64] Up to 60% of IBD patients with ongoing bowel symptoms have mucosal healing.[66-75] A normal faecal calprotectin in the context of underlying IBD and ongoing bowel symptoms has high predictive value for functional gut disorder or impaired intestinal permeability.[66,75] Infective colitis with *C. difficile* and cytomegalovirus should also be excluded.[76,77]

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.[78-87] 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-TNFα withdrawal and symptomatic treatment. However, switching out-of-class was associated with significantly improved outcomes.[39,64] Roblin et al found that those with an adalimumab level ≥4.9 μg/mL had lower response rates when switched to infliximab than those whose adalimumab levels were <4.9 μg/mL.[40] Because of the limited biological agents currently available, completely exhausting one biological drug before switching to another is recommended.[47] Due to wide inter-individual variability in the minimal drug level required for response, patients with treatment failure and drug levels within the therapeutic range may still benefit from dose intensification, although likelihood of this dramatically decreases with increasing pre-dose intensification drug levels. For example, an IBD patient with history of aggressive disease, prior failure to multiple treatments and an infliximab trough of 8 μg/mL may still be appropriate for a trial of dose intensification. Achieving remission is the endpoint of treatment with anti-TNF biological drugs rather than achieving a specific drug level.

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-III3, 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.[22,88-96] Among

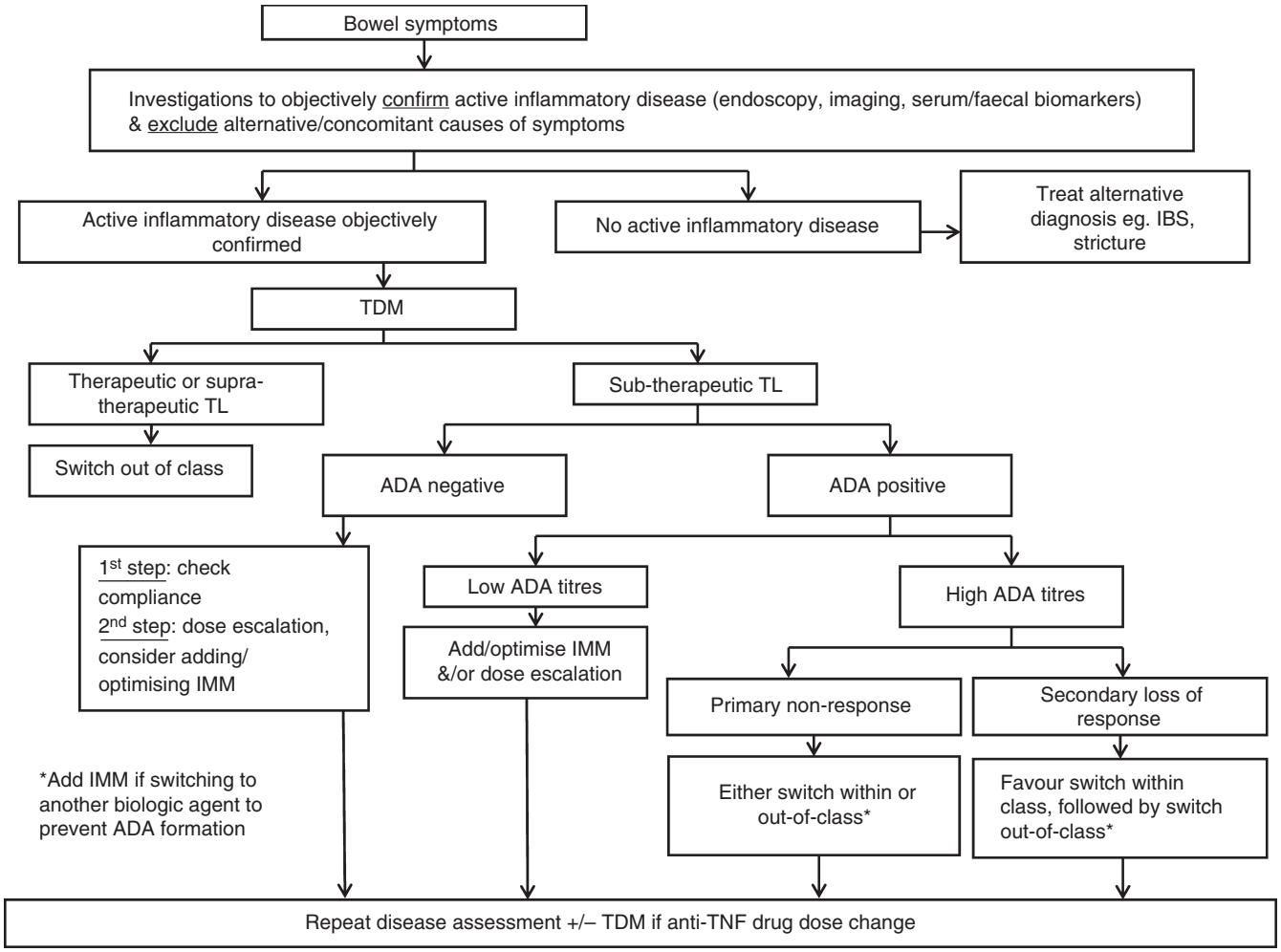

FIGURE 1 Interpreting TDM results in patients with bowel symptoms while on anti-TNF therapy. Evidence for this algorithm is mainly in secondary loss-of-response; however, it may also be used to elicit mechanisms of failure and guide treatment decisions in primary nonresponders. ADA, anti-drug antibodies; TDM, therapeutic drug monitoring; IMM, immunomodulator; IBS, irritable bowel syndrome; TL, trough level

patients with sub-therapeutic infliximab or adalimumab drug levels, absence of anti-drug antibodies is associated with response to dose escalation.[39,40,63,64] 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.[47,64,91-93,96-101]

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.[39] The addition of methotrexate or a thiopurine can also overcome anti-drug antibodies.[97,98,102]

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.[28,40,103-105] 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.[39]

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.[27,96] 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.[6,7] 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.[5]

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.[52,54-57] 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.[37,38,106,107]

