Therapeutic drug monitoring guided anti-tumour necrosis factor therapy in inflammatory bowel disease (IBD): Gastroenterological Society of Australia (GESA)/ Australian IBD Association (AIBDA) consensus statements

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STATEMENT OF ORIGINALITY

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and the sources have been acknowledged. This thesis has not been submitted for any other degree or purpose.

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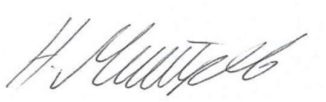
Signature: 

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ABSTRACT

INTRODUCTION: Growing evidence supports the use of therapeutic drug monitoring (TDM) to guide anti-tumour necrosis factor (TNF) drug treatment among patients with inflammatory bowel disease (IBD). Currently, TDM for anti-TNF drugs is variably practiced by gastroenterologists in Australia. Our aim was to develop consensus statements for TDM of anti-TNF drugs in IBD that will be endorsed by the Australian IBD Association (AIBDA) of the Gastroenterological Society of Australia (GESA).

METHODS: A consensus committee of 25 Australian and international experts was assembled. A systematic literature search aided the steering committee in developing the initial draft statements. A modified Delphi technique was used with three iterations, with modification of statements based on feedback and anonymous voting. Statements with 80% agreement without reservation or only minor reservation in the third voting round were accepted as consensus.

RESULTS: 22/24 statements met criteria for consensus. The committee agreed that TDM for anti-TNF agents 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 µg/mL and 5-12 µg/mL, respectively, were determined as appropriate. The therapeutic range may need to be altered for different disease phenotypes or treatment endpoints. In treatment failure, TDM may identify mechanisms to guide subsequent decision-making. Among patients in remission, TDM-guided anti-TNF drug dose optimisation may reduce treatment cost and avoid future relapse. Data indicates drug-tolerant anti-drug antibody assays do not offer an advantage over drug-sensitive assays in

predicting outcomes. Further data are required prior to recommending TDM for non-anti-TNF biologics.

CONCLUSION: These consensus statements are expected to aid use of TDM by gastroenterologists in Australia and abroad to guide anti-TNF drug treatment in IBD patients.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABBREVIATIONS

ADCC: antibody-dependent cellular cytotoxicity

AIBDA: Australian Inflammatory Bowel Disease Association

ASUC: acute severe ulcerative colitis

ATA: antibodies to adalimumab

ATI: antibodies to infliximab

AUROC: area under a receiver operating characteristic

CD: Crohn's disease

CDAI: Crohn's Disease Activity Index

CDC: complement-dependent cytotoxicity

CMV: Cytomegalovirus

ECLISA: electrochemiluminescence immunoassay

ELISA: enzyme-linked immunosorbent assay

GESA: Gastroenterological Society of Australia

GIT: gastrointestinal tract

HBI: Harvey Bradshaw Index

HMSA: homogeneous mobility shift assay

IBD: inflammatory bowel disease

NHMRC: National Health and Medical Research Council

PBS: Pharmaceutical Benefits Scheme

RCT: randomised controlled trial

RIA: radio-immunoassay

SC: subcutaneous

SES-CD: simplified endoscopic activity score for Crohn's disease

TDM: therapeutic drug monitoring

TNF: tumour necrosis factor

UC: ulcerative colitis

UCDAI: Ulcerative Colitis Disease Activity Index

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1. INTRODUCTION

1.1 Inflammatory bowel disease

Inflammatory bowel disease (IBD), a chronic inflammatory condition of the gastrointestinal tract (GIT), includes Crohn's disease (CD) and ulcerative colitis (UC). Symptoms of IBD vary and may include abdominal pain, diarrhoea and per rectal bleeding. UC affects the mucosal layer of the bowel in continuity from the anus and extending to varying lengths of the colon. In contrast, CD affects the full thickness of the bowel wall, can occur in any part of the GIT from mouth to anus, and lesions are not necessarily continuous. IBD is also a systemic disorder and can affect the eyes, bones, joints, skin, haematological system, urogenital tract, respiratory tract and cardiovascular system.[1] The widely accepted hypothesis is that IBD is an aberrant immune response to enteric commensal microbes, in a genetically predisposed host exposed to environmental triggers.[2]

Incidence and prevalence of IBD varies greatly between populations around the world.[3] Reported incidence ranges from 0.0 to 29.3 per 100,000 for UC and 0.0 to 19.2 per 100,000 for CD. Reported prevalence for UC ranges from 2.42 to 298.5 per 100,000 and that for CD ranges from 0.6 to 318.5 per 100,000. Highest incidence and prevalence rates have been reported in North America, Europe, Australia and New Zealand. Most studies of CD and UC at different time points from various populations around the world have demonstrated a statistically significant increase in incidence with time (75% of CD studies, 60% of UC studies, P value (P) < 0.05).[4] A population based study in Olmsted County, Minnesota, USA, demonstrated a marked rise in incidence of both UC and CD from 1940s to the 1970s (1.0 cases per 100,000 person-years to 7.8 cases per 100,000 person years for CD, and 0.6 cases per 100,000

person years to 9.4 cases per 100,000 person-years for UC).[4-6] It is postulated that improved hygiene, altered diet and antibiotic use within a population, which follows industrialisation, alters the gut microbiota and the immune system's interaction with it, predisposing to IBD.[7] As a result developing countries are currently experiencing a rise in IBD incidence.

IBD is not curable and treatment involves induction of remission followed by maintenance treatment. Induction of remission in IBD has classically relied on corticosteroids, 5-aminosalicylates and immunomodulators such as thiopurines and methotrexate.[8, 9] More recently developed biologic drugs are large protein molecules, usually monoclonal antibodies, which bind and inhibit a molecular target. The first developed biologic, infliximab, targets tumour necrosis factor (TNF). TNF is a major inflammatory cytokine in IBD pathogenesis. Infliximab and other anti-TNF biologics, adalimumab, certolizumab and golimumab, have proven effective at inducing and maintaining remission in IBD.[10-13] Newly developed biologic drugs effective in IBD also include vedolizumab, which blocks lymphocyte trafficking by inhibiting integrin α4β7, and ustekinumab, an inhibitor of the pro-inflammatory cytokines Interleukin 12 and 23 (IL12/23).

1.2 Anti-tumour necrosis factor drugs for treatment of inflammatory bowel disease

Anti-TNF drugs are used in inflammatory and auto-inflammatory conditions such as IBD, Ankylosing spondylitis (AS) and Rheumatoid arthritis (RA). Infliximab, is a mouse-human chimeric monoclonal IgG1 antibody that consists of a human common (Fc) domain and a mouse variable (Fv) domain responsible for TNF binding. Early on,

development of antibodies to infliximab (ATI) was recognised as an important mechanism for treatment failure and infusion reactions.[14] Newly developed anti-TNF agents have aimed to reduce immunogenicity, loss of response and side effects.[15]

The humanised monoclonal antibodies adalimumab and golimumab, have a human Fc and Fv domain. Of these only adalimumab is currently available in Australia. Adalimumab has not been compared to infliximab in head-to-head randomised studies. Although network meta-analysis and non-randomised studies indicate similar efficacy at inducing and maintaining remission, adalimumab may be superior to infliximab in maintaining remission in CD, while infliximab may be superior to adalimumab at inducing remission in UC.[16-18] Although development of anti-drug antibodies is less with adalimumab than infliximab, rates of adverse reactions and secondary loss of response appear to be similar between these two anti-TNF agents.[16-21]

Anti-TNF drugs that lack complete monoclonal antibody structure have proven less efficacious in IBD. Certolizumab, a pegylated monoclonal human F[ab']2 fragment that lacks an Fc antibody portion, was intended to reduce side-effects related to anti-TNF agents interacting with Fc receptors of immune cells. An initial randomised controlled trial (RCT) demonstrated no difference in the primary endpoint of clinical remission between the certolizumab and placebo groups, however there was increased rates of response in the certolizumab group at week 6.[22] The TNF receptor II-Fc fusion peptide entanercept was intended to increase specificity for TNF binding, following findings that anti-TNF monoclonal antibodies also bind other targets.[15] It was hoped this would reduce infusion reactions. However, although effective in rheumatoid arthritis and ankolysing spondylitis, entanercept has failed to demonstrate benefits in IBD.[23-25]

TNF is synthesised as a transmembrane protein by macrophages and other immune cells.[26] Membrane-bound TNF is subsequently cleaved to release soluble TNF. Membrane-bound and soluble TNF differ in their ability to activate one of two TNF receptors. TNF receptor 1 is activated by both soluble and membrane-bound TNF, and promotes transcription of genes responsible for inflammation and apoptosis. TNF receptor 2 is predominantly activated by membrane-bound TNF, and stimulates cell survival and healing. Anti-TNF agents differ in their ability to bind membrane-bound, soluble TNF, and soluble TNF bound to its cell surface receptor. Anti-TNF agents impart their anti-inflammatory action via a number of mechanisms including clearance of soluble TNF and passive induction of T cell apoptosis through deprivation of TNF-dependant survival signalling, or active induction of apoptosis via antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). ADCC and CDC are crucially dependent on presence of an Fc region on the anti-TNF drug molecule, and are most efficiently performed by the monoclonal antibodies infliximab, adalimumab and golimumab.[15] These mechanisms may be vital for the efficacy of anti-TNF agents in IBD and would explain the reduced effectiveness of certolizumab and lack of efficacy of entanercept in IBD.

Unfortunately, not all patients gain adequate disease control with anti-TNF therapy. Primary non-response is failure to respond to induction therapy, while secondary loss of response is disease flare following an initially demonstrated response to therapy.[27] Following initial induction therapy, primary non-response affects 10-30% of patients, while clinical remission, a harder endpoint to treatment, was only achieved in 45.3% and 24.2% of patients in infliximab and adalimumab studies respectively.[12, 13, 28] For those that respond to induction treatment, secondary loss of response affects 23-46% of anti-TNF treated IBD patients at 12 months.[27] There is potential

for significant health gains if we can optimise anti-TNF drug therapy. Recently TDM has emerged as a promising means of optimising treatment with anti-TNF drugs in IBD. TDM of anti-TNF drugs involves measurement of drug levels and anti-drug antibodies to help guide decisions around dose adjustment and timing of switching to alternate therapy. TDM of anti-TNF drugs is one aspect of personalised IBD therapy which is currently practiced.

1.3 Treatment of inflammatory bowel disease with anti-TNF drugs in the Australian context

Healthcare in Australia is predominantly public, with medications funded by the Pharmaceutical Benefits Scheme (PBS). The PBS has approved two anti-TNF agents, infliximab and adalimumab, and the lymphocyte trafficking inhibitor, vedolizumab, for treatment of both CD and UC.[29, 30] Ustekinumab has also recently been approved for CD treatment only. To qualify for treatment with biologics, a patient with either UC or CD must meet criteria for initiation of biologic therapy (Table 1). Similarly, an adequate response as defined by PBS criteria must be demonstrated on subsequent assessments in order to qualify for ongoing treatment with biologics. Patients who fail one biologic can transition onto another under the PBS, and currently UC and CD patients are permitted a maximum of three and four treatment failure events respectively, before they no longer qualify for PBS subsidised biologic therapy.

The PBS currently funds a fixed induction and maintenance regimen for both infliximab and adalimumab. Infliximab induction dosing involves administering 5mg/kg intravenously (IV) at weeks 0, 2 and 6, followed by 5mg/kg every 8 weeks. The standard dosing regimen for adalimumab involves subcutaneous (SC) administration

of 160mg at week 0, 80mg at week 2, then 40mg every 2 weeks as maintenance. Currently the PBS does not support a trial of dose escalation for patients with primary non-response or secondary loss of response to either infliximab or adalimumab, however pharmaceutical companies have been providing additional doses of these anti-TNF drugs under compassionate access schemes. As such many gastroenterologists in Australia practice dose escalation for patients failing treatment. Pharmaceutical companies have not advised how long they will continue to supply compassionate doses of anti-TNF drug and the PBS has not announced any plans to fund dose intensification in the future.

The approach to patient's failing anti-TNF therapy varies widely among gastroenterologists in Australia. On documented anti-TNF drug failure, the range of current practices includes: 1) empirically switching to another biologic drug, either within or out-of-class; 2) empirically trialling anti-TNF dose escalation and if this fails switching to another biologic drug; or 3) a TDM-guided approach. A TDM-guided approach during anti-TNF treatment failure may elicit mechanisms of failure to better select patients likely to respond to dose escalation, switching within class or switching out-of-class. As such patients are likely to be commenced on effective treatment sooner than with empiric treatment changes. In addition, TDM-guided anti-TNF drug dose optimisation for stable patients maintained in remission may reduce treatment cost and future risk of disease relapse. TDM-guided anti-TNF drug treatment is a useful means of individualising IBD treatment that is currently underutilised by gastroenterologists in Australia and abroad. Anecdotally, barriers for gastroenterologists using a TDM-guided approach to anti-TNF therapy in Australia includes lack of awareness of the available tests, when to perform TDM and how to interpret and act on results. North American and European practice guidelines are not

entirely applicable to the Australian context due to differences in the available assays and the funding structure for medications in Australian.[31] The aim of this project was to establish a committee of local and international experts in IBD and TDM, in order to develop a set of consensus statements on TDM-guided anti-TNF therapy in IBD that will be endorsed by the Australian Inflammatory Bowel Disease Association (AIBDA) of the Gastroenterological Society of Australia (GESA). It is hoped that the resultant consensus statements will help Australian gastroenterologists utilise TDM of anti-TNF drugs to improve the care of IBD patients.

Table 1: Criteria for initial and continuing treatment with biologics for adult Crohn's Disease and Ulcerative colitis on the PBS[29, 30, 32]

Disease & phenotype	**Criteria for initiation**	**Criteria for adequate response to qualify for continuation** (reassessed at 24 week intervals following induction)
Moderate to severe UC	**A)** Failure to achieve adequate response to or intolerance of 5-aminosalicylates (adequate induction doses), and at least one of the following medications: 1. Azathioprine (≥2mg/kg daily for ≥3 months) 2. 6-Mercaptopurine (≥1mg/kg daily for ≥3 months) 3. Tapered course of steroids (starting at least 40mg prednisolone and tapering over at least 6 weeks) followed by ≥3 months of appropriately dosed thiopurine agent.	Partial Mayo score ≤2, with all sub-scores ≤1

	B) <u>AND</u> at least one of: 1. Mayo score ≥6 2. Partial Mayo score ≥6 with rectal bleeding and stool frequency sub-scores both ≥2	
Luminal Crohn's disease	**A)** Failure to achieve adequate response to or intolerance of tapered course of steroids (starting at least 40mg prednisolone and tapering over at least 6 weeks), and at least one of the following medications: 1. Azathioprine (≥2mg/kg daily for ≥3 months) 2. 6-Mercaptopurine (≥1mg/kg daily for ≥3 months) 3. Methotrexate (≥15mg for ≥3 months) **B) <u>AND</u>**	CDAI ≤150, **<u>OR</u>** At least one of: 1. Normalisation of platelet count 2. ESR ≤25mm/hr 3. CRP ≤15mg/L 4. Normalisation of lactoferrin 5. Normalisation of calprotectin 6. Imaging evidence of mucosal healing 7. Reversal of high faecal output state 8. Assessed as no longer requiring surgery or TPN

	CDAI ≥300, **OR** At least one of: 1. Radiological evidence of >50cm of small intestinal involvement and CDAI ≥220 2. Short gut syndrome or ileostomy or colostomy AND at least one of: 1. Elevated platelet count 2. ESR>25mm/hr 3. CRP>15mg/L 4. Elevated faecal lactoferrin 5. Elevated faecal calprotectin 6. Imaging evidence of active mucosal inflammation 7. Assessed as being in a high faecal output state 8. Assessed as requiring surgery or TPN as the next therapeutic option in absence of biologic disease modifying drugs.	

Fistulising Crohn's disease	Complex refractory fistulising CD with externally draining enterocutaneous or rectovaginal fistula	A Fistulae Symptom Grading Score less than baseline assessment score

CD, Crohn's disease; **CDAI**, Crohn's disease activity index; **CRP**, C reactive peptide; **ESR**, erythrocyte sedimentation rate; **TPN**, total parenteral nutrition; **UC**, Ulcerative colitis

1.4 Consensus methods

Guidelines obtained via a consensus are of greater value than individual opinions. The Delphi method and its variations are a popular approach to obtaining a consensus from a panel of experts.[33, 34] The Delphi method employs several rounds of voting from an expert committee. Following each round the level of agreement for various statements is quantified, and individual panel members receive anonymous feedback on how their voting compared to the rest of the consensus committee. Each round permits individual panel members to change their position based on the opinions of the rest of the consensus committee, and anonymity facilitates this by removing pressures of dominant individuals. With each iteration of the Delphi method it is expected the group will move closer towards a consensus, with diminishing benefits beyond three to four iterations.[33, 35-38] Traditionally the first round of the Delphi method involves an open-ended questionnaire to collect ideas from panel members, which will be used as the basis for the structured questionnaire in subsequent rounds. A common modification of the Delphi method is for the first round to start with a structured questionnaire based on a literature review.[33] A panel of appropriate experts in the field is crucial for the validity of the Delphi method.[33, 34]

Within Australia, the National Health and Medical Research Council (NHMRC) has developed a system to aid developers of national healthcare guidelines, whereby each guideline recommendation is assigned a rating for level of evidence and grade of recommendation.[39] The level of supporting evidence is rated I - IV depending on the appropriateness of available studies in answering the particular clinical question (Appendix, Table 1). Grades of recommendation (A-D) for each statement are assigned based on five domains: available evidence base, consistency of the evidence, clinical impact of the recommendation, generalisability of the evidence to

the intended population and applicability of the recommendation to the Australian healthcare context (Appendix, Tables 2 & 3).

2. METHODS

2.1 Steering committee and consensus committee

A steering committee was initially formed (RL, JMA, SC, GM, NM). At the start, the steering committee decided on a timeline for work, composition of the consensus committee and criteria for nomination of panel members to the consensus committee. It was agreed for panel to consist of 15-25 gastroenterologists, 1 immunologist and 1-3 clinical pharmacologists/pharmacists, and to invite 2-3 international experts in the field of TDM for anti-TNF drugs. Criteria for nomination of gastroenterologists to the panel were as follows: publications in the IBD field over the last 12 months AND a demonstrated commitment to the IBD field through work in dedicated high-volume IBD clinics OR affiliation with an IBD association. The nominated immunologist and clinical pharmacologists/ pharmacists were to have expertise in TDM of anti-TNF drugs. The steering committee proceeded to nominate panel members who were subsequently invited.

2.2 Literature search

A structured literature search was performed to aid drafting of the consensus statements (NM). A set of broad clinical questions were formulated to guide the search (Table 2). A literature search was performed in May/ June 2016 in Pubmed and Medline using the 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. The abstracts, and if necessary the whole paper, of identified articles were screened for relevance to the pre-determined clinical questions.

Original articles and literature reviews relevant to answering at least one of the pre-determined clinical question were included. Additional papers and conference abstracts were obtained from the references section, searching abstracts from major international conferences and from consensus committee members. NM compiled the relevant articles and prepared a summary of the evidence. This was initially made available to steering committee members, and subsequently was distributed to all consensus members following the first round of voting.

Table 2: Pre-determined clinical questions for literature search. Where appropriate questions were worded in the PICO format (Patient, Intervention, Comparator, Outcome).[40]

Pre-determined clinical questions
1. Among **IBD patients treated with anti-TNF drugs** (P), what are **appropriate adalimumab and infliximab steady state trough therapeutic ranges** (I, C) for **remission** (O)?
2. Among **IBD patients treated with anti-TNF drugs** (P) does presence of **anti-drug antibodies** (I) versus **no anti-drug antibodies** (C) affect **response** (O)?
3. Among patients treated with anti-TNF drugs, are drug levels and anti-drug antibodies measured by different assays comparable?
4. Among **IBD patients failing anti-TNF drug treatment** (P), does **TDM-guided** (I) versus **clinically-guided** (C) anti-TNF drug treatment result in improved **clinical outcomes or reducing health-related cost** (O)?

5. Among **IBD patients in remission on anti-TNF drug treatment** (P), does **TDM-guided** (I) versus **clinically-guided** (C) anti-TNF drug treatment result in improved **clinical outcomes or reducing health-related cost** (O)?
6. What is the ideal TDM-guided treatment decision algorithm to follow for IBD patients on anti-TNF drug treatment who have active disease, and for those in remission?
7. In what clinical context is TDM helpful/ not helpful in guiding anti-TNF therapy?
8. Among **IBD patients treated with non-anti-TNF biologic drugs** (P), does **TDM-guided** (I) versus **clinically-guided** (C) biologic drug treatment result in improved **clinical outcomes** (O)?

2.3 Production of initial draft of the consensus statements

The first draft of the consensus statements was compiled by NM based on current evidence and international practice. The statements were distributed to members of the steering committee and discussed and refined on a meeting. The redrafted statements were reviewed for a second time by the steering committee as well as three other expert members from the consensus committee (NVC, CS, MW). The draft consensus statements were further refined based on feedback from the second round of review. The steering committee approved the final draft of the consensus statements prior to distribution to the rest of the consensus committee.

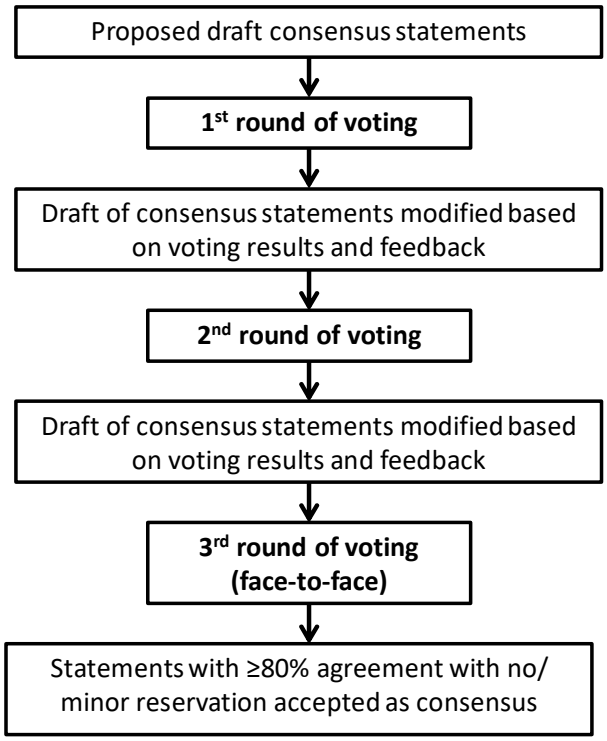
2.4 Voting

A modified Delphi method was employed with three rounds of voting in order to reach a consensus (Figure 1). The first two voting rounds were completed online using Surveymonkey™, while the final round of voting was a face-to-face session. Each consensus committee member was permitted to vote only once for each statement. Level of agreement with each statement was rated as: 1) agree without reservation, 2) agree with minor reservation, 3) agree with major reservation, 4) disagree with some reservation, 5) disagree without reservation, or 6) reserved. Consensus committee members could also leave an optional comment in relation to each statement. Between each voting round statements were modified based on voting results and comments from panellists. Compiled anonymous voting results were distributed to committee members following the two online voting rounds. The results of the literature search, including original papers and abstracts, as well as a summary of the evidence, were made available to all committee members via Dropbox™ following the first voting round. Committee members were given an opportunity to review the papers and abstracts from the literature search and evidence summaries prior to the second voting round. Committee members had access to the literature search papers and abstracts and evidence summaries through to the third and final voting round.