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

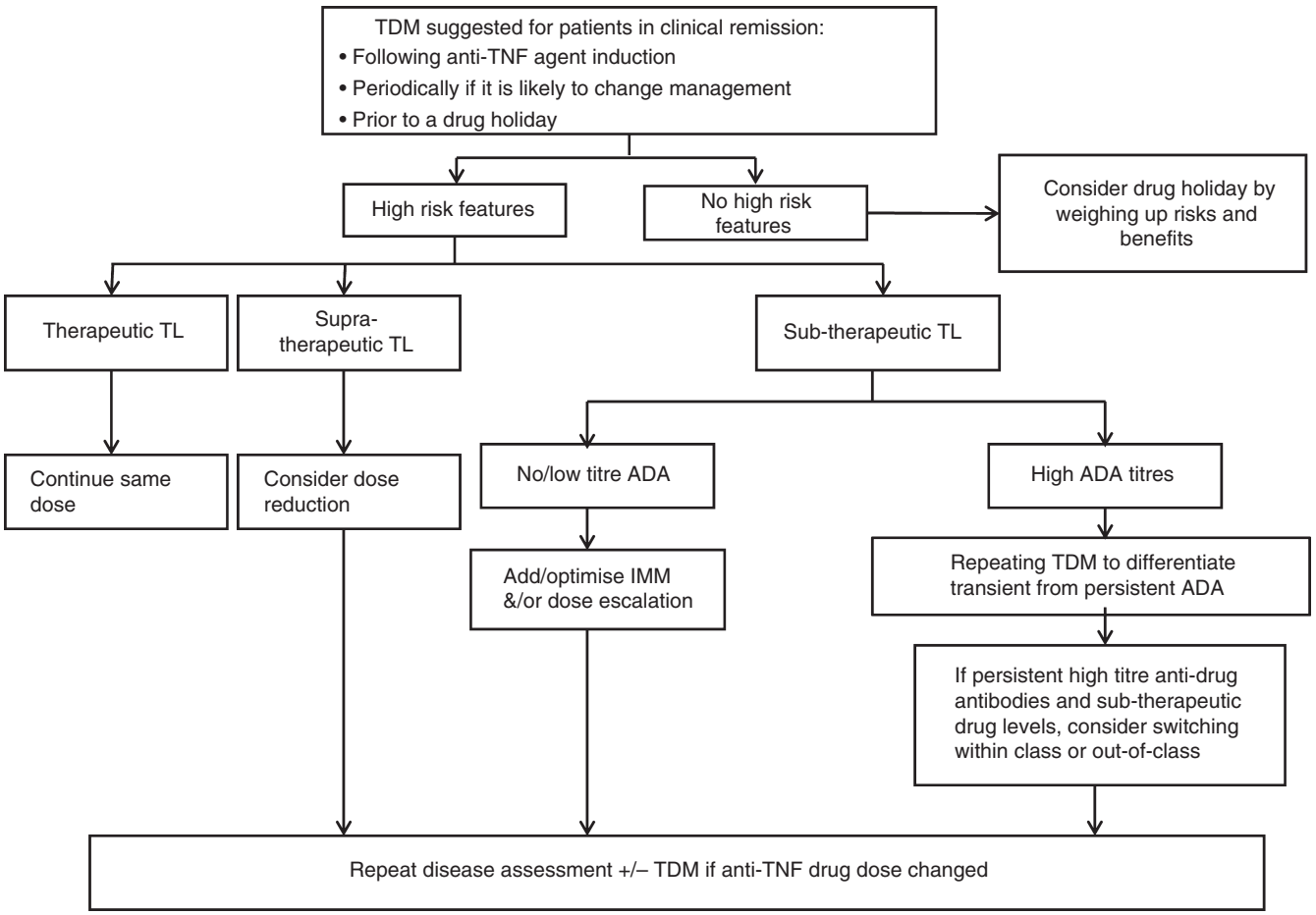

FIGURE 2 Interpreting TDM results in patients in clinical remission while on anti-TNF therapy. High-risk features include risk factors for disease relapse as well as risk factors for severe consequences in event of relapse (Statement 6). ADA, anti-drug antibodies; TDM, therapeutic drug monitoring; IMM, immunomodulator; TL, trough level

antibodies is associated with restoration of therapeutic drug levels on dose escalation.[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.[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.[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.[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-III2, 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.[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.[81,108] Few studies have related nontrough drug levels to clinical outcomes.[42,109] 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.[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.[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.[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.[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.[47,85-87,119] Hence, a therapeutic range should focus on optimising clinical efficacy rather than avoiding toxicity.[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.[58] However, the Australian Pharmaceutical Benefits Scheme funding body emphasises clinical scores to assess response to biological agents in IBD.[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.[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.[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.[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.[134-138] Several have defined an infliximab therapeutic cut-off or range that is associated with a specific endpoint.[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 ≥3.4 μg/mL was 90% specific for failure to recapture response.[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.[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.[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.[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 ≥4.5 μg/mL to be 90% specific for failure to respond.[39] Immediately following induction therapy, a cross-sectional study found a week 14 adalimumab trough level of >4.5 μg/mL to be associated with clinical response or

remission.[28,139] Rheumatological studies show that response plateaus above an adalimumab trough of 7-8 μg/mL.[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 μg/mL.[106]

19. In certain situations, higher or lower trough levels than the above ranges may be appropriate (EL-III3, 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.[47] Therapeutic ranges of 6-10 μg/mL for infliximab and 8-12 μg/mL for adalimumab were most strongly associated with endoscopic remission.[106] Perianal CD fistula healing requires higher infliximab trough levels of >10 μg/mL, and even as high as 20 μg/mL.[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-B0).

Anti-drug antibodies can interfere with the activity of anti-TNF agents by increasing drug clearance and by direct neutralisation.[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.[40,168-170] However, quantification of the anti-drug antibody level is a better predictor.[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.[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.[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.[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.[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.[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-III1, 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.[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.[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.[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.[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.[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.[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.[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 μg/mL was found to be

predictive of subsequent dose escalation for lack of response, and dose escalation was successful in inducing clinical remission in this setting.[183] Of note, vedolizumab completely saturates the α4β7 receptor at serum levels of 1 μg/mL in vitro. However at such concentrations in vivo, efficacy is no different to placebo inferring that the pharmacokinetic-pharmacodynamic relationship with vedolizumab might be different to that observed with anti-TNF therapy.[184]

Higher ustekinumab drug levels were also associated with greater rates of clinical remission.[12] Week 8 ustekinumab trough levels >4.5 and >5 μg/mL are also associated with endoscopic response and CRP normalisation respectively.[13] In psoriasis, in contrast, ustekinumab levels did not correlate with clinical response.[185]

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 statement 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 discontinuation 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 situations 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 lifelong disease affecting a young demographic with a limited choice of approved biological agents for treatment. These consensus statements address issues around the optimal use of TDM to aid clinicians 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 (Spearman's correlation co-efficient = 0.544, $P = .006$).

There are limitations to these statements. Firstly, these therapeutic 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.[106] Secondly, most of the current evidence stems from uncontrolled retrospective cross-sectional and observational studies rather than longitudinal or controlled interventional data validating different TDM strategies. Well-powered interventional 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 relationships 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 certolizumab so far.[122,123] Although a similar TDM-guided decision algorithm can be applied across different anti-TNF agents provided appropriate therapeutic ranges are defined, the use and availability of golimumab and certolizumab remain limited worldwide and only smaller cross-sectional studies are currently available to guide their usage. With emerging evidence, particularly regarding TDM of other biological agents, these guidelines would need to be revised.

In conclusion, TDM of anti-TNF agents is an important component of personalised therapy in IBD. These consensus statements should provide a practical guide to applying TDM of anti-TNF agents in treatment optimisation for IBD patients. Limitations of the evidence and hence these consensus statements relate to endpoint and phenotype appropriate therapeutic ranges, lack of longitudinal interventional studies on TDM of biological agents in different disease phenotypes, and sparse TDM data on biological agents other than infliximab and adalimumab.

ACKNOWLEDGEMENTS

We acknowledge Prof Michael Grimm and Dr Kannal Venugopal for voting in the initial voting phases, Fiona Bailey, Claire Wu and Gail Foster for attendance as nonvoting members.

Declaration of personal interests: NM has received research funding from GESA, and conference support from Takeda, Ferring and Janssen. NVC has served as a speaker and a consultant for Boehringer Ingelheim, UCB, Pfizer and Takeda. CS has served as a speaker and research/educational support personnel for Janssen and Abbvie, and advisory board member for Janssen, Abbvie, Takeda, Actavis, Takeda, Ferring and Shire. JMA has served as a speaker or consultant for and/or received research funding from Abbott, Abbvie, Allergan, AstraZeneca, Celgene, Ferring, Hospira, Janssen, MSD, Pfizer,

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, Orphan and Shire. MB has no personal interests to declare. JB has served as a speaker and consultant for Jannsen, Abbvie, Ferring, Shire, Takeda and Pfizer/Hospira, 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, Shire and Nycomed. SG has served as a speaker for Ferring, Janssen, Takeda, Shire and Abbvie, and has received research funding from GESA, Ferring, Takeda, Shire and Abbvie. 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.