In the final voting round each committee member was allocated responsibility over one or two statements. They closely examined the evidence surrounding that statement/s and presented it to the consensus committee on the face-to-face session held in Sydney, in January 2017. Statements with lower degree of agreement in the second voting round were allocated more time: statements with < 80% agreement with no/ minor reservation were allocated 15minutes, those with ≥ 80% but < 90% agreement were allocated 10 minutes, statements with ≥ 90% were allocated 5 minutes. The sequence followed for each statement was as follows: presentation of the evidence

base, discussion, modification of the statement if necessary, and voting. Statements with 80% of votes as agree without reservation or agree with minor reservation were accepted as consensus. Failure for consensus allowed the statement to be revised and revoted once only. For each statement, consensus committee members agreed on the NHMRC level of evidence and NHMRC grade of recommendation (Appendix, Tables 1, 2 and 3). Spearman's ranked order correlation was used in IBM SPSS™ to assess the relationship between NHMRC level of evidence and grade of recommendation.

Figure 1: Flow diagram for the implemented modified Delphi method.



3. LITERATURE REVIEW

3.1 Mechanisms of anti-TNF failure based on therapeutic drug monitoring

TDM for patients with active disease while on anti-TNF therapy, either primary non-response or secondary loss of response, may reveal mechanisms of treatment failure and help guide clinical decisions (Table 3).[19, 41-45] Confirmed active inflammatory disease despite therapeutic levels suggests pharmacodynamic failure. In this patient group, intestinal inflammation is driven predominantly by non-TNF pathways, or other inflammatory pathways can compensate for TNF inhibition, and such patients do not benefit significantly from being on an anti-TNF agent.

Table 3: Mechanisms of anti-TNF drug failure based on therapeutic drug monitoring results[19]

		Anti-TNF drug levels	
		Sub-therapeutic	**Therapeutic**
Anti-drug antibodies	**Absent**	Non-immune mediated PK failure	PD failure
	Present	Immune-mediated PK failure	Potentially PD failure with non-functional anti-drug antibodies (only relevant to drug-tolerant assays)

PD, Pharmacodynamic; PK, Pharmacokinetic

Active disease in the context of sub-therapeutic levels suggests pharmacokinetic failure, that is treatment failure due to inadequate drug exposure. Pharmacokinetic failure can further be subdivided into immune-mediated and non-immune-mediated based on presence or absence of anti-drug antibodies, respectively. Anti-drug antibodies may bind the anti-TNF drug and either directly interfere with its function or increase its clearance. Patients with non-immune mediated pharmacokinetic failure are either under dosed or have increased clearance due to inter-individual variability. Such individuals need a higher than standard dose of the anti-TNF drug in question in order to reach therapeutic levels. Non-compliance with dosing needs to be excluded in such patients.

Molecular mechanisms of failure vary between primary non-response and secondary loss of response. Pharmacokinetic failure in primary non-response is from increased drug clearance due to genetic factors, increased inflammatory load, or early anti-drug antibody production.[46] Anti-TNF drugs that are monoclonal antibodies are cleared from the circulation by phagocytic cells of the reticuloendothelial system, via Fcγ receptor (FcγR) dependant uptake.[46, 47] Certain polymorphisms of the FcγR increase clearance of both infliximab and adalimumab.[48] Other genetic polymorphisms likely exist to account for variation in anti-TNF drug elimination between individuals. Development of ATI has been documented during induction therapy and may contribute to primary non-response.[46, 49] In secondary loss of response, pharmacokinetic failure is predominantly from anti-drug antibodies and non-genetic factors that increase drug clearance via non-immune mechanisms.

Pharmacodynamic failure in primary non-response may be due to genetic or disease factors that result in non-TNF inflammatory pathways having a role, while in secondary loss of response it has been postulated that anti-TNF therapy can eventually promote

non-TNF inflammatory pathways.[46, 50] Genetic polymorphisms in TNF receptor 1, the FcγR as well as the apoptosis pathway proteins Fas, Fas Ligand and Caspase 9 have been shown to reduce responsiveness to infliximab.[46, 51-54] In a subset of individuals anti-TNF therapy for immune mediated conditions may trigger other paradoxical inflammatory conditions, the most well described being psoriatic skin reactions.[50, 55-57] Anti-TNF therapy in mouse models of rheumatoid arthritis has been shown to increase peripheral levels of Th1 and Th17 cells, and may provide a mechanistic explanation for the above paradoxic pro-inflammatory effects.[50, 58] Similarly with prolonged anti-TNF drug treatment in IBD, promotion of alternate inflammatory pathways within the bowel may lead to secondary loss of response.

3.2 Endpoints of IBD treatment

To implement TDM-guided anti-TNF therapy for IBD patients, endpoints of treatment need to be clearly defined. This is the so-called treat-to-target approach. Classically IBD trials have focused on clinical remission, as defined by clinical scoring tools such as the Crohn's Disease Activity Index (CDAI), Harvey Bradshaw Index (HBI) or Mayo Score. However, more recently endoscopic remission and histological remission have received attention as treatment endpoints.[59, 60]

Patients who achieve endoscopic remission, defined as no visible lesions on endoscopy, have improved outcomes compared to patients only achieving clinical remission. In a prospective study of CD patients followed up for 4 years, endoscopic remission at year 2 was the only factor predictive of steroid-free remission at years 3 and 4 (70.8% versus 27.3%, P = 0.036, odds ratio (OR) = 4.352, 95% Confidence interval (95%CI) 1.10-17.220).[61] In addition, the risk of colorectal cancer in UC patients who achieve endoscopic remission reduces back to that of the general population.[62] Histological remission indicates resolution of microscopic signs of inflammation. Currently it is a difficult treatment target to recommend owing to disagreement on standardised definition, issues with sampling error and lack of evidence of long term benefit beyond endoscopic remission.[60]

Recently the International Organisation for the Study of Inflammatory Bowel Disease (IOIBD) recommended that a combination of patient reported outcomes remission and endoscopic remission should be the endpoint for both CD and UC treatment.[60] For CD with small bowel involvement, cross-sectional imaging may be used instead of endoscopy to assess for resolution of mucosal inflammation. The IOIBD recommends

that biomarkers such as C reactive peptide (CRP) and faecal calprotectin be used as adjunctive markers of inflammation, but not as endpoints of treatment.

3.3 Comparison of assays for measuring anti-TNF drug levels and anti-drug antibodies

Assays used to measure anti-TNF drug levels and anti-drug antibody titres are broadly divided into drug-tolerant or drug-sensitive (Table 4).[63-65] Most commercial enzyme-linked immunoassay (ELISA) and radio-immunoassays (RIA) are drug-sensitive. These are generally less expensive, but can only detect anti-drug antibodies in the absence of free drug in the blood sample. More recently developed drug-tolerant assays overcome this problem, and include the homogeneous mobility shift assay (HMSA) developed by Prometheus Laboratories and electrochemiluminescence immunoassay (ECLISA) developed by Labcorp.[63, 64, 66] Drug-tolerant assays include an acid disassociation step to remove free drug from the sample before detection of anti-drug antibodies.[46] In addition the above drug-sensitive assays can be made drug-tolerant by including a pre-treatment step in the protocol.[67] Increased sensitivity of drug-tolerant assays for detecting anti-drug antibodies in samples with free anti-TNF drug may identify patients at risk of immune-mediated pharmacokinetic failure at an earlier stage.

Assays can also be divided as fluid-phase or solid-phase depending on the medium in which drug or anti-drug antibody detection occurs.[46] Solid-phase ELISAs are the most common assay used for measuring drug levels and anti-drug antibody titres. They rely on capture of drug or anti-drug antibody on a plate coated with either TNF, anti-TNF drug or an antibody. Fluid-phase assays, including the RIA, HMSA and ECLISA, detect drug or anti-drug antibodies in a fluid medium. Requirement for less wash steps among fluid-phase assays results in increased sensitivity for anti-drug antibodies with lower binding affinity, however they are more labour intensive and with the RIA handling of radioactive material is an additional concern.[46, 68]

Functional assay, such as a reporter gene assay, are unique in that they directly quantify the amount of anti-TNF activity in a serum sample.[19, 69] These assays were developed to help distinguish functional and non-functional anti-drug antibodies. Functional anti-drug antibodies bind the anti-TNF drug and either increase its clearance or interfere with binding of its target. Non-functional anti-drug antibodies on the other hand do not increase the clearance of the anti-TNF drug or interfere with its pharmacodynamic action. Although both functional and non-functional anti-drug antibodies may contribute to drug reactions, only functional anti-drug antibodies are of relevance to treatment failure.

There is generally good correlation between anti-TNF drug levels measured by the different types of assays.[70, 71] One study comparing RIA, ELISA and functional reporter gene assay, found good correlation in measured infliximab levels (R = 0.97 - 0.99μg/mL).[70] Another study compared the detection rates of infliximab using four different types of assays on the same set of blood samples from 66 CD patients.[71] Again there was very good correlation between the detection rates of the different assays: 76% ELISA, 88% HMSA, 82% RIA, and 74% functional cell-based reporter gene assay (Pearson's r = 0.91 - 0.97, $P < 0.0001$). However, of note there were systematic differences in measured levels between assays, with individual assays consistently measured higher/ lower levels relative to other assays. The highest correlation was found between the HMSA and the ELISA assay tested (Pearson r = 0.97, $P < 0.0001$). The mean difference between levels measured by the ELISA and HMSA was 0.64μg/mL (0.15-1.12 μg/mL). Studies that have compared anti-TNF drug levels measured using different commercial ELISA kits have also found good correlation of measured levels, however again with small systematic differences.[72-77] An analysis of four ELISA assays by Enciso et al. demonstrated no statistically

significant difference in the measured infliximab levels within the therapeutic range of 1-10µg/mL (intraclass correlation coefficient 0.97, 95%CI 0.96 - 0.98).[76] Similarly an analysis by Lee et al. of three of the four commercial ELISAs approved in Australia for measurement of infliximab drug levels demonstrated good overall correlation between the three kits, however again systematic differences in measured levels were noted.[77]

The above data indicates that we can generally compare drug level results obtained from different assays. A therapeutic drug cut-off that correlates with a specific treatment endpoint determined using one drug assay can generally be applied to other drug assays. This is expected as each assay is calibrated to the same easily accessible “standard”, a known concentration of the tested drug. Small systematic differences between measured levels may be overcome with better calibration against the “standard”.

Detection of anti-drug antibodies between different assays is more variable than detection of drug levels. In the study by Steenholdt et al. detection rates of ATI between the four tested assays varied considerably: 9% by ELISA, 11% by functional reporter-gene assay, 27% by RIA and 33% by HMSA.[71] However when the results of each assay were applied to a treatment decision algorithm, the different assays lead to the same decision in the majority of cases (79-94%). This is another argument against choosing a more expensive HMSA or a more cumbersome functional assay over a drug-sensitive ELISA. A universal anti-adalimumab antibody standard has been proposed to allow comparison of antibody to adalimumab (ATA) titres between laboratories.[78] However this may prove to be difficult as assays differ in their ability to measure different antibody subtypes. Bridging and capture ELISA assays cannot detect monovalent IgG4 antibodies, and on average these contribute 36% of all anti-

drug antibodies found in sera of infliximab treated patients.[20, 70, 79] The relative proportion of IgG4 antibodies from total ATI titres varies widely between individuals (range 8-89%) making adjustment between assays difficult.

It is not clear if increased antibody detection rates by drug-tolerant assays will improve clinical outcomes. Fegan et al. demonstrated that presence of anti-drug antibodies among patients with therapeutic drug levels as detected with a HMSA was associated with significantly higher CRP levels (9.90mg/L vs 1.50mg/L, $P < 0.01$).[80] However, in the study by Steenholdt et al., 68% of anti-drug antibodies detected by HMSA did not have neutralizing potential as tested by the functional assay.[71] In another study detection of antibodies at secondary loss of response to infliximab via the HMSA did not predict for lack of response to dose escalation.[81] Alternatively, detection of anti-drug antibodies via a drug-sensitive ELISA assay predicts lack of response to dose escalation for both adalimumab and infliximab.[82, 83] In a recent study, 29.6% of tested serum samples via a drug-tolerant ECLISA were found to have detectable ATI in presence of detectable infliximab levels.[84] In a post-hoc analysis of the Trough level Adapted infliXImab Treatment (TAXIT) trial, 62% of pre-optimisation blood samples were positive for ATI via the drug-tolerant assay as opposed to 21% via a drug-sensitive assay.[85] For the drug-tolerant assay, ATI titres in quartile 4 were associated with significantly higher infliximab doses to achieve therapeutic infliximab levels compared to quartiles 1 and 2 or patients with no ATI ($P < 0.001$ for all three comparisons). There was no statistically significant difference in required doses between patients with ATI titres in quartiles 3 and patients with undetectable ATI, or those with detectable ATI with titres in quartiles 1, 2 or 4. All but one of the patients with ATI titres in quartile 4 for the drug-tolerant assay were also detected as ATI positive via the drug-sensitive assay. This suggests that drug-tolerant assays may

over detect clinically irrelevant anti-drug antibodies in presence of detectable drug levels. This may not offer additional information to guide clinical decisions to justify the generally higher cost of drug-tolerant assays over drug-sensitive assays.

Recently biosimilar medications have emerged on the market and this poses questions regarding the utility of currently available commercial assays for measuring levels of biosimilar anti-TNF drugs. One study used an ELISA assay with monoclonal antibodies raised against Remicade to compare reactivity to two Remicade biosimilar, Remisma and Inflectra.[86] The assay demonstrated equal reactivity to Remicade and the two biosimilars. Similarly, anti-drug antibodies in sera of infliximab treated patients showed very strong cross-reactivity between Remicade and the two biosimilars.

Table 4: Types of assays for measuring anti-TNF drug levels and anti-drug antibodies.[19]

Type of Assay	Description	Advantage	Disadvantage
Enzyme-linked immunosorbent assay (ELISA)	Solid-phase assay: plate is coated with TNF, anti-TNF drug or a fragment of the anti-TNF drug molecule, in order to bind either the anti-TNF drug or anti-drug antibodies in the sample, directly or indirectly. Detection antibody is linked to an enzyme which catalyses a colour reaction.	Less expensive Can easily be performed by most laboratories	Cannot detect anti-drug antibodies in presence of free drug in the sample Cannot distinguish neutralising and non-neutralising anti-drug antibodies Lower detection limit than fluid-phase assays due to multiple wash steps Higher rates of false positive and false negative results
Radio-immunoassay (RIA)	Fluid-phase assay: binding of target and detecting anti-antibody occurs in fluid-phase. Detecting antibody is labelled with a γ-	Sensitive, can detect lower drug and anti-drug antibody levels	Cannot detect anti-drug antibodies in presence of free drug in the sample Cannot distinguish neutralising and

	radiation emitting radioisotope.		non-neutralising anti-drug antibodies Need for radioactive isotopes Need for specialised laboratory facilities and trained personnel
Homogeneous mobility shift assay (HMSA)	Fluid-phase assay: acid-disassociation step prior to detection of anti-drug antibodies. Fluorescent labelled anti-TNF drug or TNF is added to serum sample to detect anti-drug antibodies or anti-TNF drug respectively. The complexes formed are separated out and quantified using size-exclusion high-	Detect anti-drug antibodies in presence of free drug in the sample Sensitive, can detect lower drug and anti-drug antibody levels	Cannot distinguish neutralising and non-neutralising anti-drug antibodies Expensive Need for specialised laboratory facilities and trained personnel

	performance liquid chromatography		
Electro-chemiluminescence immunoassay (ECLISA)	Fluid-phase assay: acid-disassociation step prior to detection of anti-drug antibodies. The target antigen is captured using a monoclonal antibody linked to a magnetic microparticle. This than becomes bound to a magnetic electrode. Detection relies on a second antibody which is ruthenylated, and emits photons on application of a voltage through the electrode.	Detect anti-drug antibodies in presence of free drug in the sample Sensitive, can detect lower drug and anti-drug antibody levels	Cannot distinguish neutralising and non-neutralising anti-drug antibodies Expensive Need for specialised laboratory facilities and trained personnel
Functional assay	Anti-TNF activity in a serum sample is quantified using a reporter gene assay.	Distinguishes functional and non-functional anti-drug antibodies	Need for live cell culture, cumbersome Expensive

	Cells express TNF receptors linked to a reporter gene. TNF and the patient's serum are added to the cell culture to quantify the amount of interference with TNF binding.		Need for specialised laboratory facilities and trained personnel

3.4 Benefits of Therapeutic Drug Monitoring guided anti-TNF therapy

3.4.1 Therapeutic drug monitoring versus clinically guided anti-TNF drug treatment

Empiric dose escalation for patients failing either infliximab or adalimumab can induce remission in about 39-56% and 37% of patients respectively.[41, 87-89] An empiric dose escalation strategy for patients failing anti-TNF therapy allows for one treatment to be completely exhausted before moving onto another, a prudent approach in an era of limited biologic options.[19] However a TDM approach can potentially better select patients failing an anti-TNF drug likely to respond to dose escalation versus those likely to respond to switching within class or switching out-of-class.[82] A TDM-guided approach may lead to cost saving and effective treatment being commenced sooner compared to clinical treatment decision.

A Danish cohort study demonstrated that a TDM-based algorithm approach compared to empiric dose escalation for CD patients with secondary loss of response to infliximab, results in similar response rates at 12 weeks (58% algorithm group versus 53% empiric group, $P = 0.81$), however with 34% lower cost per patient in the algorithm group ($P < 0.001$).[41, 87] Per protocol analysis again demonstrated similar response rates with an even greater cost saving of 56% in the algorithm group. Follow up at 20 weeks and 1 year, demonstrated that the algorithm group had maintained a cost saving of 31% and 24% respectively at these two time points over the empiric dose escalation group in intention-to-treat analysis.[19, 90] Quality of life scores between the algorithm and empiric group were similar at 20 weeks despite a greater proportion of patients discontinuing infliximab therapy in the algorithm group.[91] Case studies and simulation studies in both IBD and Rheumatology have supported these findings

of significant cost saving associated with TDM guided anti-TNF treatment algorithms.[43, 92-95]

TDM-guided adjustment of anti-TNF drug dosing for stable patients on maintenance therapy, so called proactive approach, differs from the above strategy which reserves TDM for treatment failure events, a so called reactive approach. Low adalimumab and infliximab drug levels increase risk of anti-drug antibody development and treatment failure, and early dose escalation in such patients may prevent this issue.[31, 41, 96-99] In one paediatric study, a week 14 infliximab trough level was strongly predictive of week 54 clinical remission, with trough levels of > 3μg/mL, > 4μg/mL and > 7μg/mL having a positive predictive value (PPV) of 64%, 76% and 100% respectively (area under receiver operator characteristic (AUROC) = 0.68, P = 0.03).[96] In another study of 332 IBD patients on maintenance infliximab therapy, an infliximab trough level < 3μg/ml increased future risk of ATI development four-fold.[100] The increase in risk was associated with cumulative time spent at an infliximab concentration below 3μg/mL. Similarly Baert et al. found a week 4 post induction adalimumab trough level < 5μg/mL to be associated with a hazard ratio (HR) of 25.12 (95%CI 5.64 to 111.91, P = 0.0002) for development of ATA over 1 year follow up as compared to adalimumab trough levels > 5μg/mL.[41, 97] In this study there was a negative correlation between CRP and adalimumab levels (P = 0.0001) and a positive correlation between ATA and CRP (P = 0.0186). This suggests that early dose optimisation for patients in remission with sub-therapeutic trough levels may prevent subsequent secondary loss of response due to immune-mediated pharmacokinetic failure. When proactive TDM is undertaken, dose de-escalating patients with supra-therapeutic drug levels may result in significant cost saving without adversely affecting clinical outcomes. This may

completely or partially offset the cost of dose escalating patients with sub-therapeutic levels, and result in optimal drug distribution within a population of IBD patients.

A prospective observational study of 80 IBD patients stably maintained on infliximab for at least 2 years, found that TDM-guided infliximab dose adjustment lead to improved clinical outcomes compared to clinically guided dose de-escalation.[101] All patients had TDM performed initially and treating physicians were kept blind to these results throughout the study. Treating physicians determined if a patient should have infliximab dose reduction based on clinical review and CRP alone. Patients were divided into two groups, depending on whether dose adjustment decisions of their treating physician agreed or disagreed with the predetermined TDM-based treatment algorithm. There was significant improvement in clinical disease activity in patients whose treatment decision agreed with the pre-determined TDM-based algorithm compared to those whose treatment decision disagreed with the algorithm (HBI 1.62 at inclusion vs 1.06 at week 16 among CD patients, $P < 0.001$; Ulcerative Colitis Disease Activity Index (UCDAI) 1.17 at inclusion vs 0.58 at week 8 among UC patients, $P = 0.05$). There was also a significant reduction in CRP in the former group relative to the later (4.53 at inclusion vs 3.10 at week 16, $P = 0.02$).

Benefits of proactive TDM over clinical dosing have been mixed. The TAXIT study was an RCT that evaluated proactive TDM against clinically-guided dosing for CD patients on maintenance infliximab therapy.[102] Following an initial period of TDM-guided dose optimisation, patients were randomised to either ongoing proactive TDM every infusion cycle or dose adjustment based on clinical symptoms and CRP. The study failed to show an advantage of the proactive TDM arm over clinical dose adjustment in regard to its primary endpoint of clinical remission rate at 12 months (69% versus 66%, $P = 0.686$). Quality of life and cost were also very similar between the two groups.

However, significantly less patients in the proactive arm experienced a flare necessitating rescue therapy during the 12 months follow up period (7% versus 17% respectively, P = 0.018).

The initial dose optimisation phase of the TAXIT study potentially negated some of the benefits of proactive TDM over clinically adjusted dosing. The Tailored Treatment With Infliximab for Active Luminal Crohn's Disease (TAILORIX) study which followed removed this factor.[103] Following infliximab induction, CD patients who went on to infliximab maintenance treatment of 5mg/kg every 8 weeks were randomised into three groups: 1) dose escalation in 2.5mg/kg increments (maximal of 10mg/kg) based on clinical symptoms, biomarkers and TDM, 2) dose escalation to 10mg/kg (one off) based on same criteria as group 1, or 3) dose escalation to 10mg/kg based on clinical criteria alone. Again, no significant difference was demonstrated between the three groups in terms of the primary endpoint of sustained steroid-free clinical remission between weeks 22 and 54 and absence of ulceration on endoscopy at 1 year (47% for group 1, 38% for group 2, 40% for group 3, P = non-significant (NS)). There was also no statistically significant difference in endoscopic remission or financial cost at 1 year between the three groups.

3.4.2 Proactive versus reactive therapeutic drug monitoring

Although TDM-guided dosing has demonstrated some advantages over clinically-guided dosing, particularly with a reactive approach, it is less clear if proactive TDM offers an advantage over reactive TDM. A retrospective observational study compared outcomes for IBD patients in remission on infliximab who had proactive TDM versus those who had reactive TDM.[42, 104, 105] Significantly lower probability of

discontinuing infliximab was found with proactive TDM compared to reactive TDM (10% vs 31%, P = 0.009). Within the proactive TDM group the probability of stopping infliximab was lower still for those with trough concentration ≥ 5μg/mL (HR = 0.03, 95%CI 0.01 - 0.1, P < 0.0001). However, patients in the proactive TDM group were all managed by a single gastroenterologist while the remaining gastroenterologists in the clinic practiced reactive TDM. Different co-therapies and methods of disease assessment between the two groups may be significant confounders in this study.

3.4.3 Scenarios where currently TDM-guided anti-TNF agent dosing is of limited benefit

In some scenarios TDM of anti-TNF agents is currently of limited benefit, either due to the results not being available in a sufficient timeframe to influence decisions, or due to lack of evidence on how to interpret results in a particular setting. Dose adjustment in such situations should be based on other factors. In acute severe ulcerative colitis (ASUC) accelerated infliximab induction has been shown to significantly reduce short term colectomy rates compared to standard induction dosing (6.7% versus 40%, Fisher exact test, P = 0.039).[43, 106] Patients with signs of breakthrough inflammation, low albumin, and high CRP are more likely to benefit from accelerated infliximab induction. Current guidelines recommend allowing a patient with ASUC no more than 4-7 days to respond to a trial of infliximab salvage therapy before moving to an urgent colectomy.[8] TDM is currently not helpful in differentiating ASUC patients that benefit from accelerated infliximab induction from those who should move to a colectomy, due to lack of data on appropriate drug levels in this scenario, as well as a relatively long turn-around time for results, at least for most centres in Australia. In future as turnaround time for infliximab drug level testing becomes less and new data

becomes available, a role for TDM-guided infliximab dosing for patients presenting with ASUC may emerge. Of note, two rapid point-of-care assay for infliximab have recently been validated.[107, 108]

Anti-TNF drug exposure in utero increases risk of infections in newborn infants, necessitating avoidance of live vaccines for the first 6 months of life at least.[109, 110] Studies indicate that infliximab and adalimumab are actively transferred to the foetus via the placenta from 20 weeks to delivery, similarly to endogenous IgG antibodies.[111-114] Consequently anti-TNF levels in the newborn infant are 1.5-3 times that of maternal peripheral blood, and anti-TNF drug remains detectable in infants for up to 6 months following birth.[111-114] However, currently anti-TNF drug levels are not routinely measured in pregnant women as it is not clear what are acceptable anti-TNF levels and how to dose adjust based on these in order to maximise disease control and minimise anti-TNF drug exposure for the newborn infant.

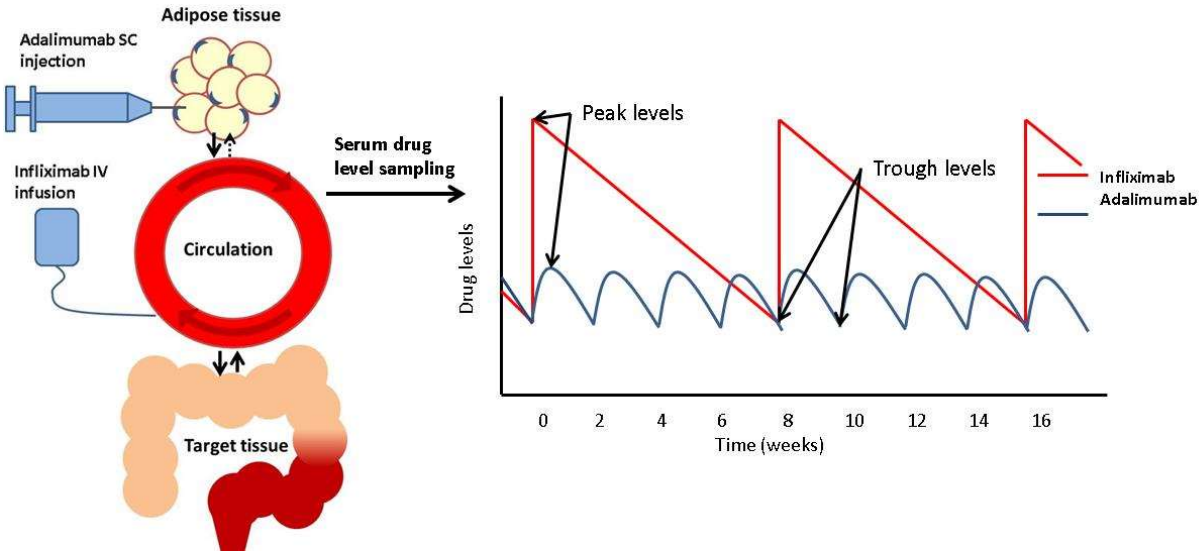
3.5 Target drug levels

Most studies of anti-TNF drug levels have examined the relationship between trough levels and clinical outcomes. Drug trough levels are taken just prior to administration of the next drug dose. Although trough levels correlate best with activity for most drugs there are exceptions to this, particularly antibiotics such as gentamicin.[115] It is unclear if trough levels are the best predictor of response to anti-TNF drugs, 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.[45, 46] Few studies have related drug levels at other points of the dosing cycle to clinical outcomes.[116, 117] Interestingly, among IBD patients on maintenance infliximab, Yamada et al. found no difference in pre-infusion trough levels between those with maintained response and those with secondary loss of response (4.7μg/mL vs 6.3μg/mL, P = NS) while post-infusion peak levels were significantly higher among patients with maintained response to infliximab (149.5μg/mL vs 126.3μg/mL, P = 0.0488).[117] This was a small study of 31 patients and we cannot conclude with confidence that peak drug levels are a better predictor of treatment response to infliximab than trough levels. Several other cohort and cross-sectional studies have found infliximab and adalimumab trough levels to predict for response to treatment.[80, 82, 83, 97, 98, 116, 118-149]

When measuring and interpreting anti-TNF drug levels we need to consider the distribution of drug in the body and the elimination half-life. The compartment model simplifies the body as different compartments between which the drug can move (Figure 2). Infliximab is administered by IV infusion while adalimumab is administered via a SC injection. Following drug administration, infliximab blood levels peak almost immediately, while adalimumab blood levels peak 5 days later due to slower diffusion out of adipose tissue.[46] Because adalimumab is administered every 2 weeks and

the SC route results in slower diffusion into the circulation, less variability is observed between peak and trough levels than with infliximab.[150] Although we measure serum levels of anti-TNF drugs due to convenience, concentrations at the target tissue are likely to relate better to their efficacy. However, circulating anti-TNF drug may also contribute to reducing bowel inflammation by neutralise TNF in the systemic circulation. It is not clear what the relative importance of this potential mechanism of action is in relation to neutralisation of TNF and depletion of lymphocytes via ADCC and CDC in the target tissue.

<u>Figure 2:</u> Compartment model for anti-TNF drug distribution and serum anti-TNF drug levels in maintenance therapy.[46]



To ensure comparable results, drug levels are typically measured once steady state is established. Steady state is a situation where the rate of drug administration is equal to the rate of drug elimination.[151] Generally a drug that is administered at a constant

dosing regimen would reach steady state 4 to 5 elimination half-lives from when this constant dosing was commenced. The half-life of both infliximab and adalimumab is variable between individuals. Median elimination half-life of infliximab is quoted between 7.7 to 9.5 days, however three population pharmacokinetic studies have estimated the elimination half-life of infliximab to be between 14 and 18.5 days.[152-157] For adalimumab, median elimination half-life based on both IV and SC dosing is approximately 20 days.[153, 158] Based on this data, a steady state trough for infliximab and adalimumab can generally be taken at least 7 and 14 weeks from commencing a constant dosing regimen, respectively.

Factors that lead to inter- and intra-individual variability of anti-TNF drug elimination half-life need to be considered. These factors including gender, body mass index (BMI), co-treatment with immunosuppressants, serum albumin concentration, severity of inflammatory burden and anti-drug antibodies.[31, 159-161] Higher BMI and male gender reduce anti-TNF drug elimination half-life.[153] Anti-drug antibodies that may develop over time can drastically increase clearance of anti-TNF agents. Concomitant use of immunomodulators significantly reduce production of anti-drug antibodies, with ATI positivity rates at week 30 of 0.9% among patients on infliximab and azathioprine combination therapy compared to 14.6% among those on infliximab monotherapy observed in the Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) trial.[162] The effect of this is reduction in clearance of infliximab as observed in a significant rise in median trough levels among patients on combination therapy versus infliximab montherapy (3.5μg/mL versus 1.6μg/mL, $P < 0.001$).[162] Concomitant immunomodulator use may also increase anti-TNF trough levels independent of suppression of anti-TNF antibody production, through reduction of

inflammatory load and hence circulating TNF, or generalised reduction of antibody clearance by the reticuloendothelial system.[19]

Elimination half-life is reduced if inflammatory burden is high due to increased TNF levels binding and clearing anti-TNF drug, as well as increased gut losses of anti-TNF drug.[163] Ungar et al. demonstrated lower week 2 infliximab trough levels among hospitalised ASUC patients compared to outpatients with moderately severe UC (7.15 ± 5.3μg/mL vs 14.4 ±1 1.2μg/mL, P = 0.007).[164] Similarly, lower infliximab elimination half-lives have been observed in IBD patients with high CRP and low albumin.[159, 160] Through this it follows that higher anti-TNF drug doses are required to establish therapeutic levels and achieve response in patients with high inflammatory burden. In a study of Rheumatoid arthritis patients, there was no difference in remission rates among patients with low baseline circulating TNF levels who were dosed with infliximab at 3mg/kg, 6mg/kg or 10mg/kg, however there was a clear trend towards increased remission rates with higher infliximab doses among patients with high baseline TNF levels.[165, 166] For patients with low baseline TNF levels all dose groups achieved detectable median infliximab trough levels, while among patients with high baseline TNF levels only the 10mg/kg group achieved detectable median trough levels. Among UC patients undergoing infliximab induction, significantly higher faecal infliximab losses have been documented among non-responders compared to responders (5.01μg/mL versus 0.54μg/mL, P = 0.0047).[163] Biopsies in patients with active inflammation have found the anti-TNF:TNF ratio to be lowest in samples with severe inflammation.[167] Similarly an observational study of patients undergoing infliximab induction for moderate-severe UC found significantly lower total infliximab exposure among patients whose baseline CRP was > 50mg/L compared to those with baseline CRP ≤ 50mg/L (587mg/L/day versus 1361mg/L/day respectively, P =

0.001).[168] This suggests that for response in high inflammatory states higher anti-TNF drug doses are needed to achieve comparable drug levels, and this requirement for increased dose may not necessarily reflect a need for higher drug trough levels. It also follows that once inflammatory burden reduces (i.e. when a patient is in remission) lower maintenance doses may be sufficient to achieve the same therapeutic trough levels.

For a given drug if a loading dose of twice the maintenance dose is administered and a constant dosing interval is maintained, than steady state is immediately achieved.[169] If the administered loading dose is greater or less than this amount than again 4 - 5 drug elimination half-lives need to pass for steady state to be established. However, these conditions are not met with standard infliximab and adalimumab induction regimens. There is also the added complexity of anti-TNF elimination half-life not being constant throughout induction and maintenance treatment. During induction therapy when inflammatory load is higher, elimination half-life of anti-TNF drugs is likely to be lower due to more rapid clearance.[163] With standard induction regimens, a steady state trough level can be taken as the first trough level 4 - 5 elimination half-lives from commencing a constant maintenance dosing regimen i.e. usually just before the week 14 dose from commencing infliximab or just before the week 18 dose from commencing adalimumab. Adalimumab displays smaller fluctuations in drug levels during the dosing cycle, and so timing of trough levels may be less critical.[150, 170] Ward et al. found that although differences in peak and trough adalimumab levels are relatively small they are still statistically significant (mean peak level 5.18μg/mL, mean trough level 4.15μg/mL, paired data, $P < 0.001$).[150]

Given the length of time before a steady state trough level can be taken following commencement of an anti-TNF drug (approximately 14 weeks for infliximab and 18 weeks for adalimumab), relying on a steady state therapeutic trough range may not always be practical. Patient's with primary non-response and severe symptoms likely cannot wait for a steady state trough level to be taken to guide therapeutic decisions. There are relatively few studies that have examined the relationship between non-steady state trough levels during anti-TNF drug induction and response.[116, 118, 143, 148, 171, 172] Golovics et al. demonstrated that week 2 infliximab trough levels among IBD patients predicted for week 14 response and remission status (for response AUROC = 0.715, P = 0.05; for remission AUROC = 0.721, P = 0.005).[171] Mean non-steady state trough levels at weeks 2 and 6 of induction were higher than presumed steady state trough levels at week 14 (weeks 2, 6 and 14 mean infliximab trough levels were 20.1μg/mL, 14.7μg/mL and 5.1μg/mL respectively). Papamichael et al. showed that mucosal healing among UC patients is optimally predicted by an infliximab concentration ≥ 28.3μg/mL at week 2 (AUROC = 0.638, P = 0.018), ≥15μg/mL at week 6 (AUROC = 0.688, P = 0.001) and ≥ 2.1μg/mL at week 14 (AUROC = 0.781, P < 0.001).[116] In contrast, Adedokun et al. found week 2 induction infliximab trough levels not to predict for clinical response at week 8.[118] During adalimumab induction among paediatric CD patients, higher trough levels correlate with remission as compared to levels during steady state (i.e. beyond 18 weeks), with a cut-off trough of > 11.6μg/mL, > 5.3μg/mL and > 3.6μg/mL being optimal for predicting clinical remission at weeks 4, 26 and 52.[143] However in this study only the week 26 trough cut-off reached statistical significance. In a study among adult CD patients, a week 4 adalimumab level of ≥ 16.2μg/mL was found to be optimal for predicting clinical response at week 24 (92% sensitivity, 67% specificity, AUROC = 0.81).[172]

In order to apply TDM-guided therapy for anti-TNF drugs, in active disease a therapeutic cut-off to differentiate pharmacokinetic failure from pharmacodynamic failure needs to be defined, while for patients on maintenance therapy defining a therapeutic range with an upper and lower limit allows dose titration. An upper limit of the therapeutic range allows for dose de-escalation and cost saving without negatively impacting clinical outcome. Methods to define the lower limit of a therapeutic range include concentration quartiles, validation of a pre-determined value, or using a Receiver Operator Characteristic (ROC) curve. The latter has the advantage of allowing a trough level cut-off with optimal sensitivity and specificity for a given treatment endpoint to be selected. The upper limit of a therapeutic range may similarly be determined using concentrations quartiles, validation of a pre-determined value, or using a population concentration-response curve. The later method more precisely defines a drug trough level above which the proportion of patients achieving the chosen endpoint plateaus. Although several algorithms apply a single therapeutic range for both active disease and clinical remission, it is an assumption that the minimal therapeutic cut-off to induce remission in patients with active disease is the same as the minimal therapeutic cut-off to maintain remission.[19, 43, 45, 63, 124]

Choice of a therapeutic range for anti-TNF agents needs to consideration several factors. There is significant inter-individual variability in the anti-TNF drug trough level required for induction of remission, manifested as considerable overlap in infliximab and adalimumab trough concentrations between responders and non-responders.[45, 138] In addition, a significant proportion of patients may never respond to an anti-TNF agent, regardless of the drug level achieved, and are classified as having pharmacodynamic failure. Due to this inter-individual variability and plateau in response, with each incremental increase in the minimal infliximab trough cut-off we

will recapture response in fewer additional patients. Selecting a higher anti-TNF drug concentration as the lower limit of the therapeutic range would result in higher overall treatment cost and more patients with anti-TNF resistant disease undergoing futile dose escalation before changing to more appropriate treatment. On the other hand, selecting a lower limit trough level that is too low risks failing to recapture response in patients who require a higher anti-TNF drug level for response. Using a TDM algorithm approach for patients with treatment failure to either infliximab and adalimumab, a patient with therapeutic trough levels is labelled as having anti-TNF resistant disease (i.e. pharmacodynamic failure) and should be switched out-of-class rather than to another anti-TNF drug.[19, 43, 45, 63] If a TDM algorithm is strictly followed, labelling a patient as a pharmacodynamic failure to any one anti-TNF drug would exclude that patient from the entire drug class. In some patients, it may be appropriate to trial dose escalation to a drug trough level close to or above the upper limit of the therapeutic range before discontinuing an anti-TNF drug. This may be appropriate for patients with active disease who have failed multiple lines of therapy and have few remaining options.

3.5.1 Infliximab steady-state therapeutic trough level

Higher mean/ median infliximab trough levels have been found among patients in remission compared to those with active disease.[118, 128, 131, 134, 173] More clinically useful studies have defined a therapeutic cut-off associated with response, either through use of ROC curves, comparing remission rates between trough level quartiles, or through validation of a pre-determined therapeutic cut-off.[19, 80, 82, 98, 116, 118-137, 147, 174-176] Most of these studies are cross-sectional and few are prospective. The studied populations and endpoints assessed have varied

considerably, such that results cannot be easily combined. In studies among patients with UC and luminal CD, steady state infliximab trough level found to correlate with mucosal healing have ranged from 2.1 to 6μg/mL, for CRP response from 1.4 to 6.4μg/mL, and clinical response/ remission from 0.5 to 6.65μg/mL (Appendix, Table 4).[80, 82, 98, 116, 118-125, 127-137, 147] Similarly, the minimal infliximab trough cut-off recommended by various published TDM algorithms has varied from 3 to 6μg/mL.[45, 63, 124]

Meta-analysis by Moore et al. identified 7 studies that reported remission rates based on infliximab thresholds.[131] Taking a somewhat arbitrary infliximab trough cut off of > 2μg/mL, four studies allowed data to be pooled. An infliximab level > 2μg/mL was found to be associated with increased likely-hood of both clinical remission (relative risk (RR) = 2.9, 95%CI 1.8 - 4.7, P < 0.001) and endoscopic remission (RR = 3, 95%CI 1.4 - 6.5, P = 0.004). Similarly, a retrospective cross-sectional study analysed infliximab levels and CRP in stored serum samples from 532 CD patients from four RCTs and cohort studies.[80] Mean CRP was found to be significantly lower in those with an Infliximab trough of ≥ 3μg/mL (1.50ng/mL versus 5.65ng/mL, P < 0.001).

When considering infliximab therapeutic cut-offs for patients with active disease, the clinically relevant question is above what infliximab trough level should the patient be deemed to have anti-TNF resistant disease (i.e. pharmacodynamic failure) and abandon further trials of dose escalation. The literature search identified only one study that correlated infliximab trough level pre-dose escalation to remission status post-dose escalation. A retrospective analysis by Yanai et al. found a trough infliximab level ≥ 3.8 μg/mL to be 90% predictive of lack of clinical response to dose escalation (PPV 56%, negative predictive value (NPV) 51%).[82]

When selecting a therapeutic infliximab cut-off to allow dose optimisation among IBD patients in remission, studies that have defined a therapeutic cut-off predictive of future remission or response are more useful than cross-sectional studies that correlate drug levels to outcome at the same time point. Post-hoc analysis of the ACCENTI study found a week 14 trough level of ≥ 3.5μg/mL to correlate with increased rates of sustained clinical response at week 54 (OR = 3.5, 95%CI 1.1 - 11.4, AUROC = 0.75).[98] Similarly a study of 85 UC patients on maintenance infliximab examined remission rates at week 54 based on infliximab trough quartiles at week 30.[118] Remission rates were significantly higher in the 2nd quartile for infliximab trough level (90.5%, level ≥ 3.5 to < 8.4μg/mL) compared to the 1st (53.4%, < 3.5μg/mL). No significant difference in remission rates between 2nd quartile and 3rd (≥ 8.4 to < 16.7μg/mL) and 4th (≥ 16.7μg/mL). The above study by Adedokun et al. indicates that clinical remission rates plateau above an infliximab trough of around 8.4μg/mL, with minimal additional benefit above this level.[118]

However, higher trough levels appear to be needed if the treatment endpoint is mucosal healing. In a retrospective cross-sectional study an infliximab level > 5μg/mL identified patients with mucosal healing with 85% specificity (AUROC = 0.75, P < 0.0001), with minimal increases in mucosal healing rates above an infliximab trough of 8μg/mL.[124] The authors propose that maintaining patients in an infliximab range of 6 to 10μg/mL would achieve mucosal healing in 85-90% of patients.

3.5.2 Adalimumab therapeutic levels

Similarly for adalimumab, studies have used a range of endpoints to define a therapeutic cut-off.[82, 83, 97, 119, 124, 138-149, 176] Lower steady state trough levels have been found to correlate with clinical remission (3.6 to 5.85μg/mL)

compared to endoscopic remission (4.9 to 9.1μg/mL) or histologic remission (7.8μg/mL) (Appendix, Table 5). Unfortunately, again most studies have been cross-sectional, with few prospective trials that correlate drug levels with future outcomes.

As with infliximab, for patients with active disease on adalimumab it is clinically most useful to define a trough cut-off above which dose escalation becomes futile (i.e. pharmacodynamic failure), to identify early on patient that should be switched out-of-class. Yanai et al. again found that a pre-dose escalation adalimumab trough ≥ 4.5μg/mL was 90% specific for failure to respond to adalimumab dose escalation (PPV 85%, NPV 39.5%).[82] In another longitudinal observational study, 82 IBD patients had TDM performed prior to empiric adalimumab dose escalation for treatment failure.[83] For patients with undetectable anti-drug antibodies, response to dose escalation was much higher among patients with trough adalimumab ≤ 4.9μg/mL than patients with levels > 4.9μg/mL (67% versus 29%, P < 0.01).

Several studies have defined a suitable maintenance trough range for patients on adalimumab. A cross-sectional study found an adalimumab trough at week 14 > 4.5μg/mL to be 90% predictive of remission or response.[41, 119] The upper limit of the maintenance therapeutic range for adalimumab steady-state trough levels is not as well defined. Post-hoc analysis of the Ulcerative colitis long-term remission and maintenance with adalimumab 2 (ULTRA2) study compared rates of response between adalimumab trough concentration quartiles among 258 UC patients.[44, 141] Remission rates were significantly higher among patients in quartile 2 (5 to 8.7μg/mL) and quartile 3 (8.7 to 11.7μg/mL) compared to quartile 1 (< 5μg/mL), and did not increase beyond quartile 3. This suggests clinical remission rates plateau above a trough of approximately 11.7μg/mL, at least for UC. However, these levels were taken at week 8 following induction and are not steady state trough levels. Studies in

psoriasis and rheumatoid arthritis have used a population concentration-response curve to define a trough of 7μg/mL and 8μg/mL, respectively, above which response plateaus.[177, 178] Based on this data, some laboratories in Australia use 8μg/mL as the upper limit of the therapeutic adalimumab trough range for IBD patients as well.[179]

When the endpoint is mucosal healing, target trough levels again appear to be higher. A cross-sectional study identified an adalimumab trough level >7.1μg/mL to be 85% specific for mucosal healing in IBD, and mucosal healing rates plateau above 12μg/mL.[124] Based on this data the authors estimate that titrating adalimumab to a trough level of 8 to 12μg/mL would achieve mucosal healing in 80 -90% of patients. However, Roblin et al. found a relatively lower adalimumab trough cut-off of 4.9μg/L as optimal for predicting mucosal healing (AUROC = 0.77, P = 0.005, likelihood ratio (LR) = 4.3, sensitivity = 66%, specificity = 85%).[142]

3.5.3 Certolizumab and golimumab therapeutic levels

There is less data on therapeutic cut offs for certolizumab and golimumab as these anti-TNF drugs are relatively new. Sandborn et al. demonstrated that clinical remission rates were significantly higher with increasing golimumab trough level quartiles among UC patients on maintenance therapy at weeks 30 and 54: 25.0% for quartile 1 (< 1.63μg/mL), 31.6% for quartile 2 (≥ 1.63 to < 2.51μg/mL), 35.0% for quartile 3 (≥ 2.51 to < 4.13μg/mL), and 59.0% for quartile 4 (≥ 4.13μg/mL).[180] Similarly Colombel et al. demonstrated a positive correlation in CD patients between week 8 certolizumab drug levels and rates of endoscopic response and remission at week 10 (for response P = 0.0016, AUROC = 0.69; for remission P = 0.0302, AUROC = 0.70).[181] There is

however less data on what the optimal maintenance range for both golimumab and certolizumab should be.

3.5.4 Different disease phenotypes

Studies that compare trough levels for a response between UC and CD patients, as well as between different disease phenotypes, are lacking. Many studies restricted their patient population to only CD or UC, and most studies that measured trough levels among all IBD patients have not performed a CD and UC subgroup analysis.[80, 82, 83, 97, 98, 116, 118-136, 138-147] One study found a higher infliximab trough level to be predictive of clinical remission in UC (≥ 6.26μg/mL, sensitivity 50.0%, specificity 87.9%) compared to CD (≥ 2.18μg/mL, sensitivity 67.4%, specificity 78.6%), however no statistical analysis was performed between the two groups. The therapeutic cut-off found by studies to be predictive of response or remission for infliximab has ranged from 0.5 to 7.3μg/mL in CD, and 0.9 to 7.19μg/mL in UC.[80, 98, 118-123, 127-133, 174, 182] For adalimumab, seven studies have identified a therapeutic trough cut-off in CD ranging from 3.6 to 5.9μg/mL, and only one study in UC patients found a trough cut-off of 5μg/mL to predict for clinical response.[82, 97, 119, 138-141, 143] Overall, the therapeutic cut-off for both infliximab and adalimumab determined in the above studies overlap considerably for CD and UC patients.