AUTHORSHIP

Guarantor of the article: Rupert W Leong.

Author contributions: NM: part of steering committee. Initial formulation of statements, refinement of statements, literature search, organisation of online voting and distribution of literature search, organisation of face-to-face meeting, voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, writing of the majority of the manuscript, editing and revision of manuscript. NVC: refinement of statements, voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. CS: refinement of statements, voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. JMA: part of steering committee. Initial formulation of statements, refinement of statements, voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. SC: part of steering committee. Initial formulation of statements, refinement of statements, voting in the first 2 online rounds, editing and revision of manuscript. GM part of steering committee. Initial formulation of statements, refinement of statements, voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. MB: voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. JB: voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. RB: voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. WC: record keeping during face-to-face meeting, editing and revision of manuscript. CC: voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. SG: voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. DL: voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. VK: voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. PL: voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. JM: voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. RM: voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. GRS: voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. PS: voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. MS: voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. CT: voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. DVL: voting in the first 2 online rounds, participation in the presentation of the allocated statement,

discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. MGW: refinement of statements, voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, editing and revision of manuscript. RWL: part of steering committee. Initial formulation of statements, refinement of statements, voting in the first 2 online rounds, participation in the presentation of the allocated statement, discussion and voting of the statements in the face-to-face meeting, writing of the manuscript, editing and revision of manuscript. All authors approved the final version of the manuscript.

ORCID

N. Mitrev http://orcid.org/0000-0001-7771-5248
C. H. Seow http://orcid.org/0000-0002-1551-9054
W. Chan http://orcid.org/0000-0002-8884-3381
M. Sparrow http://orcid.org/0000-0003-2527-8044
M. G. Ward http://orcid.org/0000-0002-2840-0108
R. W. Leong http://orcid.org/0000-0001-5944-3488

REFERENCES

1. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology*. 2007;132:52-65.
2. Sandborn WJ, vanAssche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2012;142:257-265. e1-3.
3. Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ, Moayyedi P. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*. 2011;106:644-659, quiz 660.
4. Sprakes MB, Ford AC, Warren L, Greer D, Hamlin J. Efficacy, tolerability, and predictors of response to infliximab therapy for Crohn's disease: a large single centre experience. *J Crohns Colitis*. 2012;6:143-153.
5. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2016;375:1946-1960.
6. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2013;369:699-710.
7. Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2013;369:711-721.
8. Roda G, Jharap B, Neeraj N, Colombel JF. Loss of response to anti-TNFs: definition, epidemiology, and management. *Clin Transl Gastroenterol*. 2016;7:e135.
9. Ben-Horin S, Chowers Y. Review article: loss of response to anti-TNF treatments in Crohn's disease. *Aliment Pharmacol Ther*. 2011;33:987-995.
10. Osterman MT, Roblin X, Glover SC, et al. Association of vedolizumab drug concentrations at or before week 6 with remission at week 14 in moderately to severely active ulcerative colitis patients from GEMINI 1. *Gastroenterology*. 2016;150:S105.
11. Rosario M, Abhyankar B, Sankoh S, Dirks N, Lasch K, Sandborn W. Relationship between vedolizumab pharmacokinetics and endoscopic outcomes in patients with ulcerative colitis. ECCO; 2015.
12. Adedokun OJ, Xu Z, Gasink C, et al. Sa1934 Pharmacokinetics and exposure-response relationships of Ustekinumab during IV induction and SC maintenance treatment of patients with Crohn's disease with Ustekinumab: results from the UNITI-1, UNITI-2, and IM-UNITI studies. *Gastroenterology*. 2016;150:S408.
13. Battat R, Kopylov U, Bessissow T, et al. 696 association of Ustekinumab trough concentrations with clinical, biochemical and endoscopic outcomes. *Gastroenterology*. 2016;150:S144-S145.
14. Brooks KW. Delphi technique: expanding applications. *N Central Assoc Q*. 1979;54:377-385.
15. Custer RL, Scarcella JA, Stewart BR. The modified Delphi technique: a rotational modification. *J Voc Tech Educ*. 1999;15:1-10.
16. Hsu C, Sandford BA. The Delphi technique: making sense of consensus. *Pract Assess Res Eval*. 2007;12:1-8.
17. Ludwig B. Predicting the future: have you considered using the Delphi methodology? *J Extens*. 1997;35:1-4.
18. Cyphert FR, Gant WL. The Delphi technique: a case study. *Phi Delta Kappan*. 1971;52:272-273.
19. Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ*. 1995;311:376-380.
20. Chen JH, Andrews JM, Kariyawasam V, et al. Review article: acute severe ulcerative colitis – evidence-based consensus statements. *Aliment Pharmacol Ther*. 2016;44:127-144.
21. Merlin T, Weston A, Tooher R, et al. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Canberra, ACT: Australian Government; 2009.
22. Melmed GY, Irving PM, Jones J, et al. Appropriateness of testing for anti-tumor necrosis factor agent and antibody concentrations, and interpretation of results. *Clin Gastroenterol Hepatol*. 2016;14:1302-1309.
23. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med*. 2003;348:601-608.
24. Baert F, Drobne D, Gils A, et al. Early trough levels and antibodies to infliximab predict safety and success of reinitiation of infliximab therapy. *Clin Gastroenterol Hepatol*. 2014;12:1474-1481 e2; quiz e91.
25. Steenholdt C, Bendtzen K, Brynskov J, Ainsworth MA. Optimizing treatment with TNF inhibitors in inflammatory bowel disease by monitoring drug levels and antidrug antibodies. *Inflamm Bowel Dis*. 2016;22:1999-2015.
26. Singh N, Rosenthal CJ, Melmed GY, et al. Early infliximab trough levels are associated with persistent remission in pediatric patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2014;20:1708-1713.
27. Baert F, Kondragunta V, Lockton S, et al. Antibodies to adalimumab are associated with future inflammation in Crohn's patients receiving maintenance adalimumab therapy: a post hoc analysis of the Karmiris trial. *Gut*. 2015;65:1126-1131.
28. Ding NS, Hart A, de Cruz P. Systematic review: predicting and optimising response to anti-TNF therapy in Crohn's disease – algorithm for practical management. *Aliment Pharmacol Ther*. 2016;43:30-51.
29. Cornillie F, Hanauer SB, Diamond RH, et al. Postinduction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. *Gut*. 2014;63:1721-1727.
30. Amin A, Prosser C, Kroeker K, et al. Using infliximab trough levels and fecal calprotectin levels together to guide clinical decisions has the potential to improve outcomes in inflammatory bowel disease patients on maintenance infliximab therapy. *Gastroenterology*. 2016;150:S422.
31. Brandse JF, Strik AS, Mould D, et al. Insufficient infliximab exposure predisposes to immunogenicity and enhanced clearance of infliximab in IBD. *Gastroenterology*. 2016;150 (4, Suppl. 1):S144.

32. Ungar B, Chowers Y, Yavzori M, et al. The temporal evolution of antidrug antibodies in patients with inflammatory bowel disease treated with infliximab. *Gut*. 2014;63:1258-1264.
33. Ben-Horin S. Immunogenicity of anti-TNFs – letting the immune system be the judge. In: *IXTEND 2016*. Sydney: 2016.
34. Steenholdt C, Frederiksen MT, Bendtzen K, Ainsworth MA, Thomsen OO, Brynskov J. Time course and clinical implications of development of antibodies against adalimumab in patients with inflammatory bowel disease. *J Clin Gastroenterol*. 2015;50:483-489.
35. Vande Casteele N, Compernolle G, Ballet V, et al. Results on the optimisation phase of the prospective controlled trough level adapted infliximab treatment (TAXIT) trial, 2012.
36. Vande Casteele N, Ferrante M, Van Assche G, et al. Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease. *Gastroenterology*. 2015;148:1320-1329 e3.
37. Steenholdt C, Brynskov J, Thomsen OO, et al. Individualised therapy is more cost-effective than dose intensification in patients with Crohn's disease who lose response to anti-TNF treatment: a randomised, controlled trial. *Gut*. 2014;63:919-927.
38. Steenholdt C, Brynskov J, Thomsen OO, et al. Individualized therapy is a long-term cost-effective method compared to dose intensification in Crohn's disease patients failing infliximab. *Dig Dis Sci*. 2015;60:2762-2770.
39. Yanai H, Lichtenstein L, Assa A, et al. Levels of drug and antidrug antibodies are associated with outcome of interventions after loss of response to infliximab or adalimumab. *Clin Gastroenterol Hepatol*. 2015;13:522-530 e2.
40. Roblin X, Rinaudo M, Del Tedesco E, et al. Development of an algorithm incorporating pharmacokinetics of adalimumab in inflammatory bowel diseases. *Am J Gastroenterol*. 2014;109:1250-1256.
41. Chiu YL, Rubin DT, Vermeire S, et al. Serum adalimumab concentration and clinical remission in patients with Crohn's disease. *Inflamm Bowel Dis*. 2013;19:1112-1122.
42. Papamichael K, van Stappen T, Vande Casteele N, et al. Infliximab concentration thresholds during induction therapy are associated with short-term mucosal healing in patients with ulcerative colitis. *Clin Gastroenterol Hepatol*. 2016;14:543-549.
43. Steenholdt C, Brynskov J, Thomsen OO, et al. Implications of infliximab treatment failure and influence of personalized treatment on patient-reported health-related quality of life and productivity outcomes in Crohn's disease. *J Crohns Colitis*. 2015;9:1032-1042.
44. Armuzzi A, Felice C. IBD: infliximab dose optimization in IBD-proactive or reactive? *Nat Rev Gastroenterol Hepatol*. 2014;11:706-708.
45. O'Toole A, Moss AC. Optimizing biologic agents in ulcerative colitis and Crohn's disease. *Curr Gastroenterol Rep*. 2015;17:32.
46. Vaughn BP, Martinez-Vazquez M, Patwardhan VR, Moss AC, Sandborn WJ, Cheifetz AS. 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.
47. Mitrev N, Leong RW. Therapeutic drug monitoring of anti-tumour necrosis factor-alpha agents in inflammatory bowel disease. *Expert Opin Drug Saf*. 2017;16:303-317.
48. D'Haens G, Vermeire S, Lambrecht G, et al. OP029 Drug-concentration versus symptom-driven dose adaptation of Infliximab in patients with active Crohn's disease: a prospective, randomised, multicentre trial (Tailorix). ECCO; 2016.
49. Papamichael K, Chachu KA, Vajravelu RK, et al. Improved long-term outcomes of patients with inflammatory bowel disease receiving proactive compared with reactive monitoring of serum concentrations of infliximab. *Clin Gastroenterol Hepatol*. 2017;15:1580-1588.
50. Ben-Horin S, Chowers Y, Ungar B, et al. Undetectable anti-TNF drug levels in patients with long-term remission predict successful drug withdrawal. *Aliment Pharmacol Ther*. 2015;42:356-364.
51. Flamant M, Roblin X. Could therapeutic drug monitoring of anti-TNF-alpha be useful to consider a de-escalation of treatment? *Expert Opin Biol Ther*. 2015;15:1657-1660.
52. Louis E, Mary JY, Vernier-Massouille G, et al. Maintenance of remission among patients with Crohn's disease on antimetabolite therapy after infliximab therapy is stopped. *Gastroenterology*. 2012;142:63-70 e5; quiz e31.
53. Papamichael K, Vande Casteele N, Gils A, et al. Long-term outcome of patients with Crohn's disease who discontinued infliximab therapy upon clinical remission. *Clin Gastroenterol Hepatol*. 2015;13:1103-1110.
54. Gisbert JP, Marin AC, Chaparro M. The risk of relapse after anti-TNF discontinuation in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*. 2016;111:632-647.
55. Chauvin A, Le Thuaut A, Belhassan M, et al. Infliximab as a bridge to remission maintained by antimetabolite therapy in Crohn's disease: a retrospective study. *Dig Liver Dis*. 2014;46:695-700.
56. Hlavaty T, Krajcovicova A, Letkovsky J, et al. Relapse rates of inflammatory bowel disease patients in deep and clinical remission after discontinuing anti-tumor necrosis factor alpha therapy. *Bratisl Lek Listy*. 2016;117:205-211.
57. Papamichael K, Vermeire S. Withdrawal of anti-tumour necrosis factor alpha therapy in inflammatory bowel disease. *World J Gastroenterol*. 2015;21:4773-4778.
58. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. *Am J Gastroenterol*. 2015;110:1324-1338.
59. Walsh AJ, Bryant RV, Travis SP. Current best practice for disease activity assessment in IBD. *Nat Rev Gastroenterol Hepatol*. 2016;13:567-579.
60. Peyrin-Biroulet L, Reinisch W, Colombel JF, et al. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. *Gut*. 2014;63:88-95.
61. Schoepfer AM, Beglinger C, Straumann A, et al. Fecal calprotectin correlates more closely with the Simple Endoscopic Score for Crohn's disease (SES-CD) than CRP, blood leukocytes, and the CDAI. *Am J Gastroenterol*. 2010;105:162-169.
62. Dalal SR, Cohen RD. What to do when biologic agents are not working in inflammatory bowel disease patients. *Gastroenterol Hepatol*. 2015;11:657-665.
63. Afif W, Loftus EV Jr, Faubion WA, et al. Clinical utility of measuring infliximab and human anti-chimeric antibody concentrations in patients with inflammatory bowel disease. *Am J Gastroenterol*. 2010;105:1133-1139.
64. Strik AS, Bots SJ, D'Haens G, Lowenberg M. Optimization of anti-TNF therapy in patients with inflammatory bowel disease. *Expert Rev Clin Pharmacol*. 2016;9:429-439.
65. Menees SB, Powell C, Kurlander J, Goel A, Chey WD. A meta-analysis of the utility of C-reactive protein, erythrocyte sedimentation rate, fecal calprotectin, and fecal lactoferrin to exclude inflammatory bowel disease in adults with IBS. *Am J Gastroenterol*. 2015;110:444-454.
66. Quigley EM. Overlapping irritable bowel syndrome and inflammatory bowel disease: less to this than meets the eye? *Therap Adv Gastroenterol*. 2016;9:199-212.
67. Barratt SM, Leeds JS, Robinson K, Lobo AJ, McAlindon ME, Sanders DS. Prodromal irritable bowel syndrome may be responsible for delays in diagnosis in patients presenting with unrecognized Crohn's disease and celiac disease, but not ulcerative colitis. *Dig Dis Sci*. 2011;56:3270-3275.
68. Barratt SM, Leeds JS, Robinson K, et al. Reflux and irritable bowel syndrome are negative predictors of quality of life in coeliac disease and inflammatory bowel disease. *Eur J Gastro Hepatol*. 2011;23:159-165.