Currently data on appropriate therapeutic cut-offs for different CD phenotypes are lacking, including stricturing and fistulising. Recently a study of CD patients with perianal fistulising disease suggested higher infliximab trough levels are needed to bring about fistula healing compared to therapeutic cut-offs previously quoted for luminal disease.[183] The median infliximab trough level was significantly higher

among patients with fistula healing compared to those with active fistulas (17.8μg/mL versus 4.4μg/mL respectively, P < 0.0001). Overall rate of fistula healing in this study was 54%, and fistula healing rates increased with increasing infliximab trough level quartiles: 21% in quartile 1 (0 - 2.8μg/mL), 47% in quartile 2 (2.9 - 10.0μg/mL), 71% in quartile 3 (10.1 - 20.1μg/mL), 86% in quartile 4 (20.2 - 50μg/mL). The authors advise aiming for infliximab trough levels above 10 μg/mL in perianal fistulising CD, however there appears to be a 15% absolute benefit in fistula healing with infliximab trough levels above 20 μg/mL compared to those with trough levels above 10μg/mL.[183, 184] Aiming for infliximab trough levels > 20μg/mL may be appropriate for patients with non-healing fistulas. Similarly, Davidov et al. found that week 2 and 6 infliximab induction trough levels of ≥ 9.25μg/mL and ≥ 7.25μg/mL respectively, were optimal at predicting fistula response (for week 2 AUROC = 0.942, P < 0.0001; for week 6 AUROC = 0.9, P = 0.001).[185] These studies might suggest that all patients with fistulising CD should be on higher infliximab doses, however an earlier RCT did not find a statistically significant difference between fistula response rates among patients treated with 5mg/kg versus 10mg/kg infliximab (68% versus 38% respectively, P = 0.35).[186] Higher anti-TNF drug dose does not always equate to higher trough level as the elimination half live of anti-TNF drugs is varied based on both patient and disease factors as previously discussed. [152-158]

3.6 Effects of anti-drug antibodies

Most ATI are directed against the murine variable region of the infliximab molecule as determined by neutralisation studies, while most ATA are expected to bind the much smaller hypervariable region of the all human adalimumab molecule.[78, 187] As a result ATA occur at lower rates to ATI, with detection rates of 24% and 46% respectively found by Steenholdt et al. after 12 months of anti-TNF drug treatment.[19-21, 188] However anti-drug antibody detection rates vary between different assays and risk of anti-drug antibodies developing is reduced with concomitant use of an immunomodulator, avoiding interrupted therapy and possibly through maintaining trough drug levels in the therapeutic range.[41, 46, 70, 96, 97, 162] Rutgeerts et al. found much higher rates of ATI positivity at 1 year among IBD patients treated with episodic infliximab therapy compared to those treated with continuous therapy (28% in episodic treatment group, 9% in patients maintained on 5mg/kg every 8 weeks and 6% in those maintained on 10mg/kg every 8 weeks, statistical significance between groups not reported).[189] Immunomodulator use reduces formation of anti-drug antibodies and no difference has been demonstrated between azathioprine or methotrexate.[190] In a study by Vermiere et al. ATI positivity among those on concomitant azathioprine (48%) or methotrexate (44%) was lower than patients not on an immunosupressant (73%, $P < 0.001$ compared to being on either methotrexate or azathioprine).

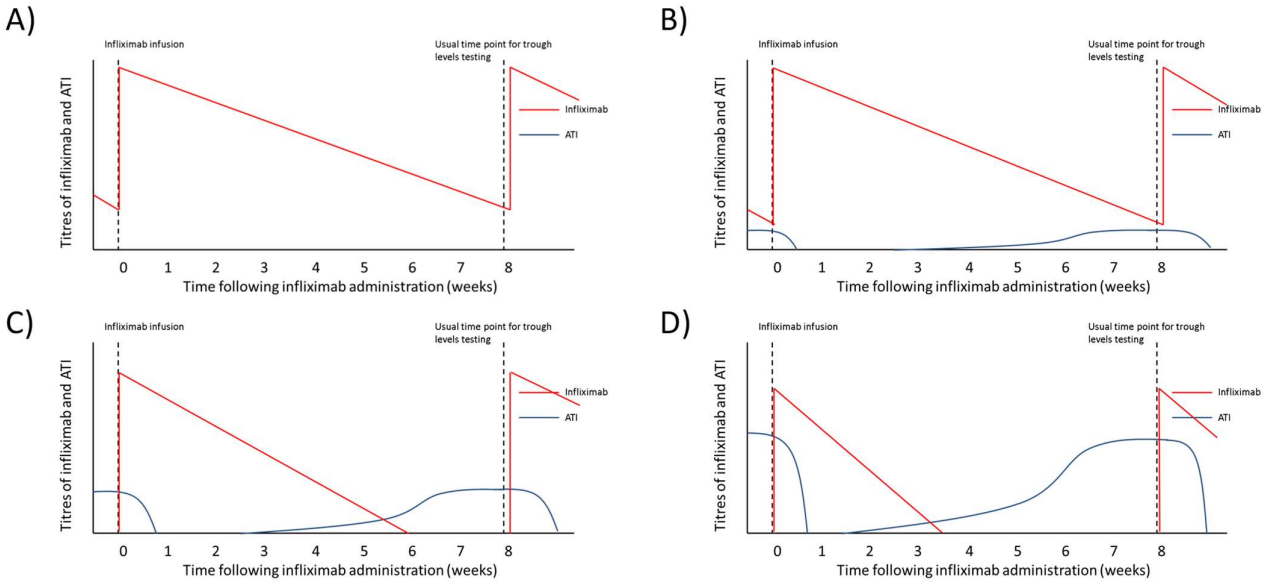
Anti-drug antibodies interfere with the activity of anti-TNF drugs via two mechanisms: complexing with the drug and increasing its clearance, and/ or directly interfering with the anti-TNF drug binding TNF or exerting its effect.[69, 191] In experimental monkeys, co-administration of infliximab and a radiolabelled ATI resulted in rapid immune complex formation as observed via serial analysis of blood samples on high

performance liquid chromatography.[191] Further gamma imaging studies indicated that the immune complexes concentrate in the reticuloendothelial system within 24 hours of co-administration, indicating accelerated drug clearance. Similarly in a human study, administration of radiolabelled infliximab to ATI positive patients resulted in increased concentration of the radiolabelled drug in the liver and spleen (i.e. the reticuloendothelial system) relative to ATI negative controls.[187, 192] In patient studies anti-drug antibodies are associated with low anti-TNF drug levels and loss of response.[132, 188, 193-195] In addition, in vitro reporter gene assays have demonstrated that ATI positive sera from infliximab treated patients directly neutralises the anti-TNF activity of infliximab compared to control sera.[69] Presence of anti-drug antibodies is strongly associated with loss of response to both infliximab and adalimumab, with meta-analysis by Steenhold et al. yielding a RR of 3.2 and 10.15 respectively.[44, 194, 195]

Anti-drug antibodies also increase risk of injection/ infusion reactions with anti-TNF drugs.[14, 19, 196] In a study of infliximab re-introduction following a drug holiday, detectable ATI just before the second or third infliximab induction dose, predicted for an infusion reaction (HR 7.7, 95%CI 1.88 - 31.3, P = 0.004).[197] Episodic infliximab treatment increases the risk of ATI and infusion reactions compared to continuous treatment. In one cohort study, episodic treatment was the only significant predictor of infliximab infusion reaction (OR 5, 95%CI 2 – 13, P < 0.001).[68] Another study found that high titres of anti-infliximab antibodies are associated with increased rate of infusion reactions, with concentrations ≥ 8µg/mL imparting a 2.40 RR (95%CI 1.65 - 3.66, P < 0.001).[14] Although risk of infusion reactions increases with increasing anti-drug antibody titres, there is no clear threshold, and most patients with ATI do not have an infusion reaction.[19] Also, lack of ATI prior to infliximab re-initiation following a drug

holiday did not predict for lack of reaction.[68] Interestingly in this study, 88% of infusion reactions following infliximab re-initiation occurred at the second infusion. It is not clear if an anti-TNF agent should be stopped in patients with detectable anti-drug antibodies on anti-TNF drug reintroduction but are otherwise responding.

<u>Figure 3</u>: Effects of anti-drug antibodies on infliximab drug pharmacokinetics as measured with a drug-tolerant assay A) Patient with no anti-drug antibodies, B) Patient with low titres of anti-drug antibodies and detectable drug trough levels, C) Patient with low titres of anti-drug antibodies and undetectable drug trough levels, D) Patient with high anti-drug antibody titres.



When an anti-TNF drug is administered in a patient with anti-drug antibodies, the drug forms complexes with the anti-drug antibodies and both are cleared from the circulation.[191, 198] This renders anti-drug antibodies undetectable even to drug-tolerant assays (Figure 3). Following the infusion, as anti-drug antibody production

continues anti-drug antibody levels rise while anti-TNF drug levels fall. The rate at which drug levels fall to undetectable limits depends on the titre of anti-drug antibodies, the avidity of anti-drug antibody binding and reticuloendothelial function that clears antibody-antigen complexes. Baert et al. found that patients with ATI titres ≥ 8μg/mL equivalent had a significantly reduced duration of infliximab effect following a single dose (mean 35 days, 95%CI 28 - 42 days) compared to those with ATI titres < 8μg/mL equivalent (mean 71 days, 95%CI 57 - 88 days, P < 0.001).[14] There was no difference in duration of response to a single infliximab dose among patients with undetectable ATI and those with ATI titres < 8μg/mL equivalent. Also for adalimumab as ATA titres increase adalimumab trough levels reduce. In a study by Mazor et al. ATA titres of < 1.5, 1.5 – 3 and ≥ 3μg/mL equivalent were associated with median adalimumab trough level of 6.7, 3.7 and 0μg/mL respectively (P < 0.001).[140, 199] ATA titres ≥ 3μg/mL equivalent were strongly predictive of active CD with 98% specificity (95%CI 95.5% - 100%) and positive LR of 10.3

Presence of anti-drug antibodies in patients failing anti-TNF therapy can also predict lack of response to dose escalation. In a retrospective study of 155 patients with loss of response to infliximab with undetectable drug levels and detectable ATI, change to another anti-TNF agent resulted in higher rates of complete or partial response when compared to dose escalation (92% versus 17%, P < 0.004).[43, 200] Similarly, in patients with secondary loss of response to adalimumab in the setting of sub-therapeutic drug trough levels (defined as < 4.9μg/mL), those with detectable ATA have significantly lower rates of response to dose escalation than patients with undetectable anti-adalimumab antibodies (12% versus 67%, P < 0.01).[83] Contrary to this, a retrospective study by Pariente et al. demonstrated that dose intensification for patients with loss of response to infliximab from 8th weekly to 4th weekly, restored

response in 6/10 (60%) of patients with detectable anti-drug antibodies.[201] Similarly, in a small observational study dose escalation of infliximab was able to restore therapeutic drug levels in 2 out of 3 patients with low drug levels and detectable ATI.[154, 202] However, titres of anti-drug antibodies correlate better with lack of response to dose escalation than qualitative detection, and this may account in part for these seemingly conflicting results. In the study by Yanai et al., ATA titres > 4μg/mL equivalent and ATI titres > 9μg/mL equivalent were 90% specific for failure to respond to adalimumab and infliximab dose escalation respectively.[82] There was no difference in response to dose escalation between patients with absent and low titre ATI or ATA. Low anti-drug antibody titres often disappear following dose escalation, with restoration of therapeutic anti-TNF drug levels. Therapeutic anti-TNF drug trough levels may be restored even in presence of high titres of anti-drug antibodies, provided large enough or frequently enough drug doses are administered, but this might be an expensive means of clearing high anti-drug antibody titres and risks an injection/ infusion reaction.[19, 81]

Anti-drug antibodies may also disappear following addition of an immunomodulator, as illustrated by case reports and observational studies.[43, 203, 204] Ben-Horin et al. reports of 5 patients with loss of response to infliximab with sub-therapeutic drug levels and ATI, in whom therapeutic drug levels and response were restored with the addition of an immunomodulator.[203] In another observational study of 17 IBD patients with secondary loss of response due to ATA while on adalimumab therapy, addition of an immunomodulator (thiopurine in 11 patients, methotrexate in 6 patients) was able to eliminate ATA, restore therapeutic drug levels and restore clinical response in 8 patients (47%).[204] This is an uncontrolled study and ATA titres were not reported. It is unclear if addition of an immunomodulator can overcome high titre anti-drug

antibodies. Addition of an immunomodulator may also reduce clearance of anti-TNF drug via mechanisms independent of suppression of anti-drug antibodies, including reduction of inflammatory load and generalised suppression of antibody clearance by the reticuloendothelial system.[43, 162, 176, 203, 204] Interestingly, Drobne et al. showed that infliximab trough levels do not reduce following immunomodulator withdrawal for patients that had been on co-treatment for at least 6 months.[205]

Anti-drug antibody transiency complicates interpretation of TDM results. Persistent anti-drug antibodies are associated with loss of response and poor recapture of response following dose escalation, while transient anti-drug antibodies are not.[19, 175] In addition false positive results may be misinterpreted as anti-drug antibody transiency.[19] In an observational study, those with persistent ATI had significantly lower response rates to dose escalation (16%) compared to patients with transient (69%) or undetectable (94%) ATI (P value between persistent ATI and no ATI < 0.0001, P value between persistent ATI and transient ATI = 0.0028, P value between transient ATI and no ATI = NS).[19, 175] In one retrospective study, two thirds of patients with positive ATI with clinical response who were continued on infliximab, cleared the ATI, indicating that antibody transiency is a common issue.[206] In contrast ATA, more often tend to persist and are functionally active due to invariably undetectable adalimumab drug levels and a high rate of loss of response to adalimumab (OR as high as 67 for loss of response in some studies, P < 0.0001).[19-21] It has been shown that persistence of ATI on two blood samples more than 2 months apart predicts for loss of response (67% absolute risk) compared to patients with ATI detected in one or no blood samples (P = 0.01).[207] Rates of loss of response were not significantly different among those with ATI detected in one blood sample and those with persistently undetectable ATI. An initial high ATI titre (defined

as >20ng/mL) was associated with persistence of the ATI and loss of response (94% specificity, 22% sensitivity, LR = 3.39, AUROC = 0.59). In another observational study, patients who met criteria for clinical response, with detectable ATI and were continued on infliximab therapy, ATI disappeared in 65% after a median of 4 infusions.[19, 20, 206] Interestingly ATI titres in this study did not differentiate transient and persistent anti-drug antibodies (median titres 52U/mL and 80U/mL respectively, P = 0.419).[206]

Anti-drug antibodies are not cross-reactive between different anti-TNF agents, but are between biosimilars.[73] Presence of ATI prior to initialisation of adalimumab does not increase the risk of developing ATA, nor does it increase risk of adalimumab therapy discontinuation or need for dose escalation.[41, 208-210] Similarly in patients with ATA, a response can be recaptured on switching to infliximab in a good proportion of patients.[83]

3.7 TDM for non-anti-TNF biologics

Evidence for TDM of non-anti-TNF biologic agents in IBD is more limited. Higher vedolizumab drug levels correlate both with higher rates of clinical and endoscopic remission in UC.[211, 212] A week 6 post-induction cross sectional study demonstrated increasing mucosal healing rates across vedolizumab concentration quartiles, with mucosal healing rates of 20.1%, 32.4%, 44.8% and 62.9% for quartiles 1, 2, 3 and 4, respectively. A recently published prospective trial found that a week 6 post induction vedolizumab level of < 19.0μg/mL to be predictive of requirement for dose escalation.[213] In this trial all patients with a week 6 vedolizumab trough level < 19.0μg/mL who were dose escalated were in clinical remission within 4 weeks.

Ustekinumab levels following both induction and maintenance treatment have also been associated with clinical remission.[214] Week 8 post induction, higher rates of clinical remission were observed for quartile 3 (range > 3.58 to ≤ 6.74μg/mL, 40.1% in remission) and 4 (> 6.74μg/mL, 39.5% in remission) than for patients in quartiles 1 (≤ 1.64μg/mL, 29.1% in remission) and 2 (> 1.64 to ≤ 3.58μg/mL, 27.9% in remission). For patients achieving clinical remission following ustekinumab induction, trough levels at week 24 predict for maintained clinical remission, with 54.3% in clinical remission in quartile 1 compared to 84.4% in quartile 4 (statistical significance not reported in abstract). Also a study found a week 8 ustekinumab trough level > 4.5μg/mL to be associated with endoscopic response (sensitivity 72.2%, specificity 83.3%, P = 0.0006, AUROC = 0.782).[215] Similarly an ustekinumab trough > 5μg/mL has been associated with higher rates of CRP normalisation (63.6% vs 33%, P = 0.024). Interestingly ustekinumab levels have not been shown to correlate with clinical response in psoriasis.[216]

4. RESULTS

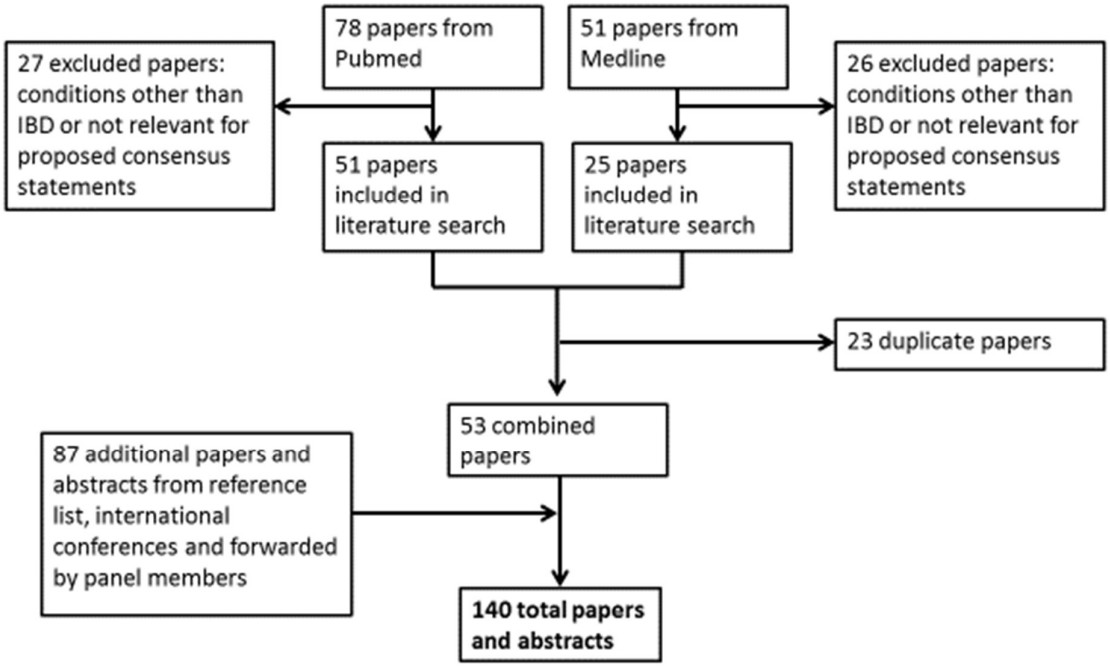
4.1 Consensus committee composition

Following the initial steering committee meeting, invitations were sent to 26 consensus committee nominees. All but one nominee (25/26) accepted the invitation to participate. The composition of the final consensus committee was as follows: 18 gastroenterologists from Australia (RL, SC, GM, JMA, SG, MG, DL, VK, CC, MW, MS, DVL, PL, JB, GRS, RB, RM, KV), 1 IBD registrar from Australia (NM), 2 international gastroenterologists (CS, MB), 1 international clinical pharmacologist (NVC), 1 local clinical pharmacists (PS), 1 local clinical pharmacologist (JM) and 1 local Immunologist (CT) (Appendix, Table 6).

4.2 Literature search

The formal literature search found a total of 53 papers which were assessed as relevant to answering at least one pre-determined clinical question (Table 2 and Figure 4). An additional 87 papers and abstracts were obtained from searching the references section of selected articles, via searching abstracts from major international conferences and from panel members. The 140 abstracts and papers were distributed to the panel members following the first round of voting, along with an evidence summary (Appendix, Table 7).

Figure 4: Literature search flow diagram.



4.3 Proposed consensus statements and voting results

The initial draft of the consensus proposed by the steering committee consisted of 25 statements (Appendix, Table 8). All 25 panellists completed the online first-round vote (Table 5). Following the first voting round 17/25 (68%) of the statements met criteria for consensus (≥ 80% of voters agreeing without or only minor reservation). Statements were modified and expanded (to 28 statements) following the first voting round based on feedback and voting results (Table 3). Again all 25 panellists participated in the second voting round which was distributed online. Following the second voting round 21/28 (75%) of statements met criteria for consensus. The third voting session was a face-to-face meeting held in Sydney (21 January 2017). It was

attended by 22 of the 25 committee members, with 3 absentees for personal reasons (SC, KV, MG). One additional committee member left before the conclusion of the face-to-face voting session, again for personal reasons (JM).

In the third and final voting round, statements were modified, combined and spilt up to produce a final set of 24 statements that panellists voted on. Overall 22/24 (92%) of statements met criteria for consensus following voting (Table 3). Statements were reordered following the final voting round based on feedback from panellists, in order to produce a more readable consensus document (Appendix, Table 9). Statements defining scenarios for performing TDM of anti-TNF agents were moved to the beginning. Statements for non-anti-TNF biologics and future therapies remained at the end. There was significant correlation between the agreed NHMRC levels of evidence and grades of recommendation for each statement (Spearman's ranked order correlation co-efficient = 0.544, P = 0.006). To add to the practicality of the document, two flow diagrams were produced to summarise the recommendations for TDM of anti-TNF drugs in patients with symptoms of active disease and those in clinical remission (Figures 5 and 6).

Table 5: Results of first, second and third voting rounds. For each voting round percentages in **green** indicate statements that met criteria for a consensus (≥ 80% agree with no reservation (A) or only minor reservation (B)), while percentages in **red** indicate statements that did not meet criteria for a consensus. Statements in grey were modified, removed or combined in subsequent voting rounds, while statements in bold were voted on in the final voting round. Panellists reached agreement via discussion on the NHMRC level of evidence (LE) and grade of recommendation (GR) for each statement. High risk features refer to risk factors for disease relapse or risk factors for severe consequences in the event of relapse (see 4.4.4 Statement 4. Interpreting TDM results among patients in clinical remission on anti-TNF therapy).