69. Berrill JW, Green JT, Hood K, Campbell AK. Symptoms of irritable bowel syndrome in patients with inflammatory bowel disease: examining the role of sub-clinical inflammation and the impact on clinical assessment of disease activity. *Aliment Pharmacol Ther*. 2013;38:44-51.
70. Halpin SJ, Ford AC. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: systematic review and meta-analysis. *Am J Gastroenterol*. 2012;107:1474-1482.
71. Jelsness-Jorgensen LP, Bernklev T, Moum B. Fatigue and disease-related worries among inflammatory bowel disease patients in remission; is it a reflection of coexisting IBS-like symptoms? A short report. *J Psychosom Res*. 2012;73:469-472.
72. Jelsness-Jorgensen LP, Bernklev T, Moum B. Calprotectin is a useful tool in distinguishing coexisting irritable bowel-like symptoms from that of occult inflammation among inflammatory bowel disease patients in remission. *Gastroenterol Res Pract*. 2013;2013:620707.
73. Jonefjall B, Strid H, Ohman L, Svedlund J, Bergstedt A, Simren M. Characterization of IBS-like symptoms in patients with ulcerative colitis in clinical remission. *Neurogastroenterol Motil*. 2013;25:756-e578.
74. Keohane J, O'Mahony C, O'Mahony L, O'Mahony S, Quigley EM, Shanahan F. Irritable bowel syndrome-type symptoms in patients with inflammatory bowel disease: a real association or reflection of occult inflammation? *Am J Gastroenterol*. 2010;105:1788, 1789–1794; quiz 1795.
75. Chang J, Leong RW, Wasinger V, Ip M, Yang M, Giang Phan T. Impaired intestinal permeability contributes to ongoing bowel symptoms in patients with inflammatory bowel disease and mucosal healing. *Gastroenterology*. 2017;153:723-731.
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.
77. Lee HS, Park SH, Kim SH, et al. Risk factors and clinical outcomes associated with cytomegalovirus colitis in patients with acute severe ulcerative colitis. *Inflamm Bowel Dis*. 2016;22:912-918.
78. Louis E, El Ghoul Z, Vermeire S, et al. Association between polymorphism in IgG Fc receptor IIIa coding gene and biological response to infliximab in Crohn's disease. *Aliment Pharmacol Ther*. 2004;19:511-519.
79. Louis EJ, Watier HE, Schreiber S, et al. Polymorphism in IgG Fc receptor gene FCGR3A and response to infliximab in Crohn's disease: a subanalysis of the ACCENT I study. *Pharmacogenet Genomics*. 2006;16:911-914.
80. Pierik M, Vermeire S, Steen KV, et al. Tumour necrosis factor-alpha receptor 1 and 2 polymorphisms in inflammatory bowel disease and their association with response to infliximab. *Aliment Pharmacol Ther*. 2004;20:303-310.
81. Vande Casteele N, Gils A. Pharmacokinetics of anti-TNF monoclonal antibodies in inflammatory bowel disease: adding value to current practice. *J Clin Pharmacol*. 2015;55(Suppl. 3):S39-S50.
82. Siegel CA, Melmed GY. Predicting response to anti-TNF agents for the treatment of Crohn's disease. *Therap Adv Gastroenterol*. 2009;2:245-251.
83. Chowers Y, Sturm A, Sans M, et al. Report of the ECCO workshop on anti-TNF therapy failures in inflammatory bowel diseases: biological roles and effects of TNF and TNF antagonists. *J Crohns Colitis*. 2010;4:367-376.
84. Notley CA, Inglis JJ, Alzabin S, McCann FE, McNamee KE, Williams RO. Blockade of tumor necrosis factor in collagen-induced arthritis reveals a novel immunoregulatory pathway for Th1 and Th17 cells. *J Exp Med*. 2008;205:2491-2497.
85. Harrison MJ, Dixon WG, Watson KD, et al. Rates of new-onset psoriasis in patients with rheumatoid arthritis receiving anti-tumour necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis*. 2009;68:209-215.
86. Cleynen I, Van Moerkercke W, Juergens M, et al. Anti-TNF induced cutaneous lesions in IBD patients: characterization and search for predisposing factors. *Gut*. 2010;59(S3):A1.
87. Cleynen I, Vermeire S. Paradoxical inflammation induced by anti-TNF agents in patients with IBD. *Nat Rev Gastroenterol Hepatol*. 2012;9:496-503.
88. Billiet T, Cleynen I, Ferrante M, Van Assche G, Gils A, Vermeire S. A variable number of tandem repeat polymorphism in the promotor region of the neonatal FC receptor affects anti-TNF serum levels in IBD. Digestive Diseases Week; 2016; San Diego, CA, 2016.
89. Lallemand C, Kavrochorianou N, Steenholdt C, et al. Reporter gene assay for the quantification of the activity and neutralizing antibody response to TNFalpha antagonists. *J Immunol Methods*. 2011;373:229-239.
90. Rojas JR, Taylor RP, Cunningham MR, et al. Formation, distribution, and elimination of infliximab and anti-infliximab immune complexes in cynomolgus monkeys. *J Pharmacol Exp Ther*. 2005;313:578-585.
91. Brandse JF, van den Brink GR, Wildenberg ME, et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. *Gastroenterology*. 2015;149:350-355 e2.
92. Altwegg R, Vincent T. TNF blocking therapies and immunomonitoring in patients with inflammatory bowel disease. *Mediators Inflamm*. 2014;2014:172821.
93. Dotan I, Ron Y, Yanai H, et al. Patient factors that increase infliximab clearance and shorten half-life in inflammatory bowel disease: a population pharmacokinetic study. *Inflamm Bowel Dis*. 2014;20:2247-2259.
94. Ungar B, Mazor Y, Weisshof R, et al. Induction infliximab levels among patients with acute severe ulcerative colitis compared with patients with moderately severe ulcerative colitis. *Aliment Pharmacol Ther*. 2016;43:1293-1299.
95. Noertersheuser PA, Eckert D, Sharma S, et al. Factors affecting adalimumab pharmacokinetics in adult patients with moderate to severe CD. *Gastroenterology*. 2013;144:S230.
96. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med*. 2010;362:1383-1395.
97. Ben-Horin S, Waterman M, Kopylov U, et al. Addition of an immunomodulator to infliximab therapy eliminates antidrug antibodies in serum and restores clinical response of patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2013;11:444-447.
98. Ungar B, Yavzori M, Fudim E, et al. Addition of an immunomodulator can reverse antibody formation and loss of response in patients treated with adalimumab. Digestive Diseases Week 2016, San Diego, CA, 2016.
99. Papamichael K, Gils A, Rutgeerts P, et al. Role for therapeutic drug monitoring during induction therapy with TNF antagonists in IBD: evolution in the definition and management of primary nonresponse. *Inflamm Bowel Dis*. 2015;21:182-197.
100. Takeuchi T, Miyasaka N, Tatsuki Y, et al. Baseline tumour necrosis factor alpha levels predict the necessity for dose escalation of infliximab therapy in patients with rheumatoid arthritis. *Ann Rheum Dis*. 2011;70:1208-1215.
101. Yarur AJ, Jain A, Sussman DA, et al. 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.

102. Leclerc M, Marotte H, Paul S, et al. Persistence of antibodies to infliximab for more than two months strongly predicts loss of response to infliximab in inflammatory bowel diseases. DDW. Chicago, IL, 2014.
103. Karmiris K, Paintaud G, Noman M, et al. Influence of trough serum levels and immunogenicity on long-term outcome of adalimumab therapy in Crohn's disease. *Gastroenterology*. 2009;137:1628-1640.
104. Minar P, Saeed SA, Afreen M, Kim MO, Denson LA. Practical use of infliximab concentration monitoring in pediatric Crohn disease. *J Pediatr Gastroenterol Nutr*. 2016;62:715-722.
105. Viola F, Civitelli F, Di Nardo G, et al. Efficacy of adalimumab in moderate-to-severe pediatric Crohn's disease. *Am J Gastroenterol*. 2009;104:2566-2571.
106. Ungar B, Levy I, Yavne Y, et al. Optimizing anti-TNF-alpha therapy: serum levels of infliximab and adalimumab are associated with mucosal healing in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol*. 2016;14:550-557. e2.
107. Vande Casteele N, Khanna R, Levesque BG, et al. The relationship between infliximab concentrations, antibodies to infliximab and disease activity in Crohn's disease. *Gut*. 2015;64:1539-1545.
108. Yarur AJ, Rubin DT. Therapeutic drug monitoring of anti-tumor necrosis factor agents in patients with inflammatory bowel diseases. *Inflamm Bowel Dis*. 2015;21:1709-1718.
109. Yamada A, Sono K, Hosoe N, Takada N, Suzuki Y. Monitoring functional serum antitumor necrosis factor antibody level in Crohn's disease patients who maintained and those who lost response to anti-TNF. *Inflamm Bowel Dis*. 2010;16:1898-1904.
110. Eser A, Primas C, Reinisch W. Drug monitoring of biologics in inflammatory bowel disease. *Curr Opin Gastroenterol*. 2013;29:391-396.
111. Ordas 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.
112. Ternant D, Aubourg A, Magdelaine-Beuzelin C, et al. Infliximab pharmacokinetics in inflammatory bowel disease patients. *Ther Drug Monit*. 2008;30:523-529.
113. Klotz U, Teml A, Schwab M. Clinical pharmacokinetics and use of infliximab. *Clin Pharmacokinet*. 2007;46:645-660.
114. Buurman DJ, Maurer JM, Keizer RJ, Kosterink JG, Dijkstra G. Population pharmacokinetics of infliximab in patients with inflammatory bowel disease: potential implications for dosing in clinical practice. *Aliment Pharmacol Ther*. 2015;42:529-539.
115. Fasanmade AA, Adedokun OJ, Ford J, et al. Population pharmacokinetic analysis of infliximab in patients with ulcerative colitis. *Eur J Clin Pharmacol*. 2009;65:1211-1228.
116. Ternant D, Ducourau E, Fuzibet P, et al. Pharmacokinetics and concentration-effect relationship of adalimumab in rheumatoid arthritis. *Br J Clin Pharmacol*. 2015;79:286-297.
117. Ward MG, Thwaites PA, Beswick L, et al. Intra-patient variability in adalimumab drug levels within and between cycles in Crohn's disease. *Aliment Pharmacol Ther*. 2017;45:1135-1145.
118. Stewart MJ, Dubinsky M, Morganstern B, et al. Sa1965 the steady-state pharmacokinetics of adalimumab: do we need to drink from the "Trough"? *Gastroenterology*. 2016;150:S418-S419.
119. Baumgart DC, Grittner U, Steingraber A, Azzaro M, Philipp S. Frequency, phenotype, outcome, and therapeutic impact of skin reactions following initiation of adalimumab therapy: experience from a consecutive cohort of inflammatory bowel disease patients. *Inflamm Bowel Dis*. 2011;17:2512-2520.
120. Department of Human Services. *Ulcerative colitis*. Australia: Australian Government, 2016.
121. Department of Human Services. *Crohn's disease – adult patient*. Australia: Australian Government, 2016.
122. Colombel JF, Sandborn WJ, Allez M, et al. Association between plasma concentrations of certolizumab pegol and endoscopic outcomes of patients with Crohn's disease. *Clin Gastroenterol Hepatol*. 2014;12:423-431. e1.
123. Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2014;146:96-109. e1.
124. Bader L, Solberg SM, Kaada SH, et al. Assays for infliximab drug levels and antibodies: a matter of scales and categories. *Scand J Immunol*. 2017;86:165-170.
125. Steenholdt C, Ainsworth MA, Tovey M, et al. Comparison of techniques for monitoring infliximab and antibodies against infliximab in Crohn's disease. *Ther Drug Monit*. 2013;35:530-538.
126. Steenholdt C, Bendtzen K, Brynskov J, Thomsen OO, Ainsworth MA. Clinical implications of measuring drug and anti-drug antibodies by different assays when optimizing infliximab treatment failure in Crohn's disease: post hoc analysis of a randomized controlled trial. *Am J Gastroenterol*. 2014;109:1055-1064.
127. Ananthakrishnan AN. Epidemiology and risk factors for IBD. *Nat Rev Gastroenterol Hepatol*. 2015;12:205-217.
128. Enciso IP, Paredes LF, Sanchez-Ramon S, et al. Comparison of four assay kits for measuring infliximab trough levels and antibodies to infliximab in patients with inflammatory bowel disease. DDW, San Diego, CA; 2016.
129. Guiotto C, Daperno M, Frigerio F, et al. Clinical relevance and inter-test reliability of anti-infliximab antibodies and infliximab trough levels in patients with inflammatory bowel disease. *Dig Liver Dis*. 2016;48:138-143.
130. Lee MW, Connor S, Ng W, Toong CM. Comparison of infliximab drug measurement across three commercially available ELISA kits. *Pathology*. 2016;48:608-612.
131. Malickova K, Duricova D, Bortlik M, et al. Serum trough infliximab levels: a comparison of three different immunoassays for the monitoring of CT-P13 (infliximab) treatment in patients with inflammatory bowel disease. *Biologicals*. 2016; 44: 33-36.
132. Schmitz EM, van de Kerkhof D, Hamann D, et al. Therapeutic drug monitoring of infliximab: performance evaluation of three commercial ELISA kits. Clinical Chemistry and Laboratory Medicine: CCLM/FESCC 2015.
133. van Bezooijen JS, Koch BC, Doorn MV, Prens EP, Gelder TV, Schreurs MW. A comparison of three assays to quantify infliximab, adalimumab and etanercept serum concentrations. *Ther Drug Monit*. 2016;38:432-438.
134. Adedokun OJ, Sandborn WJ, Feagan BG, et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. *Gastroenterology*. 2014;147:1296-1307 e5.
135. Bortlik M, Duricova D, Malickova K, et al. Infliximab trough levels may predict sustained response to infliximab in patients with Crohn's disease. *J Crohns Colitis*. 2013;7:736-743.
136. Paul S, Del Tedesco E, Marotte H, et al. Therapeutic drug monitoring of infliximab and mucosal healing in inflammatory bowel disease: a prospective study. *Inflamm Bowel Dis*. 2013;19:2568-2576.
137. Steenholdt C, Bendtzen K, Brynskov J, Thomsen OO, Ainsworth MA. Cut-off levels and diagnostic accuracy of infliximab trough levels and anti-infliximab antibodies in Crohn's disease. *Scand J Gastroenterol*. 2011;46:310-318.
138. 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;10:619-625.
139. Echarri A, Ferreiro R, Fraga-Iriso R, et al. Sa1264 drug trough levels and primary nonresponse to antiTNF therapy in moderate-severe Crohn disease. Results of the optimiza study. *Gastroenterology*. 2014;146(Suppl. 1):S-247.
140. Feagan BG, Singh S, Lockton S, et al. 565 novel infliximab (IFX) and antibody-to-infliximab (ATI) assays are predictive of disease activity