		First voting round		Second voting round		Third voting round		LE	GR
No. (no. after re-ordering statements following 3rd round vote)	**Proposed consensus statement**	**Breakdown**	**A + B**	**Breakdown**	**A + B**	**Breakdown**	**A + B**		
1.	***Target drug trough levels***								
1a[12]	In patients with ***luminal disease*** we generally recommend a steady state trough ***infliximab*** level between 3.8 and 8.4µg/mL.	A= 12% (3/25)	**80.0%**	A= 28% (7/25)	**92%**				
		B= 68% (17/25)		B= 64% (16/25)					
		C= 12% (3/25)		C= 8% (2/25)					
		D= 8% (2/25)		D= 0% (0/25)					
		E= 0% (0/25)		E= 0% (0/25)					
		F= 0% (0/25)		F= 0% (0/25)					
						A= 29% (6/21)			

1a[3] **(5a)**	In patients with ***luminal disease*** we generally recommend a steady state trough ***infliximab*** level between 3 and 8µg/mL.					B= 67% (14/21)	**96%**	II	B
						C= 0% (0/21)			
						D= 5% (1/21)			
						E= 0% (0/21)			
						F= 0% (0/21)			
1b[12]	In patients with ***luminal disease*** we generally recommend a steady state ***adalimumab*** trough level between 4.9 and 8.7µg/mL.	A= 24% (6/25)	**84%**	A= 32% (8/25)	**92%**				
		B= 60% (15/25)		B= 60% (15/25)					
		C= 8% (2/25)		C= 4% (1/25)					
		D=8% (2/25)		D= 4% (1/25)					
		E= 0% (0/25)		E= 0% (0/25)					
		F=0% (0/25)		F= 0% (0/25)					
1b[3] **(5b)**	In patients with ***luminal disease*** we generally recommend a steady state trough ***adalimumab*** level between 5 and 12µg/mL.					A= 40% (8/20)	**95%**	II	C
						B= 55% (11/20)			
						C= 5% (1/20)			
						D= 0% (0/20)			
						E= 0% (0/20)			
						F= 0% (0/20)			
1c[1]	In certain situations higher trough levels than the above ranges may be appropriate.	A= 64% (16/25)	**100%**						
		B= 36% (9/25)							
		C=0% (0/25)							
		D=0% (0/25)							
		E=0% (0/25)							
		F=0% (0/25)							

1c[23] **(5c)**	In certain situations higher or lower trough levels than the above ranges may be appropriate.			A= 92% (23/25)	**96%**	A= 67% (14/21)	**100%**	III-3	B
				B= 4% (1/25)		B= 33% (7/21)			
				C= 4% (1/25)		C= 0% (0/21)			
				D= 0% (0/25)		D= 0% (0/21)			
				E= 0% (0/25)		E= 0% (0/21)			
				F= 0% (0/25)		F= 0% (0/21)			
	2. Interpreting anti-drug antibodies								
2a[123] **(6a)**	When interpreting anti-drug antibodies, quantifying titres is clinically more useful than positive/ negative status.	A=56% (14/25)	**88%**	A= 64% (16/25)	**96%**	A= 76% (16/21)	**100%**	II	B
		B= 32% (8/25)		B= 32% (8/25)		B= 24% (5/21)			
		C= 4% (1/25)		C= 0% (0/25)		C= 0% (0/21)			
		D= 4% (1/25)		D= 4% (1/25)		D= 0% (0/21)			
		E= 0% (0/25)		E= 0% (0/25)		E= 0% (0/21)			
		F=1% (0/25)		F= 0% (0/25)		F= 0% (0/21)			
2b[12]	When interpreting anti-drug antibodies, repeat testing is useful to determine if antibodies are transient or persistent before acting on a result, particularly for patients that meet criteria for clinical remission.	A= 52% (13/25)	**80%**	A= 72% (18/25)	**92%**				
		B= 28% (7/25)		B= 20% (5/25)					
		C= 8% (2/25)		C= 4% (1/25)					
		D= 12% (3/25)		D= 0% (0/25)					
		E= 0% (0/25)		E= 4% (1/25)					
		F=0% (0/25)		F= 0% (0/25)					
2b[3] **(6b)**	When interpreting anti-drug antibodies, repeat testing is useful to determine if antibodies are transient or persistent.					A= 57% (12/21)	**100%**	II	B
						B= 43% (9/21)			
						C= 0% (0/21)			
						D= 0% (0/21)			

						E= 0% (0/21)			
						F= 0% (0/21)			
	3. Scenarios when anti-drug Ab levels and anti-TNF levels should be measured to help guide clinical decision making:								
3a[1]	Patients should have therapeutic drug monitoring performed when in steady state following induction therapy whether or not they achieve clinical remission.	A= 28% (7/25)	**44%**						
		B= 16% (4/25)							
		C= 36% (9/25)							
		D= 12% (3/25)							
		E= 8% (2/25)							
		F= 0% (0/25)							
3a[2]	Patients in clinical remission following anti-TNF therapy induction should have therapeutic drug monitoring performed when in steady state to allow dose optimisation.			A= 16% (4/25)	**64%**				
				B= 48% (12/25)					
				C= 24% (6/25)					
				D= 12% (3/25)					
				E= 0% (0/25)					
				F= 0% (0/25)					
3a[3] **(1a)**	In patients in clinical remission following anti-TNF therapy induction, TDM should be considered to guide management.					A= 52% (11/21)	**100%**	II	C
						B= 48% (10/21)			
						C= 0% (0/21)			
						D= 0% (0/21)			
						E= 0% (0/21)			
						F= 0% (0/21)			

3b[2]	Patients with primary non-response or secondary loss of response should have therapeutic drug monitoring performed in order to guide clinical decision making.			A= 80% (20/25)	**96%**				
				B= 16% (4/25)					
				C= 0% (0/25)					
				D= 0% (0/25)					
				E= 4% (1/25)					
				F= 0% (0/25)					
3b1[3] **(1b)**	Therapeutic drug monitoring can inform clinical decision making in patients with primary non-response					A= 76% (16/21)	**100%**	III2	C
						B= 24% (5/21)			
						C= 0% (0/21)			
						D= 0% (0/21)			
						E= 0% (0/21)			
						F= 0% (0/21)			
3b1[3] **(1c)**	Therapeutic drug monitoring should be performed in patients with secondary loss of response to guide clinical decision making					A= 90% (19/21)	**100%**	I	B
						B= 10% (2/21)			
						C= 0% (0/21)			
						D= 0% (0/21)			
						E= 0% (0/21)			
						F= 0% (0/21)			
3c[2]	Patients maintained in clinical remission are suggested to have periodic testing performed at least every 12 months.			A= 28% (7/25)	**60%**				
				B= 32% (8/25)					
				C= 20% (5/25)					
				D= 16% (4/25)					
				E= 4% (1/25)					

				F= 0% (0/25)					
3c[3] **(1d)**	TDM should be considered periodically in patients in clinical remission if the results are likely to impact management.					A= 57% (12/21)	**90%**	IV	D
						B= 33% (7/21)			
						C= 5% (1/21)			
						D= 5% (1/21)			
						E= 0% (0/21)			
						F= 0% (0/21)			
3d[2] **(1e)**	Patients maintained in clinical remission in whom a drug holiday is contemplated, are suggested to have therapeutic drug monitoring along with other investigations to help guide this decision.			A= 52% (13/25)	**84%**	A= 62% (13/21)	**100%**	III2	C
				B= 32% (8/25)		B= 38%(8/21)			
				C= 4% (1/25)		C= 0% (0/21)			
				D= 8% (2/25)		D= 0% (0/21)			
				E= 0% (0/25)		E= 0% (0/21)			
				F= 4% (1/25)		F= 0% (0/21)			
3e[12]	Therapeutic drug monitoring should not be performed in scenarios where results ***will not influence clinical decisions.***	A= 52% (17/25)	**84%**	A= 64% (16/25)	**92%**				
		B= 32% (8/25)		B= 28% (7/25)					
		C= 4% (1/25)		C= 8% (2/25)					
		D= 12% (3/25)		D= 0% (0/25)					
		E= 0% (0/25)		E= 0% (0/25)					
		F= 0% (0/25)		F= 0% (0/25)					
4.	***Interpreting drug levels in patients with confirmed active inflammatory disease***								
4a[12]	Patients with ***confirmed active inflammatory disease*** and ***therapeutic***	A= 44% (11/25)	**88%**	A= 32% (8/25)	**88%**	A= 48% (10/21)	**91%**	III2	C
		B= 44% (11/25)		B= 56% (14/25)		B= 43% (9/21)			

(3a)	***drug trough levels*** (suggests pharmacodynamic failure) should be ***switched out-of-class***.	C= 4% (1/25)		C= 4% (1/25)		C= 10% (2/21)			
		D= 8% (2/25)		D= 8% (2/25)		D= 0% (0/21)			
		E= 0% (0/25)		E= 0% (0/25)		E= 0% (0/21)			
		F= 0% (0/25)		F= 0% (0/25)		F= 0% (0/21)			
4b[12]	Patients with ***confirmed active inflammatory disease*** and ***sub-therapeutic drug trough levels*** & **no detectable anti-drug antibodies** (suggests non-immune mediated pharmacokinetic failure) should have compliance checked first, followed by **dose escalation**.	A= 80% (20/25)	**100%**	A= 88% (22/25)	**92%**				
		B= 20% (5/25)		B= 4% (1/25)					
		C= 0% (0/25)		C= 4% (1/25)					
		D= 0% (0/25)		D= 4% (1/25)					
		E= 0% (0/25)		E= 0% (0/25)					
		F= 0% (0/25)		F= 0% (0/25)					
4b[3] **(3b)**	Patients with ***confirmed active inflammatory disease***, ***sub-therapeutic drug trough levels*** and **no detectable anti-drug antibodies** (suggests non-immune mediated pharmacokinetic failure) should have compliance checked first, followed by **dose escalation** of the anti-TNF agent. Optimization/ introduction of an **immunomodulator** should be considered.					A= 81% (17/21)	**100%**	III3	B
						B= 19% (4/21)			
						C= 0% (0/21)			
						D= 0% (0/21)			
						E= 0% (0/21)			
						F= 0% (0/21)			
4c[23] **(3c)**	Patients with ***confirmed active inflammatory disease***, ***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**.			A= 68% (17/25)	**92%**	A= 52% (11/21)	**100%**	III3	B
				B= 24% (6/25)		B= 48% (10/21)			
				C= 0% (0/25)		C= 0% (0/21)			
				D= 4% (1/25)		D= 0% (0/21)			
				E= 4% (1/25)		E= 0% (0/21)			
				F= 0% (0/25)		F= 0% (0/21)			

4d[12]	Patients with ***confirmed active inflammatory disease*** and ***undetectable drug trough levels*** & **high titres of anti-drug antibodies** (suggests immune mediated pharmacokinetic failure) should be **switched within class**.	A= 52% (13/25)	**96%**	A= 36% (9/25)	**96%**				
		B= 44% (11/25)		B= 60% (15/25)					
		C= 4% (1/25)		C= 4% (1/25)					
		D= 0% (0/25)		D= 0% (0/25)					
		E= 0% (0/25)		E= 0% (0/25)					
		F= 0% (0/25)		F= 0% (0/25)					
4d[3] **(3d)**	Patients with ***confirmed active inflammatory disease***, ***sub-therapeutic drug trough levels*** and **high titres of anti-drug antibodies** (suggests immune mediated pharmacokinetic failure) should be **switched within class** for secondary loss of response, or alternatively ***switched within class*** or ***switched out-of-class*** for primary non-response.					A= 62% (13/21)	**100%**	III2	B
						B= 38% (8/21)			
						C= 0% (0/21)			
						D= 0% (0/21)			
						E= 0% (0/21)			
						F= 0% (0/21)			
	5. Interpreting drug levels among patients in clinical remission:								
5a[123] **(4a)**	Patients in ***clinical remission*** and ***therapeutic drug trough levels*** should be continued on the **same dose**.	A= 60% (15/25)	**100%**	A= 68% (17/25)	**96%**	A= 67% (14/21)	**100%**	II	B
		B= 40% (10/25)		B= 28% (7/25		B= 24% (5/21)			
		C= 4% (0/25)		C= 4% (1/25)		C= 5% (1/21)			
		D= 0% (0/25)		D= 0% (0/25)		D= 5% (1/21)			
		E= 0% (0/25)		E= 0% (0/25)		E= 0% (0/21)			
		F= 0% (0/25)		F= 0% (0/25)		F= 0% (0/21)			
5b[123] **(4b)**	Patients in ***clinical remission*** and with ***supra-therapeutic drug trough levels*** should be considered for **dose reduction**.	A= 40% (10/25)	**88%**	A= 56% (14/25)	**96%**	A= 48% (10/21)	**91%**	III1	B
		B= 48% (12/25)		B= 40% (10/25)		B= 43% (9/21)			
		C= 8% (2/25)		C= 4% (1/25)		C= 10% (2/21)			
		D= 4% (1/25)		D= 0% (0/25)		D= 0% (0/21)			

		E= 0% (0/25)		E= 0% (0/25)		E= 0% (0/21)			
		F= 0% (0/25)		F= 0% (0/25)		F= 0% (0/21)			
5c[123] **(4c)**	Patients in ***clinical remission*** and with ***sub-therapeutic drug trough levels*** should be individually assessed for suitability for a drug holiday.	A= 36% (9/25)	**80%**	A= 52% (13/25)	**84%**	A= 10% (2/21)	**24%**	III3	C
		B= 44% (11/25)		B= 32% (8/25)		B= 14% (3/21)			
		C= 8% (2/25)		C= 4% (1/25)		C= 24% (5/21)			
		D= 8% (2/25)		D= 8% (2/25)		D= 48% (10/21)			
		E= 4% (1/25)		E= 4% (1/25)		E= 5% (1/21)			
		F= 0% (0/25)		F= 0% (0/25)		F= 0% (0/21)			
5d[12]	Patients in ***clinical remission*** who are deemed not suitable for a drug holiday, and with ***sub-therapeutic drug trough levels*** & **undetectable anti-drug antibodies** should have **dose escalation**.	A= 16% (4/25)	**48%**	A= 32% (8/25)	**56%**				
		B= 32% (8/25)		B= 24% (6/25)					
		C= 24% (6/25)		C= 8% (2/25)					
		D= 24% (6/25)		D= 36% (9/25)					
		E= 0% (0/25)		E= 0% (0/25)					
		F= 4% (1/25)		F= 0% (0/25)					
5d[3] **(4d)**	Patients in ***clinical remission*** who have high risk features, ***sub-therapeutic drug trough levels*** and ***undetectable anti-drug antibodies*** should have optimisation or addition of an ***immunomodulator*** and /or ***dose escalation***	A= 16% (4/25)	**48%**	A= 32% (8/25)	**56%**	A= 24% (5/21)	**95%**	III3	C
		B= 32% (8/25)		B= 24% (6/25)		B= 71% (15/21)			
		C= 24% (6/25)		C= 8% (2/25)		C= 5%(1/21)			
		D= 24% (6/25)		D= 36% (9/25)		D= 0% (0/21)			
		E= 0% (0/25)		E= 0% (0/25)		E= 0% (0/21)			
		F= 4% (1/25)		F= 0% (0/25)		F= 0% (0/21)			
5e[1]	Patients in ***clinical remission*** who are deemed not suitable for a drug holiday, and with ***sub-therapeutic drug trough levels*** & **low titres of anti-drug**	A= 24% (6/25)	**64%**						
		B= 40% (10/25)							
		C= 16% (4/25)							

	antibodies should have an immunomodulatory added/ optimised & **dose escalation**.	D= 16% (4/25)							
		E= 0% (0/25)							
		F= 4% (1/25)							
5e[2]	Patients in ***clinical remission*** who are deemed not suitable for a drug holiday, and with ***sub-therapeutic drug trough levels*** & **low titres of anti-drug antibodies** should have an immunomodulatory added/ optimised &/or **dose escalation**.			A= 32% (8/25)	**76%**				
				B= 44% (11/25)					
				C= 12% (3/25)					
				D= 12% (3/25)					
				E= 0% (0/25)					
				F= 0% (0/25)					
5e[3] **(4e)**	Patients in ***clinical remission*** who have high risk features, with ***sub-therapeutic drug trough levels*** and ***low titres of anti-drug antibodies*** should have an **immunomodulatory** added/ optimised and/or **dose escalation**.					A= 62% (13/21)	**100%**	III1	B
						B= 38% (8/21)			
						C= 0% (0/21)			
						D= 0% (0/21)			
						E= 0% (0/21)			
						F= 0% (0/21)			
5f[1]	Patients in ***clinical remission*** who are deemed not suitable for a drug holiday, and with ***undetectable drug trough levels*** & **high titres of anti-drug antibodies,** should be **switched within class**.	A= 8% (2/25)	**52%**						
		B= 44% (11/25)							
		C= 20% (5/25)							
		D= 24% (6/25)							
		E= 4% (1/25)							
		F= 0% (0/25)							
5f[2]	Patients in ***clinical remission*** who are deemed not suitable for a drug holiday, and with ***undetectable drug trough levels***			A= 20% (5/25)	**68%**				
				B= 48% (12/25)					

	& **high titres of anti-drug antibodies,** should have a trial of addition/optimisation of an immunomodulator to try to overcome anti drug-antibodies. If this fails or the patient develops active disease they should be **switched within class**.			C= 20% (5/25)					
				D= 8% (2/25)					
				E= 4% (1/25)					
				F= 0% (0/25)					
5f[3] **(4f)**	Patients in ***clinical remission*** who have high risk features, with **undetectable drug trough levels** and persistently high titres of anti-drug antibodies, should be considered for **switching within** or **out-of-class**.					A= 10% (2/21)	**86%**	III2	C
						B= 76% (16/21)			
						C= 10% (2/21)			
						D= 5% (1/21)			
						E= 0% (0/21)			
						F= 0% (0/21)			
6.	***General steps to take for patients with symptoms of clinically active disease on anti-TNF therapy along with therapeutic drug monitoring:***								
6a[12]	Patients with ***symptoms of active disease*** on anti-TNF therapy should have active inflammatory disease confirmed via objective measures (endoscopy, radiology and/or biochemistry).	A= 72% (18/25)	**96%**	A= 84% (21/25)	**88%**				
		B= 24% (6/25)		B= 4% (1/25)					
		C= 4% (1/25)		C= 0% (0/25)					
		D= 0% (0/25)		D= 8% (2/25)					
		E= 0% (0/25)		E= 4% (1/25)					
		F= 0% (0/25)		F= 0% (0/25)					
6b[12]	Patients with ***symptoms of active disease*** on anti-TNF therapy should have investigations to exclude alternate/concomitant causes of	A= 76% (19/25)	**92%**	A= 80% (20/25)	**92%**				
		B= 16% (4/25)		B= 12% (3/25)					
		C= 4% (1/25)		C= 4% (1/25)					

	symptoms along with therapeutic drug monitoring.	D= 4% (1/25)		D= 4% (1/25)					
		E= 0% (0/25)		E= 0% (0/25)					
		F= 0% (0/25)		F= 0% (0/25)					
6ab[3] **(2)**	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.					A= 81% (17/21)	**100%**	III3	C
						B= 19% (4/21)			
						C= 0% (0/21)			
						D= 0% (0/21)			
						E= 0% (0/21)			
						F= 0% (0/21)			
6c[12]	Patients with ***confirmed active inflammatory disease*** on anti-TNF therapy should have other IBD medications/ immunosuppressants optimised along with performing therapeutic drug monitoring.	A= 76% (19/25)	**92%**	A= 84% (21/25)	**92%**				
		B= 16% (4/25)		B= 8% (2/25)					
		C= 4% (1/25)		C= 4% (1/25)					
		D= 4% (1/25)		D= 0% (0/25)					
		E= 0% (0/25)		E= 4% (1/25)					
		F= 0% (0/25)		F= 0% (0/25)					
	7. Standards for therapeutic drug monitoring								
7[12]	We recommend the use of a **drug-tolerant assay** over a drug sensitive assay for measurement of anti-drug antibodies.	A= 20% (5/25)	**60%**	A= 36% (9/25)	**64%**				
		B= 40% (10/25)		B= 28% (7/25)					
		C= 20% (5/25)		C= 8% (2/25)					
		D= 8% (2/25)		D= 20% (5/25)					
		E= 4% (1/25)		E= 0% (0/25)					
		F= 8% (2/25)		F= 8% (2/25)					
						A= 62% (13/21)			

7[3] **(6c)**	There is insufficient evidence to recommend a drug-tolerant assay for anti-drug antibody detection					B= 33% (7/21)	**95%**	III1	C
						C= 5% (1/21)			
						D= 0% (0/21)			
						E= 0% (0/21)			
						F= 0% (0/21)			
8. TDM for non-anti-TNF biologics									
8[12]	Due to lack of evidence on appropriate troughs associated with specific endpoints for ***non-anti-TNF biologic agents*** currently used in IBD, we cannot recommend routine use of therapeutic drug monitoring to guide clinical decision making.	A= 40% (10/25)	**72%**	A= 44% (11/25)	**92%**				
		B= 32% (8/25)		B= 48% (12/25)					
		C= 8% (2/25)		C= 4% (1/25)					
		D= 12% (3/25)		D= 4% (1/25)					
		E= 8% (2/25)		E= 0% (0/25)					
		F= 0% (0/25)		F= 0% (0/25)					
8[3] **(7a)**	There is emerging evidence that trough levels of **non-anti-TNF biological agents** may be relevant to clinical endpoints. However, more longitudinal data are required before routine use of therapeutic drug monitoring to guide clinical decision making on the use of non-anti-TNF biological agents.					A= 67% (14/21)	**96%**	IV	D
						B= 29% (6/21)			
						C= 5% (1/21)			
						D= 0% (0/21)			
						E= 0% (0/21)			
						F= 0% (0/21)			
9. Future directions									
9[12]	Data on therapeutic drug monitoring should be available at time of registration for all **future biologics**.	A= 64% (16/25)	**68%**	A= 60% (15/25)	**88%**				
		B= 4% (1/25)		B= 28% (7/25)					
		C= 8% (2/25)		C= 4% (1/25)					
		D= 12% (3/25)		D= 4% (1/25)					

		E= 4% (1/25)		E= 0% (0/25)					
		F= 8% (2/25)		F= 4% (1/25)					
9[3] **(7b)**	Data on therapeutic drug monitoring should be available at time of registration for all **future therapies**.					A= 29% (6/21)	**77%**	III1	B
						B= 48% (10/21)			
						C= 19% (4/21)			
						D= 5% (1/21)			
						E= 0% (0/21)			
						F= 0% (0/21)			

Legend:

A= agree without reservation

B= agree with minor reservation

C= agree with major reservation

D= disagree with some reservation

E= disagree without reservation

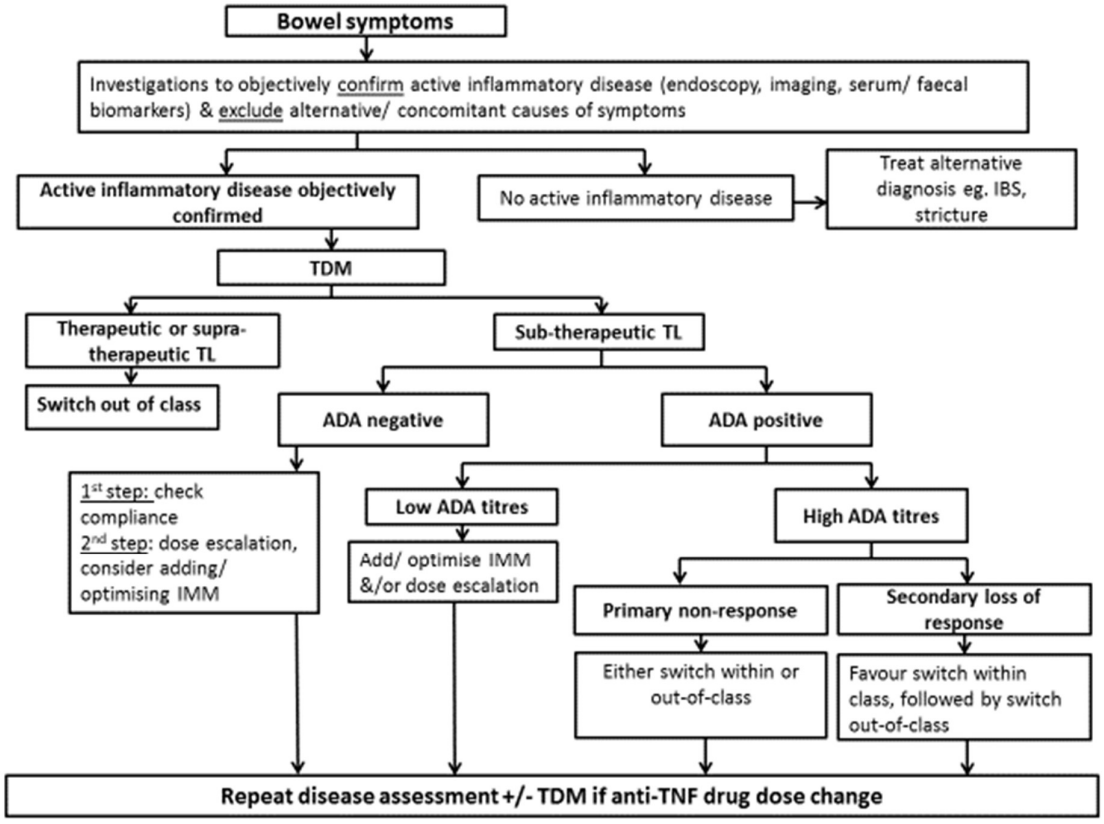
F= reserved

[1] Statement featured in first round of voting

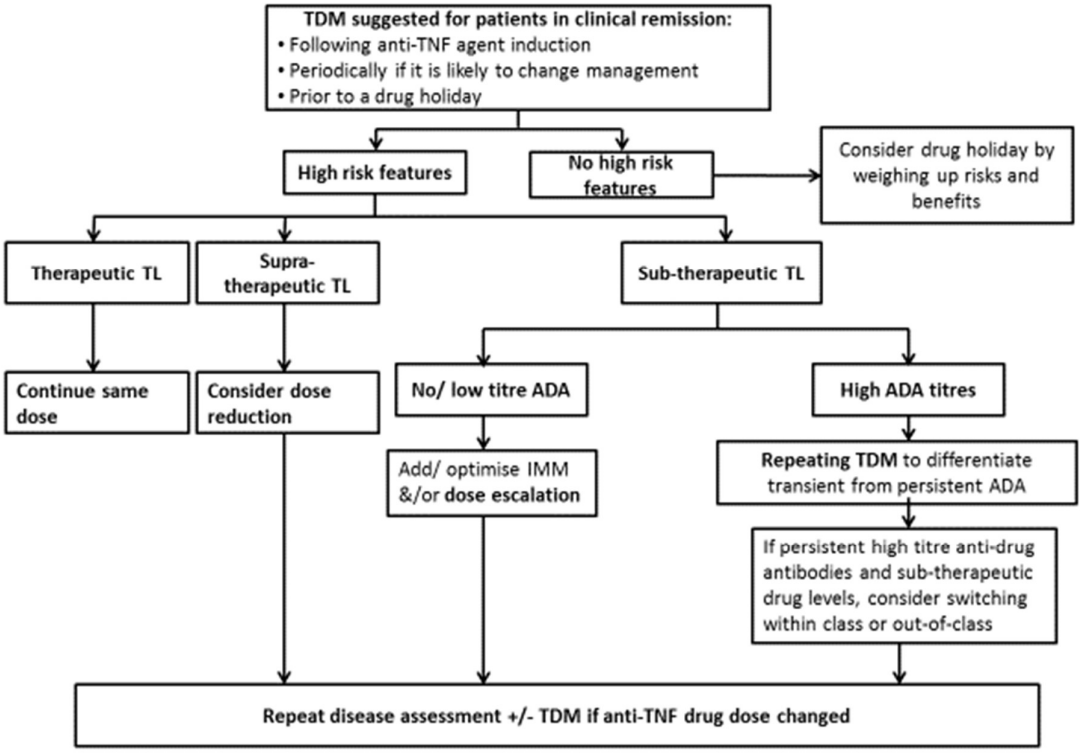
[2] Statement featured in second round of voting

[3] Statement featured in third round of voting

Figure 5: Therapeutic drug monitoring in patients with symptoms suggesting active disease while on anti-TNF therapy. ADA, anti-drug antibodies; IBS, irritable bowel syndrome; IMM, immunomodulator; TDM, therapeutic drug monitoring; TL, trough level.



<u>Figure 6</u>: Therapeutic drug monitoring for patients in clinical remission while on anti-TNF therapy. High risk features refer to risk factors for disease relapse or risk factors for severe consequences in the event of relapse (see 4.4.4 Statement 4. Interpreting TDM results among patients in clinical remission on anti-TNF therapy). ADA, anti-drug antibodies; IBS, irritable bowel syndrome; IMM, immunomodulator; TDM, therapeutic drug monitoring; TL, trough level.



4.4 Elaboration on individual statements

Below statements are ordered as they appear in the final document (Appendix, Table 9).

4.4.1 Statement 1: Scenarios when TDM of anti-TNF agents should be performed

1a. *In patients in clinical remission following anti-TNF therapy induction, TDM should be considered to guide management.*

Sub-therapeutic adalimumab and infliximab drug levels are associated with increase future risk of developing anti-drug antibodies and disease relapse.[31, 41, 96-100] The risk of anti-drug antibodies increases with cumulative time spent at sub-therapeutic drug levels and most anti-drug antibodies develop in the first 12 months from starting anti-TNF drug therapy.[21, 41, 97, 100, 188, 217] TDM for patients who achieve remission following anti-TNF drug induction may identify patients with sub-therapeutic anti-TNF drug levels, and dose escalating such patients early may prevent future anti-drug antibody formation and secondary loss of response. In addition, dose reducing patients with supra-therapeutic anti-TNF drug levels results in cost saving without worsening clinical outcomes.[43, 102, 218]

1b. *Therapeutic drug monitoring can inform clinical decision making in patients with primary non-response*

Currently, most studies have assessed TDM in secondary loss of response to anti-TNF drugs with relatively few studies assessing TDM-guided therapy in primary non-response. [116, 138] TDM during primary non-response may still reveal if failure is

driven by inadequate drug levels (i.e. pharmacokinetic failure) or by anti-TNF resistant disease (i.e. pharmacodynamic failure), to guide appropriate treatment decisions.

1c. *Therapeutic drug monitoring should be performed in patients with secondary loss of response to guide clinical decision making*

TDM of anti-TNF drugs during secondary loss of response predicts for likelihood of response to various interventions: dose escalation, change within class or change out-of-class.[82, 83] TDM-guided treatment following secondary loss of response to infliximab has also been shown to result in significant cost savings for up to 1 year compared to an empiric trial of dose escalation, despite equivalent clinical outcomes.[19, 41, 87, 90, 91]

1d. *TDM should be considered periodically in patients in clinical remission if the results are likely to impact management.*

Recommending a routine interval for repeating TDM for stable patients on ant-TNF therapy who are in remission is difficult. A regular testing interval needs to balance potential benefits against costs and the demands it places on health services. Vaughn et al. empirically recommends repeating proactive TDM every 6 to 12 months.[63] In the TAXIT study TDM-guided dose adjustment was performed every infusion cycle.[102] Despite this intensity of dose adjustment there was only benefit in the secondary endpoint of reduced need for rescue treatment. These benefits were not replicated in the more recent TAILORIX trial.[103] Given the mixed evidence of

benefits of routine proactive TDM for anti-TNF agents, the committee could not recommend a routine TDM interval for patients in remission.

1e. *Patients maintained in clinical remission in whom a drug holiday is contemplated, are suggested to have therapeutic drug monitoring along with other investigations to help guide this decision*

Some TDM algorithms assume IBD patient in remission should be continued on biologic therapy, and fail to consider the possibility of a drug holiday.[45, 63] The decision for an anti-TNF drug holiday should be individualised and take into account the risk of relapse, potential consequences of relapse, likelihood of recapture of response on anti-TNF drug re-introduction and risk of drug reactions with interrupted therapy. TDM results can form part of an algorithm to select patients for a drug holiday with low relapse risk. Maintained remission on anti-TNF therapy despite sub-therapeutic trough levels may be explained by adequate anti-TNF drug exposure at other points of the dosing cycle, an individual with lower drug requirement, sub-clinical impending loss of response, or disease remission no longer dependent on anti-TNF drug exposure. The former two may be the case with levels slightly below the therapeutic range, however the latter two appear more plausible if drug levels are very low or undetectable. Maintained remission despite persistently very low or undetectable anti-TNF drug levels on repeat measurements several months apart may increase confidence that the particular patient will remain in remission on anti-TNF drug withdrawal.

For patients in clinical remission, studies indicate that sub-therapeutic anti-TNF trough levels are predictive of sustained clinical remission following cessation of anti-TNF

therapy.[182, 219-221] Ben-Horin et al. found those with undetectable anti-TNF drug trough levels on cessation had much higher 12 month relapse free survival compared to patients with detectable drug levels (83% versus 14%, OR 30, 95%CI 5.8 - 153, P < 0.001).[219, 220] Similarly the study of infliximab diSconTinuation in CrOhn's disease patients in stable Remission on combined therapy with Immunosuppressors (STORI) trial found that infliximab trough levels ≥ 2μg/mL were predictive of relapse following drug discontinuation (OR 2.5, 95%CI 1.1 – 5.4).[221] Other factors that predict for relapse following anti-TNF discontinuation include recent corticosteroid use, prior surgical resection, male sex, active smoker, lack of endoscopic remission and biochemical evidence of active inflammation (raised white cell count, CRP, faecal calprotectin, low haemoglobin).[221-225] A meta-analysis found that risk of relapse following anti-TNF withdrawal in CD at 1 year is 42% for patient in clinical remission, and 26% for those who were also in endoscopic remission prior to anti-TNF drug discontinuation.[222]

Patients in whom the potential consequences of relapse are high may not be suitable for a drug holiday despite being at low risk of relapse. Patients with prior history of aggressive disease who have failed multiple lines of therapy, have had bowel resections and are at-risk of short gut syndrome in the event of further disease flares are unlikely to be suitable for a drug holiday. Interruptions in treatment with an anti-TNF drug is associated with increased risk of anti-drug antibody formation, a major risk factor for loss of response and drug reactions.[14, 19, 44, 101, 194-197, 226] However most ATI and ATA develop within 12 months, and patients that are maintained on anti-TNF therapy beyond this period are much less likely to develop anti-drug antibodies.[21, 188, 217] This accounts for the high infliximab retreatment response rates in the STORI trial among patients who relapsed following drug

withdrawal (98% clinical response rate and 88% clinical remission rate assessed just before the third infusion).[217, 221] In the STORI trial all patients were on infliximab for more than 12 months before treatment discontinuation (mean duration 2.2 years, range 1.5-3.1 years).

4.4.2 Statement 2. General approach to patients with symptoms of active disease on anti-TNF therapy

2. *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.*

For IBD patients on anti-TNF drug treatment and bowel symptoms suggesting treatment failure, active inflammatory disease should be confirmed via objective measures.[227] Some treatment algorithms advocate performing TDM as part of the initial work up for patients on anti-TNF therapy with clinical relapse.[228, 229] The main intention with this approach is to reduce the number of unnecessary endoscopies. If sub-therapeutic anti-TNF drug levels are found a trial of dose escalation would be the next step, and endoscopy would be reserved for symptomatic patient with therapeutic anti-TNF drug levels in order to exclude alternative causes of bowel symptoms before changing therapy. In one study 62% of patients with bowel symptoms in the setting of therapeutic drug levels and no anti-drug antibodies had no objective evidence of inflammation on endoscopy or imaging.[43, 200] Symptoms in such patients may be secondary to a fibrotic stricture, bile salt malabsorption, malignancy, small bowel bacterial overgrowth or overlapping irritable bowel syndrome (IBS).[43] However anti-TNF drugs are expensive (e.g. cost of treating an 80kg patient

with standard infliximab doses over a 1 year period is over AU$14,000 for the drug alone) and the committee felt that active disease should be objectively confirmed prior to altering dosing or changing treatment in all symptomatic patients.

Prevalence rates of IBS among patients with IBD have been reported to be 40-60%, which are 4-5 times higher than rates in the general population.[230-238] It has been postulated that IBD may predispose to development of IBS either directly through functional changes in the gut, or indirectly due to chronic illness-related anxiety.[238] In the general population, where rates of IBS are much higher compared to rates of IBD, a normal faecal calprotectin and CRP are very good at excluding IBD in those presenting with bowel symptoms.[238, 239] The utility of faecal calprotectin in diagnosing concomitant IBS in patients with prior diagnosis of IBD is less clear, however Quingley et al. recommends that young IBD patients with a normal faecal calprotectin be given a trial of IBS treatment prior to further investigations or changing IBD treatment.[238]

The choice of imaging, endoscopy or inflammatory biomarkers for confirming active inflammation needs to be decided on an individual basis, considering factors such as the reliability of inflammatory biomarkers, disease location, exposure to ionising radiation and risks of performing an endoscopy. A meta-analysis found CRP to have sensitivity of 49% (95%CI 34% - 64%) and specificity of 92% (95%CI 72% - 96%) for detecting active inflammatory disease in IBD, while faecal calprotectin had a sensitivity of 88% (95%CI 84 - 90%) and specificity of 73% (95%CI 66 - 79%).[240] In this meta-analysis faecal calprotectin was found to be more sensitive than CRP, and also faecal calprotectin was more sensitive in UC than CD.[240] Although faecal calprotectin correlates with active small bowel CD, its sensitivity is less than that for colonic IBD.[241, 242] Furthermore faecal calprotectin has not been validated in CD patients

with isolated involvement of the proximal ileum.[243] On an individual basis, there are patients in whom faecal calprotectin correlates poorly with disease activity, and so the STRIDE committee advised caution in use of inflammatory biomarkers as an endpoint to treatment.[60, 244] It may be prudent to first confirm the utility of faecal calprotectin within an individual patient by documenting a high level during times of endoscopically or radiologically confirmed active inflammatory disease, and normalisation during times of endoscopic or radiologic remission.

Among patients with symptoms of active disease and objectively confirmed active inflammation, alternative and/or contributing causes of bowel inflammation should also be considered. Clinically, non-IBD causes of colitis such as infection, ischemia or radiation, may present identical to IBD-related colitis. *Clostridium difficile* and Cytomegalovirus (CMV) colitis are relatively common among IBD patients and may mimic or exacerbate an IBD flare. Prevalence rates of *C. difificile* infection are higher among UC (37.3 per 1,000, 95%CI 34.0 - 40.7 per 1,000) and CD patients (10.9 per 1,000, 95%CI 9.9 - 12.0 per 1,000) than non-IBD gastrointestinal patients (4.8 per 1,000, 95%CI 4.6 - 5.0 per 1,000).[245] Compared to non-IBD patients where > 90% of *C. difficile* is associated with hospitalisation and antibiotic use, an observational study found that < 50% of IBD patients with *C. difficile* infection have these classic risk factors.[246] In one retrospective study concurrent CMV colitis was diagnosed in 33.6% of patients with ASUC based on tissue histopathology or immunohistochemistry.[247]

4.4.3 Statement 3. Interpreting TDM results in patients with confirmed active inflammatory disease on anti-TNF therapy

For patients with objectively confirmed anti-TNF treatment failure (primary non-response or secondary loss of response), TDM may help elicit mechanisms of failure to help guide treatment decisions (Figure 5).[248]

3a. *Patients with confirmed active inflammatory disease and therapeutic drug trough levels (suggests pharmacodynamic failure) should be switched out-of-class.*

Patients with objectively confirmed active disease, in the setting of therapeutic trough levels of anti-TNF agent (i.e. phamracodynamic failure), likely have TNF-resistant disease. As previously outlined, pre-intervention therapeutic infliximab and adalimumab trough levels predicts for lack of recapture of response with dose escalation, or with switching to another anti-TNF drug.[43, 82, 83] Due to large inter-individual variability in the minimal anti-TNF drug level required for response, a proportion of patients with treatment failure and trough levels at the lower end of the therapeutic range may still benefit from dose intensification. This may be considered for patients who have failed multiple lines of therapy and lack other treatment options.

3b. *Patients with confirmed active inflammatory disease, 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. Optimization/ introduction of an immunomodulator should be considered.*

Absence of anti-drug antibodies in patients with sub-therapeutic drug levels and active disease (i.e. non-immune mediated pharmacokinetic failure) predicts for response to

dose escalation to both infliximab and adalimumab.[43, 82, 83, 200] Roblin et al. demonstrated that patients with secondary loss of response to adalimumab, and sub-therapeutic drug levels (<4.9μg/mL) had higher response rates on switching to infliximab compared to patients with therapeutic trough levels (80% versus 6.9%, P<0.01).[83] This enriches the earlier group with patients with anti-TNF responsive disease, and these patients may have also responded to adalimumab dose escalation provided therapeutic trough levels were achieved. Although patients with treatment failure and sub-therapeutic anti-TNF drug levels (i.e. pharmacokinetic failure) may respond to either dose escalation or switching to another anti-TNF agent, completely exhausting one biologic before switching to another is wise in the current era of limited biologic options.[176] Interestingly, Afif et al. found that dose intensifying patients with undetectable infliximab levels and no ATI resulted in higher response rates than switching to adalimumab (86% versus 33%, P < 0.016).[43, 200] Yanai et al. similarly found that patients with sub-therapeutic infliximab or adalimumab drug levels with absent or only low titre anti-drug antibodies had higher response rates with dose escalation rather than switching to another anti-TNF agent.[82] A significant proportion of patients with non-immune pharmacokinetic failure to an anti-TNF drug may have a generally increased clearance of all anti-TNF monoclonal antibodies, due to genetic polymorphisms or increased inflammatory load.[48, 159, 160, 164] This may explain the greater response rates observed with dose escalation compared to switching within class among such patients.

Dose escalation for patients with non-immune mediated pharmacokinetic failure can be performed by increasing the dose per administration or reducing the dosing interval. In a retrospective study of patients with secondary loss of response to infliximab, there was no difference in remission rates between patients whose dose was doubled

versus those whose infusion interval was halved.[43, 249] The authors recommend increasing the dose per infusion for most to save on healthcare costs and resources associated with increased number of infusions. However, patients with breakthrough symptoms near the end of their infusion cycle may benefit more from reducing the dosing interval.

Following dose optimisation it is important to confirm therapeutic drug levels as restoration of therapeutic drug levels correlates with effective dose escalation.[31, 137] In one study a post dose optimisation trough of >4.05μg/mL was found to be predictive of clinical response at 12 months (AUROC = 0.648, sensitivity 60%, specificity 75%, P = 0.05), as well as CRP normalisation both after 6 (AUROC = 0.652, sensitivity 59%, specificity 77%, P = 0.05) and 12 months (AUROC = 0.677, sensitivity 59%, specificity 80%, P = 0.02).[250] Alternatively patients with sub-therapeutic drug levels may also have overlying pharmacodynamic failure. However, this will be difficult to elicit till persistent active inflammation is demonstrated in the setting of therapeutic trough levels.

Addition or optimisation of an immunomodulator should be considered for patients with non-immune mediated pharmacokinetic failure. Apart from directly supressing inflammation and improving disease control, it is postulated that this intervention may also increase anti-TNF drug levels through decrease in circulating TNF and reduction of anti-TNF drug clearance by the reticuloendothelial system.[43, 162, 176, 203, 204]

3c. *Patients with confirmed active inflammatory disease, 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.

Among patients with anti-TNF treatment failure due to sub-therapeutic drug levels and anti-drug antibodies (i.e. immune-mediated pharmacokinetic failure), anti-drug antibody titres influence response to various interventions. Yenai et al. demonstrated that low titre anti-drug antibodies may be overcome with anti-TNF dose escalation to restore therapeutic levels and response.[43, 82] Case reports and observational studies indicate that addition of immunomodulator may also suppress anti-drug antibodies to restore anti-TNF drug levels and response.[43, 203, 204]

Dose escalation or addition of an immunomodulator may in some cases only transiently suppress anti-drug antibodies due to increased circulating anti-TNF drug binding and clearing anti-drug antibodies.[198] With time anti-drug antibody production may increase again with a fall in anti-TNF drug trough concentrations to sub-therapeutic levels. Repeat TDM to measure anti-TNF drug levels and anti-drug antibodies following dose escalation is important to ensure the intervention was successful in restoring therapeutic drug levels.

3d. *Patients with confirmed active inflammatory disease, undetectable drug trough levels and high titres of anti-drug antibodies (suggests immune mediated pharmacokinetic failure) should be switched within class for secondary loss of response, or alternatively switched within class or switched out-of-class for primary non-response.*

Patients with anti-TNF treatment failure who have sub-therapeutic drug levels and high titre anti-drug antibodies, are unlikely to have therapeutic drug levels restored with dose escalation or addition of an immunomodulator. Yanai et al. found that such patients had longer duration of response when switched to another anti-TNF agent than when dose escalation (P = 0.03).[43, 82] It should be noted that the study population was patients with secondary loss of response to infliximab or adalimumab who by definition have previously demonstrated anti-TNF responsive disease. Such patients who lose response and are found to have sub-therapeutic trough levels and high titre anti-drug antibodies are likely to respond when switched to another anti-TNF agent provided therapeutic levels are established. Patients with primary non-response with sub-therapeutic anti-TNF drug levels and high titre anti-drug antibodies, who have no prior documentation of anti-TNF responsive disease may equally be considered for switching within class or out-of-class. Although addition of an immunomodulator may overcome anti-drug antibodies, this may be only effective among those with low titre anti-drug antibodies, as high titre anti-drug antibodies are likely to persist.[207] Studies that correlate titre of anti-drug antibodies to restoration of therapeutic anti-TNF drug levels following addition of an immunomodulator are lacking.

4.4.4 Statement 4. Interpreting TDM results among patients in clinical remission on anti-TNF therapy

TDM can inform treatment decisions among IBD patients in clinical remission while on anti-TNF drug therapy (Figure 6). The below statements assume the patient is not considered for a biologic drug holiday due to some combination of high-risk features. High-risk features refer to both risk factors for disease relapse (recent corticosteroid use, elevated serum/stool biomarkers, active disease at endoscopy, shorter duration

of disease remission, prior surgical resection, current smoker status, male sex) and risk factors for severe consequences in the event of relapse (eg. risk factors for further bowel resections and short gut syndrome).[221-225]

4a. *Patients in clinical remission and therapeutic drug trough levels should be continued on the same dose.*

The above statement assumes the therapeutic range chosen is appropriate for the selected treatment endpoint of clinical remission.

4b. *Patients in clinical remission and with supra-therapeutic drug trough levels should be considered for dose reduction.*

TDM algorithms for patients responding to anti-TNF therapy generally recommend dose de-escalating patients with supra-therapeutic levels.[45, 63] Due to plateau of anti-TNF response at high trough levels, it is hopped this would reduce cost without worsening clinical outcomes.[124] In the TAXIT study, de-escalate infliximab dose in patients with a supra-therapeutic trough level resulted in 28% drug cost reduction ($P < 0.001$) without statistically significant decrease in clinical remission rates in both CD (80.4% pre dose reduction to 89.4% post dose reduction, $P = 0.3$) and UC patients (85.0% pre dose reduction to 85.0% post dose reduction, $P = 1.0$).[43, 102] A recent pilot study assessed infliximab dose de-escalating among CD patients in clinical remission, supra-therapeutic levels (> 10μg/mL) and undetectable ATI.[218] All 10 dose de-escalated patients maintained a HBI of 0 during the 24 week follow up period.

4c. *Patients in clinical remission and with sub-therapeutic drug trough levels should be individually assessed for suitability for a drug holiday (**consensus not reached**).*

There was a marked swing in voting against this statement in the third voting round, compared to the first and second voting rounds (24% agreed with no or only minor reservation in the third voting round as compared to 80% and 84% in the first and second voting rounds respectively). This came about as a result of discussion around of when a drug holiday should be considered. Although TDM can help risk stratify patients planned for an anti-TNF drug holiday, an 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. The rejection of statement 4c was also so as to restrict the remaining statements in section 4 to high-risk patients that are not considered suitable for a biologic drug holiday. This is also in agreement with statement 1d, that a routine proactive TDM interval for patients in clinical remission is not recommended and that TDM should only be performed if results will alter management.