in patients with Crohn's disease (CD). *Gastroenterology*. 2012;142 (5, Suppl. 1):S-114.
141. Lamblin C, Aubourg A, Ternant D, Picon L, Lecomte T, Paintaud G. P334. Concentration–effect relationship of infliximab in Crohn's disease: results of a cohort study. *J Crohns Colitis*. 2012;6:S142-S143.
142. Levesque BG, Greenberg GR, Zou G, et al. A prospective cohort study to determine the relationship between serum infliximab concentration and efficacy in patients with luminal Crohn's disease. *Aliment Pharmacol Ther*. 2014;39:1126-1135.
143. Maser EA, Villela R, Silverberg MS, Greenberg GR. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin Gastroenterol Hepatol*. 2006;4:1248-1254.
144. Seow CH, Newman A, Irwin SP, Steinhart AH, Silverberg MS, Greenberg GR. Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. *Gut*. 2010;59:49-54.
145. Yarur A, Kanagala V, Stein D, et al. 514 Higher infliximab trough levels are associated with a higher rate of perianal fistula healing in patients with Crohn's disease. *Gastroenterology*. 2016;150:S105-S106.
146. Ben-Bassat O, Romanova A, Iacono A, Irwin SP, Greenberg GR. Association of serum infliximab and antibodies to infliximab to long-term clinical outcome and mucosal healing in Crohn's disease. *Gastroenterology*. 2013;144:S775.
147. Drobne D, Bossuyt PJ, Breynaert C, et al. Crohn's disease: infliximab trough levels and CRP during infliximab-immunomodulator combination treatment are associated with clinical outcome after immunomodulator withdrawal. *Gastroenterology*. 2011;140(5, Suppl. 1):S-62.
148. Huang VW, Prosser C, Kroeker KI, et al. Knowledge of fecal calprotectin and infliximab trough levels alters clinical decision-making for IBD outpatients on maintenance infliximab therapy. *Inflamm Bowel Dis*. 2015;21:1359-1367.
149. Warman A, Straathof JW, Derijks LJ. Therapeutic drug monitoring of infliximab in inflammatory bowel disease patients in a teaching hospital setting: results of a prospective cohort study. *Eur J Gastro Hepatol*. 2015;27:242-248.
150. Drobne D, Kurent T, Rajar P, et al. High infliximab trough levels are associated with better control of inflammation in IBD. Digestive Diseases Week, San Diego, CA, 2016.
151. Van Assche G, Magdelaine-Beuzelin C, D'Haens G, et al. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. *Gastroenterology*. 2008;134:1861-1868.
152. Hibi T, Sakuraba A, Watanabe M, et al. Retrieval of serum infliximab level by shortening the maintenance infusion interval is correlated with clinical efficacy in Crohn's disease. *Inflamm Bowel Dis*. 2012;18:1480-1487.
153. Imaeda H, Takahashi K, Fujimoto T, et al. Clinical utility of newly developed immunoassays for serum concentrations of adalimumab and anti-adalimumab antibodies in patients with Crohn's disease. *J Gastroenterol*. 2014;49:100-109.
154. Mazor Y, Almog R, Kopylov U, et al. Adalimumab drug and antibody levels as predictors of clinical and laboratory response in patients with Crohn's disease. *Aliment Pharmacol Ther*. 2014;40:620-628.
155. Mostafa NM, Eckert D, Pradhan RS, Mensing S, Robinson AM, Sandborn WJ. P333 Exposure-efficacy relationship (ER) for adalimumab during induction phase of treatment of adult patients with moderate to severe ulcerative colitis (UC). *U Eur Gastroenterol J*. 2013;1:A221-A222.
156. Roblin X, Marotte H, Rinaudo M, et al. Association between pharmacokinetics of adalimumab and mucosal healing in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol*. 2014;12:80-84 e2.
157. Sharma S, Eckert D, Hyams JS, et al. Pharmacokinetics and exposure-efficacy relationship of adalimumab in pediatric patients with moderate to severe Crohn's disease: results from a randomized, multicenter, phase-3 study. *Inflamm Bowel Dis*. 2015;21:783-792.
158. Velayos FS, Sheibani S, Lockton S, et al. 490 prevalence of antibodies to adalimumab (ATA) and correlation between ata and low serum drug concentration on crp and clinical symptoms in a prospective sample of IBD patients. *Gastroenterology*. 2013;144:S-91.
159. Yarur AJ, Deshpande AR, Sussman DA, et al. Serum adalimumab levels and antibodies correlate with endoscopic intestinal inflammation and inflammatory markers in patients with inflammatory bowel disease. *Gastroenterology*. 2013;144:S774-S775.
160. Yarur AJ, Jain A, Hauenstein SI, et al. Higher Adalimumab levels are associated with histologic and endoscopic remission in patients with Crohn's disease and ulcerative colitis. *Inflamm Bowel Dis*. 2016;22:409-415.
161. Chaparro M, de Barreiro-Acosta M, Echarri A, et al. Correlation between anti-TNF serum levels and mucosal healing (MH) in inflammatory bowel disease (IBD) patient. Digestive Diseases Week, San Diego, CA, 2016.
162. Menting SP, Coussens E, Pouw MF, et al. Developing a therapeutic range of adalimumab serum concentrations in management of psoriasis: a step toward personalized treatment. *JAMA Dermatol*. 2015;151:616-622.
163. Pouw MF, Krieckaert CL, Nurmohamed MT, et al. Key findings towards optimising adalimumab treatment: the concentration-effect curve. *Ann Rheum Dis*. 2015;74:513-518.
164. Yarur AJ, Kanagala V, Stein DJ, et al. Higher infliximab trough levels are associated with perianal fistula healing in patients with Crohn's disease. *Aliment Pharmacol Ther*. 2017;45:933-940.
165. Mitrev N, Karijawasam V, Leong RW. Infliximab trough cut-off for perianal Crohn's disease: another piece of the therapeutic drug monitoring-guided infliximab dosing puzzle. *Aliment Pharmacol Ther*. 2017;45:1279-1280.
166. Kosmac M, Avcin T, Toplak N, Simonini G, Cimaz R, Curin Serbec V. Exploring the binding sites of anti-infliximab antibodies in pediatric patients with rheumatic diseases treated with infliximab. *Pediatr Res*. 2011;69:243-248.
167. van der Laken CJ, Voskuyl AE, Roos JC, et al. Imaging and serum analysis of immune complex formation of radiolabelled infliximab and anti-infliximab in responders and non-responders to therapy for rheumatoid arthritis. *Ann Rheum Dis*. 2007;66:253-256.
168. Nanda KS, Cheifetz AS, Moss AC. Impact of antibodies to infliximab on clinical outcomes and serum infliximab levels in patients with inflammatory bowel disease (IBD): a meta-analysis. *Am J Gastroenterol*. 2013;108:40-47; quiz 48.
169. Vande Casteele N, Feagan BG, Gils A, et al. Therapeutic drug monitoring in inflammatory bowel disease: current state and future perspectives. *Curr Gastroenterol Rep*. 2014;16:378.
170. Paul S, Moreau AC, Del Tedesco E, et al. Pharmacokinetics of adalimumab in inflammatory bowel diseases: a systematic review and meta-analysis. *Inflamm Bowel Dis*. 2014;20:1288-1295.
171. Swoger JM, Levesque BG. Editorial: drug monitoring targets for optimising adalimumab in Crohn's disease. *Aliment Pharmacol Ther*. 2014;40:854-855.
172. Svenson M, Geborek P, Saxne T, Bendtzen K. Monitoring patients treated with anti-TNF-alpha biopharmaceuticals: assessing serum infliximab and anti-infliximab antibodies. *Rheumatology*. 2007;46:1828-1834.
173. Steenholdt C, Brynskov J, Bendtzen K. Letter: persistence of anti-infliximab antibodies after discontinuation of infliximab in patients with IBD. *Aliment Pharmacol Ther*. 2012;36:499-500; author reply 501.