4d. *Patients in clinical remission who have high risk features, sub-therapeutic drug trough levels and undetectable anti-drug antibodies should have optimization or addition of an immunomodulator and/ or dose escalation*

Sub-therapeutic anti-TNF drug levels in absence of anti-drug antibodies increase the risk of future anti-drug antibody formation to both infliximab and adalimumab, and dose escalating these patients may prevent loss of response secondary to immune-

mediated pharmacokinetic failure.[31, 41, 96-100, 132] In the optimisation phase of the TAXIT study, dose escalating patients on long-term infliximab maintenance with sub-therapeutic trough levels results in increased rate of remission (from 65.1% to 88.4%, P = 0.02), and reduced median CRP (from 4.3mg/L to 3.2mg/L, P < 0.001) among CD patients.[43, 102] However no significant change was observed among UC patients. As discussed previously, addition of an immunomodulator may also increase anti-TNF drug levels in patients without detectable anti-drug antibodies.[19]

4e. *Patients in clinical remission who have high risk features, with sub-therapeutic drug trough levels and low titres of anti-drug antibodies should have an immunomodulatory added/ optimised and/ or dose escalation.*

IBD patients in clinical remission with sub-therapeutic anti-TNF drug levels should have anti-drug antibodies measured in order to guide treatment decisions.[45, 63] Extrapolating from studies in patients with treatment failure to infliximab and adalimumab, dose escalation or addition of an immunomodulator can restore therapeutic drug levels in patients with low titre anti-drug antibodies.[43, 82, 203, 204, 250] It is hoped this will prevent a future disease flare. Panellists could not reach agreement if in the first instance clinicians should attempt addition/ optimisation of an immunomodulator, anti-TNF drug dose escalation, or both, in order to elevate anti-TNF drug trough levels. There is no data directly comparing the effectiveness of these three potential interventions in elevating anti-TNF drug levels. Addition/ optimisation of an immunomodulator would be a relatively less expensive intervention than anti-TNF drug dose escalation. On the other hand, both dose escalating and adding/ optimising an immunomodulator in the first instance may

potentially be more effective at achieving therapeutic anti-TNF drug levels than either alone.

4f. *Patients in clinical remission who have high risk features, with undetectable drug trough levels and persistently high titres of anti-drug antibodies, should be considered for switching within or out-of-class.*

As discussed for patients with treatment failure on anti-TNF therapy, dose escalation or addition of an immunomodulator is unlikely to overcome high titres of anti-drug antibodies to restore therapeutic levels.[82, 207, 250] In addition there is a concern for drug reactions with continued anti-TNF administration in patients with high titre anti-drug antibodies.[14, 19, 196, 197] Although high titre anti-drug antibodies have been associated with persistence, there is overlap between titres of persistent and transient anti-drug antibodies.[19, 20, 206, 207] There may be less urgency to change treatment in asymptomatic patients, and repeating TDM first to exclude anti-drug antibody transiency may be worthwhile even among patients with high-titre anti-drug antibodies.

4.4.5 Statement 5. Target drug trough levels

These consensus statements are predominantly intended to aid gastroenterologists in Australia, so the treatment endpoints they are based on must be compatible with the current PBS system. Continuation of PBS subsidised biologic maintenance treatment in Australia depends on demonstrating ongoing adequate response every 24 weeks, as defined by several criteria (Table 1). These criteria emphasise clinical disease activity scores and do not include endoscopic remission. Despite endoscopic

remission being a more objective treatment endpoint associated with improved outcome over clinical remission alone, guidelines for TDM of anti-TNF agents based around endoscopic remission cannot easily be integrated with the currently PBS system.[60-62] As such appropriate steady state therapeutic ranges were determined for infliximab and adalimumab for clinical remission as the treatment endpoint.

Most TDM data, particularly for adalimumab, are for luminal CD patients, however studies among UC patients have found similar cut-offs.[176] The committee agreed that the defined therapeutic ranges for adalimumab and infliximab should be applied with a degree of caution to UC patients. Due to measurement error, it was agreed to round off the upper and lower limits of the proposed therapeutic ranges to whole numbers.

5a. *In patients with luminal disease we generally recommend a steady state trough infliximab level between 3 and 8µg/mL.*

Studies that determined a steady state therapeutic cut-off or range for infliximab among IBD patients with luminal disease were considered (Appendix, Table 4).[80, 82, 98, 116, 118-137, 147, 174-176] The agreed therapeutic range for infliximab (3 to 8µg/mL) was similar to prospective studies by Steenholdt et al. and Vande Casteele et al. which demonstrated cost saving and reduced disease flares respectively using a maintenance range of 3 to 7µg/mL.[19, 41, 87, 90, 102] Similarly Yenai et al. found a pre-dose escalation infliximab trough of ≥3.4µg/mL as optimal for predicting lack of response to dose escalation in secondary loss of response, while Adendokun et al. demonstrated that response to infliximab in UC plateaus above a trough of 8.4µg/mL.[82, 118]

5b. *In patients with luminal disease we generally recommend a steady state adalimumab trough level between 5 and 12 µg/mL.*

Similarly in selecting a therapeutic range for adalimumab among IBD patients with luminal disease, studies determining a steady state therapeutic cut-off or range were considered (Appendix, Table 5).[82, 83, 97, 119, 124, 138-147, 176] The lower limit of the determined adalimumab therapeutic range (5 to 12µg/mL) is based on studies by Yanai et al. and Echarri et al. which found a trough of > 4.5µg/mL to predict for lack of response to dose escalation in secondary loss of response as well as clinical response or remission among patients on maintenance therapy, respectively.[82, 119] The upper limit of the adalimumab therapeutic range (12µg/mL) is based on endoscopic remission data, as data with clinical remission as the treatment endpoint are lacking.[124] This is significantly higher than an upper limit of 8µg/mL quoted by some laboratories in Australia, based largely on rheumatological data.[177-179]

5c. *In certain situations higher or lower trough levels than the above ranges may be appropriate.*

The above recommended therapeutic ranges for infliximab and adalimumab may need to be altered for different disease phenotypes or treatment endpoints. Higher infliximab trough levels have been found to be needed for fistula healing in peri-anal CD.[183, 185] Similarly, the therapeutic ranges to achieve endoscopic remission with infliximab or adalimumab appear to be higher than what is required for clinical remission.[124]

4.4.6 Statement 6. Anti-drug antibodies

6a. *When interpreting anti-drug antibodies, quantifying titres is clinically more useful than positive/ negative status.*

Qualitative detection of ATA and ATI is associated with sub-therapeutic drug trough levels, loss of response, and lack of recapture of response following dose escalation.[44, 83, 194, 195] However, quantification of anti-drug antibody titres rather than qualitative detection, is a better predictor of the above.[14, 82, 140, 199] Low titre anti-drug antibodies can often be overcome with dose escalation, and do not appear to reduce the likelihood of response as compared to patients with undetectable anti-drug antibodies.[82] Anti-drug antibody cut offs that distinguish anti-drug antibodies as low or high titre are assay specific. As previously discussed titres cannot easily be standardised between different assays.[20, 70, 71, 79] As such clinicians are advised to use an assay with an anti-drug antibody cut off that has been correlated with outcome data.

6b. *When interpreting anti-drug antibodies, repeat testing is useful to determine if antibodies are transient or persistent before acting on a result, particularly for patients that meet criteria for clinical remission.*

There is generally less urgency to alter treatment for patients in remission, and repeat TDM to differentiate transient and persistent anti-drug antibodies may be clinically useful. Transient anti-drug antibodies are relatively common, especially among patients who are responding to therapy, and are not associated with loss of

response.[19, 20, 188, 206] Repeat TDM to differentiate transient and persistent anti-drug antibodies may be particularly useful in patients planned for a drug holiday, or in those planning to change to another treatment. The ideal time frame for repeating TDM in order to differentiate transient/ persistent anti-drug antibodies is not clear. Also, an initial finding of high titre anti-drug antibodies has not consistently been found to predict for anti-drug antibody persistence.[206, 207] In view of this, it may be prudent to repeat TDM in all patients in remission found to have sub-therapeutic anti-TNF drug levels and anti-drug antibodies regardless of titre, provided there is no urgency to change treatment before TDM results are available.

6c. *There is insufficient evidence to recommend a drug-tolerant assay for anti-drug antibody detection*

The ability of drug-tolerant anti-drug antibody assays to detect anti-drug antibodies in serum samples with free drug, has not translated to a clear clinical advantage over drug-sensitive assays. Anti-bodies detected in presence of free drug most often lack neutralising potential, while high titre anti-drug antibodies that are of clinical significance appear to be detected equally well by both drug-tolerant and drug-sensitive assays.[71, 85] In addition, drug-tolerant assays are significantly more expensive and currently not available in Australia.

4.4.7 Statement 7. TDM for non-anti-TNF biologics and future therapies

7a. *There is emerging evidence that trough levels of non-anti-TNF biological agents may be relevant to clinical endpoints. However, more longitudinal data are required*

before routine use of therapeutic drug monitoring to guide clinical decision making on the use of non-anti-TNF biological agents.

Cross-sectional studies have found that vedolizumab and ustekinumab drug levels are associated with clinical and endoscopic remission, and in the case of vedolizumab also need for dose escalation.[211-215] Mechanisms of treatment failure for non-anti-TNF biologics are likely to be similar to anti-TNF biologics. Patients found to have therapeutic levels of a non-anti-TNF biologic drug (i.e. pharmacodynamic failure) are not likely to benefit from further dose escalation and should be changed to another biologic, where as those found to have sub-therapeutic drug levels and active disease (i.e. pharmacokinetic failure) would likely benefit from dose escalation provided anti-drug antibodies are absent or present in only low titres. Anti-drug antibodies tend to occur at much lower rates with vedolizumab (0.4 – 1.0% at 52 weeks) and ustekinumab (2.3% at 52 weeks) as compared to treatment with anti-TNF biologics.[251-253] It is not clear if antibodies to vedolizumab or antibodies to ustekinumab can be overcome with dose escalation or addition of an immunomodulator in a similar fashion to anti-drug antibodies against anti-TNF drugs, and if anti-drug antibody titres influence ability to restore therapeutic drug levels with these interventions.

7b. *Data on therapeutic drug monitoring should be available at time of registration for all future therapies (**consensus not reached**).*

Although the majority of the consensus committee agreed that TDM data should accompany pivotal clinical studies of all future IBD drugs, consensus was not reached.

Several panellists felt that this recommendation is best left to regulatory bodies to endorse.

5. DISCUSSION

IBD treatment currently is moving towards personalised therapy. Personalised therapy in IBD utilises various predictive and prognostic markers in order to optimise IBD treatment for individual patients. TDM of anti-TNF drugs is an important aspect of personalised IBD treatment currently being practiced. At the moment uptake of TDM-guided anti-TNF therapy is variable among Australian gastroenterologists. Lack of awareness of when to perform TDM and how to act on results are potentially major barriers. These consensus statements should provide a practical guide to assist gastroenterologists in Australia and abroad in utilising TDM-guided anti-TNF therapy. Biologic drugs are expensive and treatment failure is a significant issue. TDM-guided anti-TNF therapy can better select patients with treatment failure who are likely to benefit from dose escalation, and identify patients who should be switched to other treatments earlier. This may avoid futile, empiric, dose escalation trials, allow effective treatment to be commenced sooner, and so reduce disease burden and treatment cost. Early dose optimisation in patients who achieve remission to anti-TNF drug induction may further reduce future disease flares, treatment failure secondary to anti-drug antibody development, and treatment cost. Uptake of TDM-guided anti-TNF therapy among gastroenterologists is important to ensure benefits of these drugs are maximised.

Recommendations around reactive TDM of anti-TNF agents were stronger compared to recommendations around proactive TDM, reflecting the current evidence. The panel could not recommend routine proactive TDM for patients who are in clinical remission beyond TDM-guided anti-TNF drug dose optimisation shortly following successful anti-TNF induction. The recommendation for proactive TDM among patients in clinical

remission was to perform it only if results are likely to impact management. The level of evidence for this recommendation was low (IV), consequently attracting a low NHMRC grade of recommendation (D, Appendix, Tables 1, 2 and 3). Despite several observational studies, currently there is lack of high-quality evidence to guide treatment decisions for patients with anti-TNF treatment failure based on TDM results. RCTs are currently underway with adequate power to compare outcomes of different interventions (dose escalation, switching within class or switching out-of-class) between different treatment failure subgroups as defined by TDM (pharmacodynamic failure, immune-mediated pharmacokinetic failure, non-immune mediated pharmacokinetic failure).[19]

Compared to the recently published consensus on TDM-guided anti-TNF therapy from the Building Research in Inflammatory Bowel Disease Globally (BRIDGe) group, these consensus statements have considerable similarities but also some notable differences.[31] The literature search which formed the basis of the BRIDGe group guidelines was completed in November 2013. Several important studies have since been published, particularly related to appropriate infliximab and adalimumab trough levels in luminal and peri-anal fistulising disease, as well as data on TDM of non-anti-TNF biologics.[82, 97, 98, 116, 118, 119, 124, 130, 131, 133, 135, 147, 183, 185, 211-216] Overall, our consensus statements were more applicable to clinical practice through the definition of therapeutic ranges, the inclusion of decision flow diagrams and through rating of the level of evidence and grade of recommendation for each consensus statement.

There are several limitations to the therapeutic ranges for infliximab and adalimumab recommended by our consensus committee. The agreed therapeutic ranges are for luminal disease and for clinical remission as the treatment endpoint. Despite the

emphasis on clinical scoring tools in PBS criteria for initiation and continuation of biologic treatment in Australia, panel members agreed that endoscopic and/or histologic remission are better treatment endpoint than clinical remission, in line with evidence for improved rates of steroid-free remission among CD patients and reduction in colorectal cancer among UC patients.[29, 30, 60-62] Although the committee acknowledged that evidence indicates higher anti-TNF drug levels are required for endoscopic remission and to heal fistulising disease, it did not make recommendations about appropriate ranges for these two scenarios.[124, 126, 183] Also, the committee felt that most TDM data are in CD, particularly for adalimumab, and the determined therapeutic ranges should be applied with greater caution to UC patients. For example, in the study by Ungar et al. only 14% of the included IBD patients had UC as their diagnosis, and subgroup analysis was not attempted.[124] Due to relatively little data, our consensus committee did not define appropriate adalimumab and infliximab levels taken during induction treatment (i.e. not in steady state) or at other parts of the dosing cycle.[116-118, 143, 171, 172] Although our consensus committee agreed that TDM of anti-TNF agents may elicit mechanisms of failure in primary non-response so as to guide treatment decisions, by not defining appropriate induction therapeutic ranges, readers of these consensus statements cannot easily differentiate mechanisms of failure in this setting (i.e. pharmacodynamic versus pharmacokinetic failure) unless drug levels are found to be very high or very low. This detracts somewhat from the clinical applicability of these consensus statements. The consensus statements focused on TDM for infliximab and adalimumab, and did not make recommendations about appropriate therapeutic ranges for anti-TNF drugs used to treat IBD that are currently not available in Australia, golimumab and certolizumab. Although similar TDM-decision algorithms can be

applied for golimumab and certolizumab, TDM data defining appropriate therapeutic ranges for these anti-TNF agents are limited to smaller cross-sectional studies.[180, 181]

A further limitation to the current guidelines relates to difficulty in defining anti-drug antibody titre cut-offs as high and low. Such cut-offs are assay specific and differences in assays cannot be easily adjusted owing to different sensitivity of assays for different antibody subtypes, and the vastly varied proportion of such subtypes in anti-drug antibody positive serum samples.[20, 70, 79] Despite universal standardisation for anti-drug antibody detection being proposed, similar to the international ratio (INR) used to standardise pro-thrombin time (PT) measured across different laboratories, the former scenario is more complex.[78] The treatment algorithms derived from the consensus statements (Figures 5 and 6) rely on anti-TNF titres to be quantified, and for the anti-drug antibody assay used to have validated cut-offs for differentiating low and high titres. Some laboratories in Australia qualitatively report anti-drug antibodies as present or absent, making these two algorithms more difficult to apply in cases where anti-drug antibodies are positive. Similarly, the algorithms were based around drug-sensitive assays and did not consider detectable anti-drug antibodies in the setting of therapeutic anti-TNF drug levels. This scenario is specific for drug-tolerant assays which are not currently available in Australia, are considerably more expensive, and do not appear to offer an advantage clinically.[71, 81, 84, 85]

The BRIDGe group consensus described TDM in five patient groups: 1) primary non-responders following induction, 2) patients with secondary loss of response, 3) responders following induction therapy, 4) responders during maintenance therapy and 5) patients undergoing anti-TNF re-introduction following a drug holiday.[31] The BRIDGe group could not reach agreement in recommending routine TDM for

responders following induction, however recommended TDM be performed within the first 12 months of successful induction. Our consensus panel recommended TDM in similar scenarios, but with some exceptions. Our committee felt it was appropriate to perform TDM shortly following successful anti-TNF drug induction, to allow dose optimisation and reduce future risk of anti-drug antibody development and subsequent loss of response.[41, 43, 97, 100] Also, unlike the BRIDGe consensus our panel considered and recommended TDM as part of the assessment for patients planned for an anti-TNF drug holiday to help stratify relapse risk. This is based on studies indicating sub-therapeutic anti-TNF drug levels predict for sustained remission following anti-TNF withdrawal.[219, 221] Unlike the BRIDGe group our panel did not consider TDM for patients on re-introduction of an anti-TNF agent post drug holiday, to stratify risk of infusion reactions. Although anti-drug antibodies are a risk factor for drug reactions, transient anti-drug antibodies on anti-TNF drug reintroduction are common, most patients with detectable anti-drug antibodies do not have a reaction, titres of anti-drug antibodies have not consistently predicted for likelihood of reaction, and absence of anti-drug antibodies does not predict for lack of reaction.[14, 19, 20, 68, 196, 206] Discontinuing patients with anti-drug antibodies following anti-TNF drug re-introduction who are otherwise responding, may result in more futile treatment changes than prevented drug reactions. Overall, TDM on anti-TNF drug reintroduction may not be useful in avoiding drug reactions. TDM of anti-TNF drugs during pregnancy was not considered by neither our consensus committee nor the BRIDGe group consensus. Data are lacking on what are optimal drug levels in pregnant women to balance the benefits of disease control against the risks of anti-TNF drug exposure for newborn infants.

Our consensus committee considered TDM for non-anti-TNF biologics, namely vedolizumab and ustekinumab, but this could not be recommended in routine clinical practice due to relatively little data.[211-216] More studies are required to confirm that the similar TDM principles apply for non-anti-TNF biologics, to define appropriate therapeutic ranges to differentiate pharmacokinetic and pharmacodynamic failure, and to determine if anti-drug antibodies can be overcome with dose escalation or addition of an immunomodulators and whether anti-drug antibody titres influence response to these interventions. Currently assays to measure drug levels and anti-drug antibodies for non-anti-TNF biologics are not available for routine clinical use in Australia. Although vedolizumab can be dose escalated via compassionate access in Australia, this is currently not within the Therapeutic Goods Administration (TGA) label. Only 300mg IV every 8 weeks is on the TGA label and not 300mg IV every 4 weeks. However, the pivotal data indicate that incremental therapeutic gain can be achieved with dose interval decrease.

Although cost saving is a potential benefit of following these guidelines, there was no separate statements dealing with cost saving. These consensus statements are intended for clinicians rather than policy makers. As such they primarily provide recommendations around when to perform TDM of anti-TNF agents and how to act on results. Although not specifically stated within the body of statements 3a-d and 4a-f, the aim of each TDM-guided intervention is either improvement in clinical outcomes or cost saving.

6. CONCLUSION

To conclude, TDM of anti-TNF drugs is an important aspect of personalised IBD therapy that aims to maximise benefit and reduce treatment cost with these agents.

These consensus statements are intended to act as a practical guide for use of TDM in optimising IBD treatment, and it is hoped they will improve use of TDM-guided anti-TNF therapy among gastroenterologists in Australia and abroad. Evidence is most supportive for reactive TDM, however there are selected scenarios where proactive TDM for patients in remission may be beneficial, including treatment optimisation shortly following anti-TNF treatment induction and relapse risk stratification prior to an anti-TNF drug holiday. Limitations of the evidence and hence these consensus statements relate to endpoint and phenotype appropriate therapeutic ranges, scarce data on appropriate therapeutic ranges during anti-TNF drug induction, lack of longitudinal interventional studies on TDM of biologics in different disease phenotypes, and sparse TDM data on biologics other than infliximab and adalimumab. These consensus guidelines will need to be updated with emerging data that answers the above questions.

APPENDIX

Table 1: NHMRC Evidence Hierarchy.[39]

Designation of "level of evidence" according to type of research question

Level	Intervention	Diagnostic accuracy	Prognosis	Aetiology	Screening intervention
I	Systematic review of level II studies				
II	RCT	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation	Prospective cohort study	Prospective cohort study	RCT
III-1	Pseud-RCT (ie. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a	Case series where all or none of the people with the risk factor(s) experience the outcome	Case series where all or none of the people with the risk factor(s) experience the outcome	Pseudo-RCT (ie. alternate allocation or some other method

		defined clinical presentation			
III-2	Comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case-control study • Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a RCT	Retrospective cohort study	A comparative study with concurrent controls: • Non-randomised, experimental trial • Cohort study • Case-control study
III-3	Comparative study without concurrent controls: • Historical control study • Two or more single arm study • Interrupted time series without a parallel control group	Diagnostic case-control study	Retrospective cohort study	Case-control study	A comparative study without concurrent controls: • Historical control study • Two or more single arm study

IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)	Case series, or cohort study of persons at different stages of disease	Cross-sectional study or case series	Case series

RCT, randomised controlled trial

Table 2: NHMRC Body of evidence matrix.[39]

Each of the five domains is ranked A-D and the grade of recommendation is taken as the average ranking.