174. Vande Casteele N, Gils A, Singh S, et al. Antibody response to infliximab and its impact on pharmacokinetics can be transient. *Am J Gastroenterol*. 2013;108:962-971.
175. Steenholdt C, Al-khalaf M, Brynskov J, Bendtzen K, Thomsen OO, Ainsworth MA. Clinical implications of variations in anti-infliximab antibody levels in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2012;18:2209-2217.
176. Vaughn BP, Sandborn WJ, Cheifetz AS. Biologic concentration testing in inflammatory bowel disease. *Inflamm Bowel Dis*. 2015;21:1435-1442.
177. Wang SL, Ohrmund L, Hauenstein S, et al. Development and validation of a homogeneous mobility shift assay for the measurement of infliximab and antibodies-to-infliximab levels in patient serum. *J Immunol Methods*. 2012;382:177-188.
178. Scott FI, Lichtenstein GR. Therapeutic drug monitoring of anti-TNF therapy in inflammatory bowel disease. *Curr Treat Opt Gastroenterol*. 2014;12:59-75.
179. Balsanek J, Willrich MAV, Murray DL, Snyder M. Sa1268 clinical development of an electrochemiluminescent immunoassay to measure antibodies-to-infliximab. *Gastroenterology*. 2014;146:S248.
180. Van Stappen T, Brouwers E, Vermeire S, Gils A. Validation of a sample pretreatment protocol to convert a drug-sensitive into a drug-tolerant anti-infliximab antibody immunoassay. *Drug Test Anal*. 2016;9:243-247.
181. Steenholdt C, Bendtzen K, Brynskov J, et al. Changes in serum trough levels of infliximab during treatment intensification but not in anti-infliximab antibody detection are associated with clinical outcomes after therapeutic failure in Crohn's disease. *J Crohns Colitis*. 2015;9:238-245.
182. Van Stappen T, Vande Casteele N, Van Assche G, Ferrante M, Vermeire S, Gils A. Clinical relevance of detecting anti-infliximab antibodies with a drug-tolerant assay: post hoc analysis of the TAXIT trial. *Gut*. 2017; https://doi.org/10.1136/gutjnl-2016-313071 [Epub ahead of print].
183. Williet N, Boschetti G, Fovet M, et al. Association between low trough levels of vedolizumab during induction therapy for inflammatory bowel diseases with need for additional doses within 6 months. *Clin Gastroenterol Hepatol*. 2016; https://doi.org/10.1016/j.cgh.2016.11.023. [Epub ahead of print].
184. Rosario M, Dirks NL, Gastonguay MR, et al. Population pharmacokinetics-pharmacodynamics of vedolizumab in patients with ulcerative colitis and Crohn's disease. *Aliment Pharmacol Ther*. 2015;42:188-202.
185. Menting SP, van den Reek JM, Baerveldt EM, et al. The correlation of clinical efficacy, serum trough levels and antidrug antibodies in ustekinumab-treated patients with psoriasis in a clinical-practice setting. *Br J Dermatol*. 2015;173:855-857.

SUPPORTING INFORMATION

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

How to cite this article: Mitrev N, Vande Casteele N, Seow CH, et al. Review article: consensus statements on therapeutic drug monitoring of anti-tumour necrosis factor therapy in inflammatory bowel diseases. *Aliment Pharmacol Ther*. 2017;00:1–17. https://doi.org/10.1111/apt.14368

APPENDIX 1

AUTHORS' COMPLETE AFFILIATIONS

Nikola Mitrev, Concord Hospital IBD Service, Sydney, NSW, Australia, Niels Vande Casteele, Department of Medicine, University of California San Diego, La Jolla, CA, USA, Cynthia H. Seow, Division of Gastroenterology and Hepatology, Departments of Medicine and Community Health Sciences, University of Calgary, Calgary, AB, Canada, Jane M. Andrews, Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, Adelaide, SA, Australia, Susan J. Connor, Department of Gastroenterology, Liverpool Hospital, Liverpool, NSW, Australia; South Western Sydney Clinical School, University of NSW, Sydney, NSW, Australia; Ingham Institute of Applied Medical Research, Sydney, NSW, Australia; Gregory T. Moore, Department of Gastroenterology & Hepatology, Monash Health, Clayton, Vic., Australia, Monash University, Melbourne, Vic., Australia; Murray Barclay, Department of Gastroenterology, Christchurch Hospital, Christchurch, New Zealand; Department of Medicine, University of Otago Christchurch, Christchurch, New Zealand; Jakob Begun, Mater Hospital Brisbane, Mater Research Institute – University of Queensland, Brisbane, Qld, Australia; Robert Bryant, IBD Service, The Queen Elizabeth Hospital, Woodville South, SA, Australia; Webber Chan, Concord Hospital IBD Service, Sydney, NSW, Australia; Crispin Corte, Royal Prince Alfred Hospital, Sydney, NSW, Australia; Simon Ghaly, Department of Gastroenterology, St. Vincent's Hospital Sydney, Darlinghurst, NSW, Australia; UNSW School of Medicine, Darlinghurst, NSW, Australia; Daniel A. Lemberg, Department of Gastroenterology, The Sydney Children's Hospital, Randwick, NSW, Australia; Viraj Kariyawasam, Concord Hospital IBD Service, Sydney, NSW, Australia; Peter Lewindon, Department of Gastroenterology, Lady Cilento Children's Hospital, Brisbane, Qld, Australia; Jennifer Martin, University of Newcastle and Hunter New England Health, NSW, Australia; Reme Mountifield, Department of Gastroenterology and Hepatology, Flinders Medical Centre, SA, Australia; Graham Radford-Smith, Royal Brisbane and Women's Hospital, Herston, Qld, Australia; Peter Slobodian, Pharmacy Investigational Drugs Service, Royal Adelaide Hospital, Adelaide, SA, Australia; Miles Sparrow, Monash University, Melbourne, Vic., Australia; Department of Gastroenterology, The Alfred Hospital, Melbourne, Vic., Australia; Catherine Toong, Department of Immunology, Sydney South West Pathology Service, Liverpool Hospital and Concord Repatriation General Hospital, Concord, NSW, Australia; Daniel van Langenberg, IBD Service, Department of Gastroenterology, Eastern Health, Box Hill Hospital, Vic., Australia; Mark G. Ward, Monash University, Melbourne, Vic., Australia; Department of Gastroenterology, The Alfred Hospital, Melbourne, Vic., Australia; Rupert W. Leong, Concord Hospital IBD Service, Sydney, NSW, Australia; IBD Sydney Organisation and the Australian Inflammatory Bowel Diseases Consensus Working Group.