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence base (Level of evidence from NHMRC evidence hierarchy)	one or more level I studies with a low risk of bias or several level II studies with a low risk of bias	one or two level II studies with a low risk of bias or a SR/several level III studies with a low risk of bias	one or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	level IV studies, or level I to III studies/SRs with a high risk of bias
Consistency (not applicable if only one study)	all studies consistent	most studies consistent and inconsistency may be explained	some inconsistency reflecting genuine uncertainty around clinical question	evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	population/s studied in body of evidence are the same as the	population/s studied in the body of evidence are similar to the	population/s studied in body of evidence differ to target population for guideline but it is clinically	population/s studied in body of evidence differ to target population and hard to judge whether it is

	target population for the guideline	target population for the guideline	sensible to apply this evidence to target population	sensible to generalise to target population
Applicability	directly applicable to Australian healthcare context	applicable to Australian healthcare context with few caveats	probably applicable to Australian healthcare context with some caveats	not applicable to Australian healthcare context

SR, systematic review

Table 3: NHMRC grades of recommendation. [39]

Grade of recommendation	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendation must be applied with caution

Table 4: Studies defining a steady state therapeutic trough cut-off or range for infliximab in luminal IBD

Study	Study type	Population	Therapeutic cut-off or range (assay type)	Endpoints
Adedokun et al. 2014[118]	Prospective cohort study (post-hoc analysis)	N=85, UC in clinical remission, week 30 of IFX maintenance post initiation	3.5 - 8.4μg/mL, therapeutic range (ELISA)	Remission (Mayo score) at week 54
Arias et al. 2012[174]	Retrospective cohort study	N=135, UC, week 14 post IFX induction	>7.19μg/mL (ELISA)	Sustained benefit (not defined)
Ben-Bassat et al. 2013[127]	Cross-sectional study	N=234, CD, maintenance IFX	>2μg/mL (HMSA)	Steroid-free clinical remission (HBI), endoscopic remission & CRP
Bortlik et al. 2013[128]	Retrospective cohort study	N=84, CD, week 14 -22 following IFX initiation. Median follow up 25 months (range 14-37)	>3μg/mL (ELISA)	Treatment failure (loss of response or drug intolerance) on follow up (median 25

				months, range 14-37)
Chaparro et al. 2016[147]	Cross-sectional study	N=44, IBD, on IFX maintenance	≥2.4µg/mL (ELISA)	Mucosal healing
Cornillie et al. 2014[98]	Retrospective cohort study (post hoc analysis of RCT)	N=147, CD, week 14 post IFX induction	≥3.5ug/mL (ELISA)	Clinical response at week 54 (CDAI)
Drobne et al. 2011[129]	Prospective cohort study	N=117, CD, co treated with IFX & immunomodulator for 1 year, immunomodulator discontinued after 1 year	Detectable (ELISA, lower limit of detection not given)	Maintained clinical response
Drobne et al. 2016[135]	Prospective cross-sectional	N=83, IBD, on IFX maintenance	>6.4µg/mL (ELISA)	Lower CRP and faecal calprotectin
Echarri et al. 2014[119]	Prospective cross-sectional study	N=15, CD, week 14 post IFX induction	>3µg/mL (ELISA)	Clinical response or remission (HBI)
Feagan et al. 2012[80]	Cross-sectional study	N=532, CD, not specified at what time point during	≥3µg/mL (HMSA)	Difference in CRP concentration

	(post-hoc analysis)	induction/ maintenance		
Huang et al. 2015[130]	Cross-sectional study	N=36, IBD, on maintenance IFX	≥6.65µg/mL (ELISA) ≥7.3µg/mL (ELISA)	Clinical remission (HBI for CD, partial Mayo for UC) Faecal calprotectin <250µg/g
Lamblin et al. 2012[120]	Cross-sectional study	N=44, CD, on maintenance IFX	≥5.6µg/mL (assay not specified)	CRP normalisation, at same time-point
Levesque et al. 2014[121]	Prospective cohort study	N=327, CD on maintenance IFX (received at least 5 infusions)	>2.8-4.6µg/mL (HMSA) >2.7-2.8µg/mL (HMSA)	Lack of CDAI increase of ≥70 between two infusions Maintaining normal CRP
Maser et al. 2006[122]	Prospective cohort study	N=105, CD, week 52 post IFX initiation	>1.40µg/mL, detectable limit (ELISA)	Clinical remission (HBI), CRP reduction, endoscopic improvement/

				remission (SES-CD)
Moore et al. 2016[131]	Meta-analysis	IBD, 4 studies allowed remission rates to be pooled	>2μg/mL	Clinical remission, or endoscopic remission
Papamichael et al. 2016[116]	Retrospective cohort study	N=101, UC, week 14 post IFX induction	≥2.1μg/mL (ELISA)	Mucosal healing at weeks 10-14 (Mayo endoscopy score ≤1)
Seow et al. 2010[123]	Cross-sectional study	N=115, UC, maintenance IFX	>1.40μg/mL, detectable limit (ELISA)	Clinical remission (Mayo score)
Steenholdt et al. 2011[134]	Cross-sectional study	N=106, IBD, on IFX maintenance	>0.5μg/mL for CD (RIA) >0.8μg/mL for UC (RIA)	Maintaining clinical response Maintaining clinical response
Ungar et al. 2016[124]	Cross-sectional study	N=78, IBD, on IFX maintenance	6-10μg/mL, therapeutic range (ELISA)	Mucosal healing (SES-CD or Mayo score)

Van Assche et al. 2008[136]	Prospective cross-sectional	N=, IBD, on IFX maintenance > 6 months	>2.24µg/mL (ELISA) >0.90 µg/mL (ELISA)	Lower mean CRP between quartiles 3 and 1/2 Lower mean CDAI between quartiles 2 and 1
Vande Casteele et al. 2012[125]	Prospective cohort study	N=275, IBD, on maintenance IFX	3-7µg/mL (ELISA)	CRP reduction
Vande Casteele et al. 2013[175]	Retrospective cohort study	N =90, IBD, week 14 post IFX initiation	≥2.2µg/mL	Remaining on IFX & lack of ATI
Vande Casteele et al. 2015[132]	Cross-sectional study	N=483, CD, on maintenance IFX	>2.79µg/mL (HMSA)	CRP normalisation (<5mg/L)
Warman et al. 2015[133]	Cross-sectional study	N=61, IBD, maintenance IFX	≥2.18µg/mL (ELISA) for CD ≥6.26µg/mL (ELISA) for UC	Clinical remission (CDAI) Clinical remission (Truelove-Witts index)

Yanai et al. 2015[82]	Retrospective cohort study	N=188, IBD patients with secondary loss of response to IFX	>3.8µg/mL (ELISA)	Failure to respond to dose escalation
Hibi et al. 2012[137]	Cross-sectional study	N=57, CD, on IFX therapy at least 14 weeks	≥5µg/mL (ELISA)	Clinical response/ remission (CDAI)

ATI, Antibodies to infliximab; **CRP**, C reactive peptide; **ELISA,** enzyme-linked immunosorbent assay; **CD**, Crohn's disease; **CDAI**, Crohn's disease activity index; **HBI**, Harvey Bradshaw Index; **HMSA**, homogeneous mobility shift assay; **IBD**, inflammatory bowel disease; **IFX**, infliximab; **RCT**, randomised controlled trial; **RIA**, radio-immunoassay; **SES-CD**, simplified endoscopic activity score for Crohn's disease; **UC**, ulcerative colitis;

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Table 5: Studies defining a steady state therapeutic trough cut-off or range for adalimumab in luminal IBD

Study name	Study type	Population	Therapeutic cut-off or range (assay type)	Endpoints
Chaparro et al. 2016[147]	Prospective cross-sectional	N=26, IBD patients on ADA maintenance	≥9.1µg/mL (ELISA)	Mucosal healing
Chiu et al. 2013[138]	Cross-sectional study (post hoc analysis)	N=275, CD, levels at week 4,24 and 56 post ADA initiation	Cut-off not identified as considerable overlap (ELISA)	Clinical remission or response (CDAI)
Echarri et al. 2014[119]	Prospective cohort study	N=17, CD, ADA trough at week 14 post initiation	>4.5 /mL (ELISA)	Good response (not defined) and remission (HBI <5)
Imaeda et al. 2014[139]	Cross-sectional study	N=40, CD, on ADA maintenance	≥5.9µg/mL (ELISA)	Undetectable CRP (≤0.3mg/dL)
Mazor et al. 2014[140]	Cross-sectional study	N=71, CD, on ADA maintenance	>5.85µg/mL (ELISA, drug-tolerant)	Remission (physician global

				assessment) and CRP normal
Roblin et al. 2014[142]	Cross-sectional study	N=40, IBD, maintenance therapy	≥4.9µg/mL (ELISA)	Mucosal healing (endoscopic Mayo score for UC, no ulceration for CD)
Roblin et al. 2014[83]	Prospective cohort study	N=82, IBD (55% CD, 45% UC), secondary loss of response to ADA	>4.9µg/mL (ELISA)	Response to dose escalation
Sharma et al. 2015[143]	Cross-sectional study	N=192, Paediatric CD, at weeks 26 and 52 following ADA initiation	≥3.6µg/mL (ELISA) ≥5.3µg/mL (ELISA)	Clinical remission at week 26 (PCDAI ≤10) Clinical remission at week 52 (PCDAI ≤10)
Ungar et al. 2016[124]	Retrospective cross-sectional study	N=67, IBD, ADA maintenance treatment	7 – 12µg/mL range (ELISA, drug tolerant)	Mucosal healing (SES-CD or Mayo score)

Velayos et al. 2013[144]	Cross-sectional study	N=54, IBD (52 CD, 2 UC), ADA maintenance treatment	>5µg/mL (HMSA)	CRP normalisation and remission/ response (self reported questionnaire)
Ward et al. 2013[149]	Cross-sectional study	N=31, IBD (27 CD, 3 IBDU, 1 UC), ADA maintenance treatment	≥4.9µg/mL (ELISA)	Clinical remission
Yanai et al. 2015[82]	Retrospective cohort study	N=142, IBD patients with secondary loss of response to ADA	>4.5µg/mL (ELISA)	Failure to respond to dose escalation
Yarur et al. 2013[145]	Cross-sectional study	N=66, IBD (59 CD, 7 UC), maintenance treatment	>5µg/mL (HMSA)	CRP normalisation (level not specified)
Yarur et al. 2016[146]	Cross-sectional study	N=66, IBD on maintenance ADA	≥7.5µg/mL (HMSA)	Endoscopic remission (no inflammatory findings on endoscopy)

			≥7.8µg/mL (HMSA)	Histological remission (no inflammation on biopsies)

ADA, adalimumab; **ATA**, antibodies to adalimumab; **CD,** Crohn's disease; **CDAI**, Crohn's disease activity index; **CRP**, C reactive peptide; **ELISA,** enzyme-linked immunosorbent assay; **HBI**, Harvey Bradshaw Index; **HMSA**, homogeneous mobility shift assay; **IBD**, inflammatory bowel disease; **IBDU,** IBD-unclassified; **PCDAI**, paediatric Crohn's disease activity index; **SES-CD**, simplified endoscopic activity score for Crohn's disease; **UC**, ulcerative colitis

Table 6: Nominated panel members

Name of nominee	Initials	Occupation	Place of practice	Accepted/ declined nomination
Prof Rupert Leong	RL	Gastroenterologist	Australia, NSW	Accepted
A/ Prof Susan Connor	SC	Gastroenterologist	Australia, NSW	Accepted
Dr Simon Ghaly	SG	Gastroenterologist	Australia, NSW	Accepted
Prof Michael Grimm	MG	Gastroenterologist	Australia, NSW	Accepted
A/Prof Daniel Lemberg	DL	Paediatric gastroenterologist	Australia, NSW	Accepted
Dr Viraj Kariyawasam	VK	Gastroenterologist	Australia, NSW	Accepted
Dr Crispin Corte	CC	Gastroenterologist	Australia, NSW	Accepted
Dr Nikola Mitrev	NM	IBD research registrar	Australia, NSW	Accepted
Dr Greg Moore	GM	Gastroenterologist	Australia, VIC	Accepted
Dr Mark Ward	MW	Gastroenterologist	Australia, VIC	Accepted
Prof Peter Gibson	PG	Gastroenterologist	Australia, VIC	Declined

Dr Miles Sparrow	MS	Gastroenterologist	Australia, VIC	Accepted
Dr Daniel van Langenberg	DVL	Gastroenterologist	Australia, VIC	Accepted
A/Prof Peter Lewindon	PL	Paediatric gastroenterologist	Australia, QLD	Accepted
Dr Jakob Begun	JB	Gastroenterologist	Australia, QLD	Accepted
A/Prof Graham Radford-Smith	GRS	Gastroenterologist	Australia, QLD	Accepted
Prof Jane M. Andrews	JMA	Gastroenterologist	Australia, SA	Accepted
Dr Robert Bryant	RB	Gastroenterologist	Australia, SA	Accepted
Dr Reme Mountifield	RM	Gastroenterologist	Australia, SA	Accepted
Dr Kannan Venugopal	KV	Gastroenterologist	Australia, WA	Accepted
A/Prof Cynthia Seow	CS	Gastroenterologist	Canada	Accepted
Prof Murray Barclay	MB	Gastroenterologist	New Zealand	Accepted

Dr Niels Vande Casteele	NVC	Clinical pharmacologist	United States of America, California	Accepted
Prof Jennifer Martin	JM	Clinical pharmacologist	Australia, NSW	Accepted
Peter Slobodian	PS	Clinical pharmacist	Australia, NSW	Accepted
Dr Catherine Toong	CT	Immunologist	Australia, NSW	Accepted

Table 7: Papers and abstracts sent to panel members following the second round of voting

Reference	**Predetermined clinical question addressed by article** (Table 2, Methods, for questions)
Adedokun et al. 2014[118]	1
Adendokun et al. 2016[214]	8
Afif et al. 2010[200]	4,6,7
Allgretti et al. 2016[218]	5,6,7
Amin et al. 2016[99]	7
Amiot et al. 2016[101]	5, 6, 7
Arias et al. 2016[174]	1
Armuzzi et al. 2014[104]	6, 7
Baert et al. 2003[14]	2
Baert et al. 2014[197]	2
Baert et al. 2015[97]	1
Battat et al. 2016[215]	8
Ben-Bassat et al. 2013[127]	1,2
Ben-Horin et al. 2013[203]	4, 6, 7

Ben-Horin et al. 2015[219]	5,6,7
Bortlik et al. 2013[128]	1
Brandse et al. 2014[49]	1, 2, 7
Brandse et al. 2016[100]	2,5,6,7
Brandseet al. 2015[163]	7
Bressler et al. 2015[244]	4
Chaparro et al. 2016[147]	1
Chiu et al. 2013[138]	1
Connor 2016[228]	2, 6, 7
Cornillie et al. 2014[98]	1, 2, 6, 7
Dalal et al. 2015[227]	4
Davidov et al. 2016[185]	1
D'Haens et al. 2016[103]	5,6,7
Ding et al. 2015[41]	2, 6, 7
Drobne et al. 2011[129]	1
Drobne et al. 2016[135]	1
Echarri et al. 2014[119]	1
Eser et al. 2013[152]	1, 2, 5, 6, 7

Fegan et al. 2012[80]	1
Feurestein et al. 2015 [196]	2
Flamant et al. 2015[220]	5, 6, 7
Gibson et al. 2015[106]	7
Gils et al. 2014[78]	3
Gils et al. 2016[86]	3
Gisbert et al 2016[222]	5,6,7
Glovics et al. 2016[171]	2,3, 6
Guidi et al. 2016[250]	4,6,7
Guiotto et al. 2016[73]	2, 3
Halpin et al. 2012[233]	6
Hibi et al 2012[137]	1
Huang et al. 2015[130]	1
Imaeda et al. 2014[139]	1
Karmiris et al. 2009[208]	2
Katz et al. 2012[249]	4,6,7
Khanna et al. 2013[229]	2, 6, 7
Klotz et al. 2007[155]	6

Kobayashi et al. 2016[254]	7
Lallemand et al. 2011[69]	3
Lamblin et al. 2012[120]	1
Leclerc et al. 2014[207]	2
Lee et al. 2016[247]	4
Lee et al. 2016[77]	3
Levesque et al. 2014[121]	1
Lin et al. 2014[202]	2, 6, 7
Louis et al. 2012[221]	5,6,7
Malickova et al. 2016[74]	3
Maser et al. 2006[122]	1
Mazor et al. 2014[140]	1
Melmed et al. 2016[31]	2, 6, 7
Menting et al. 2015[216]	8
Minar et al. 2016[209]	2
Moore et al. 2016[131]	1
Mosli et al. 2015[240]	4
Mostafa et al. 2013[141]	1

Nanda et al. 2013[194]	2
Nguyen et al. 2008[245]	4
Nguyen et al. 2015[93]	2,6,7
Ordas et al. 2012[153]	6
Ordas et al. 2012[255]	2, 6, 7
Osterman et al. 2016[211]	8
O'Toole et al. 2015[42]	2, 6, 7
Papamichael et al. 2015[165]	1, 2, 6, 7
Papamichael et al. 2015[182]	5,6,7
Papamichael et al. 2016[116]	1
Pariente et al. 2012[201]	1, 2
Paul et al. 2014[195]	2
Quingley et al. 2015[238]	4
Roblin et al. 2014[142]	1
Roblin et al. 2014[83]	1, 2, 4, 6, 7
Rosario et al. 2015[212]	8
Rosen et al. 2015[256]	2, 6, 7
Schmitz et al. 2015[75]	3

Scott et al. 2014[65]	3
Seow et al. 2010[123]	1
Sharma et al. 2015[143]	1
Singh et al. 2014[96]	5,6,7
Sorrentino et al. 2016[248]	2, 6, 7
Steenhold et al. 2012[206]	2
Steenholdt et al. 2011[134]	1,2
Steenholdt et al. 2012[20]	2, 5,6,7
Steenholdt et al. 2013[70]	3
Steenholdt et al. 2014[71]	3
Steenholdt et al. 2014[87]	4, 6, 7
Steenholdt et al. 2015[21]	2
Steenholdt et al. 2015[198]	2
Steenholdt et al. 2015[81]	3
Steenholdt et al. 2015[87]	4, 6, 7
Steenholdt et al. 2015[91]	4, 6, 7
Steenholdt et al. 2016[19]	2, 6, 7
Stein et al. 2016[94]	4, 5, 7

Strik et al. 2016[43]	2, 6, 7
Svenson et al. 2007[79]	3
Swoger et al. 2014[199]	1, 6
Ternant et al. 2008[154]	4, 5, 6, 7
Ungar et al. 2014[188]	2, 5, 6, 7
Ungar et al. 2016[124]	1
Ungar et al. 2016[204]	1
Van Assche et al. 2008[136]	1
van Bezooijen et al. 2016[72]	3
Van Stappen et al. 2016[67]	3
Van Stappen et al. 2016[107]	7
Vande Casteele et al. 2012[125]	1
Vande Casteele et al. 2013[175]	1, 2,5 ,6,7
Vande Casteele et al. 2014[44]	2, 6, 7
Vande Casteele et al. 2015[132]	1, 2
Vande Casteele et al. 2015[46]	2,3,5,6,7
Vande Casteele et al. 2015[102]	4, 6, 5, 7
Vaughn et al. 2014[105]	5, 6, 7

Vaughn et al. 2015[63]	3
Velayos et al. 2013[144]	1
Velayos et al. 2013[95]	4,6,7
Viola et al. 2009[210]	2
Wang et al. 2012[64]	3
Ward et al. 2013[149]	1
Ward et al. 2016[150]	1, 7
Warman et al. 2015[133]	1
Weisshof et al. 2016[257]	2
Williet et al. 2016[213]	8
Yamamotto et al. 2016[243]	4
Yanai et al. 2015[82]	1,2,4,5,6,7
Yarur 2015[45]	2, 6, 7
Yarur et al. 2013[145]	1
Yarur et al. 2016[126]	1
Yarur et al. 2016[146]	1
Yarur et al. 2016[167]	1, 4
Zittan et al. 2016[172]	1

Table 8: First draft of the consensus statements on TDM-guided anti-TNF therapy in IBD

1. Target drug trough levels
1a. In patients with luminal disease we generally recommend a steady state trough infliximab level between 3.8 and 8.4 µg/mL.
1b. In patients with luminal disease we generally recommend a steady state adalimumab trough level between 4.9 and 8.7 µg/mL.
1c. In certain situations higher trough levels than the above ranges may be appropriate.
2. Interpreting anti-drug antibodies
2a. When interpreting anti-drug antibodies, quantifying titres is clinically more useful than positive/ negative status.
2b. When interpreting anti-drug antibodies, repeat testing is useful to determine if antibodies are transient or persistent before acting on a result, particularly for patients that meet criteria for clinical remission.
3. Scenarios for therapeutic drug monitoring
3a. Patients should have therapeutic drug monitoring performed when in steady state following induction therapy whether or not they achieve clinical remission.
3b. Patients with secondary loss of response at any time should have therapeutic drug monitoring performed in order to guide clinical decision making.
3c. Patients maintained in clinical remission are suggested to have periodic testing performed every one to two years.

3d. Therapeutic drug monitoring should not be performed in scenarios where results will not influence clinical decisions.
4. Interpreting drug levels in patients with confirmed active inflammatory disease
4a. Patients with confirmed active inflammatory disease and therapeutic drug trough levels (suggests pharmacodynamic failure) should be switched out-of-class.
4b. Patients with confirmed active inflammatory disease and sub-therapeutic drug trough levels & no detectable anti-drug antibodies (suggests non-immune mediated pharmacokinetic failure) should have compliance checked first, followed by dose escalation.
4c. Patients with confirmed active inflammatory disease and undetectable drug trough levels & low titres of anti-drug antibodies (suggests immune mediated pharmacokinetic failure) should have an immunomodulatory added/ optimised & anti-TNF dose escalation.
4d. Patients with confirmed active inflammatory disease and & undetectable drug trough levels & high titres of anti-drug antibodies (suggests immune mediated pharmacokinetic failure) should be switched within class.
5. Interpreting drug levels among patients in clinical remission:
5a. Patients in clinical remission and therapeutic drug trough levels should be continued on the same dose.
5b. Patients in clinical remission and with supra-therapeutic drug trough levels should be considered for dose reduction.

5c. Patients in clinical remission and with sub-therapeutic drug trough levels should be individually assessed for suitability for a drug holiday.
5d. Patients in clinical remission who are deemed not suitable for a drug holiday, and with sub-therapeutic drug trough levels & undetectable anti-drug antibodies should have dose escalation.
5e. Patients in clinical remission who are deemed not suitable for a drug holiday, and with sub-therapeutic drug trough levels & low titres of anti-drug antibodies should have an immunomodulatory added/ optimised & dose escalation.
5f. Patients in clinical remission who are deemed not suitable for a drug holiday, and with undetectable drug trough levels & high titres of anti-drug antibodies, should be switched within class.
6. General steps to take for patients with symptoms of clinically active disease on anti-TNF therapy along with therapeutic drug monitoring:
6a. Patients with clinically active disease on anti-TNF therapy should have active inflammatory disease confirmed via objective measures (endoscopy, radiology and/or biochemistry).
6b. Patients with clinically active disease on anti-TNF therapy should have investigations to exclude other causes of symptoms along with therapeutic drug monitoring.
6c. Patients with confirmed active inflammatory disease on anti-TNF therapy should have other IBD treatments optimised along with performing therapeutic drug monitoring.
7. Standards for therapeutic drug monitoring

7. We recommend the use of a drug-tolerant assay over a drug sensitive assay for measurement of anti-drug antibodies.
8. TDM for non-anti-TNF biologics
8. Due to lack of evidence on appropriate troughs associated with specific endpoints for non-anti-TNF biologic agents currently used in IBD, we cannot recommend routine use of therapeutic drug monitoring to guide clinical decision making.
9. Future directions
9. Data on therapeutic drug monitoring should be available at time of registration for all future biologics.

Table 9: Final consensus on TDM-guided anti-TNF therapy in IBD following three iterations of a modified Delphi method

Statements in grey did not reach consensus.

1. Scenarios when TDM of anti-TNF agents should be performed
1a. In patients in clinical remission following anti-TNF therapy induction, TDM should be considered to guide management.
1b. Therapeutic drug monitoring can inform clinical decision making in patients with primary non-response
1c. Therapeutic drug monitoring should be performed in patients with secondary loss of response to guide clinical decision making
1d. TDM should be considered periodically in patients in clinical remission if the results are likely to impact management.
1e. Patients maintained in clinical remission in whom a drug holiday is contemplated, are suggested to have therapeutic drug monitoring along with other investigations to help guide this decision
2. General approach to patients with symptoms of active disease on anti-TNF therapy
2. 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.

3. Interpreting TDM results in patients with confirmed active inflammatory disease on anti-TNF therapy
3a. Patients with confirmed active inflammatory disease and therapeutic drug trough levels (suggests pharmacodynamic failure) should be switched out-of-class.
3b. Patients with confirmed active inflammatory disease, 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. Optimization/ introduction of an immunomodulator should be considered.
3c. Patients with confirmed active inflammatory disease, 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.
3d. Patients with confirmed active inflammatory disease, undetectable drug trough levels and high titres of anti-drug antibodies (suggests immune mediated pharmacokinetic failure) should be switched within class for secondary loss of response, or alternatively switched within class or switched out-of-class for primary non-response.
4. Interpreting TDM results among patients in clinical remission on anti-TNF therapy
4a. Patients in clinical remission and therapeutic drug trough levels should be continued on the same dose.

4b. Patients in clinical remission and with supra-therapeutic drug trough levels should be considered for dose reduction.
4c. Patients in clinical remission and with sub-therapeutic drug trough levels should be individually assessed for suitability for a drug holiday (consensus not reached).
4d. Patients in clinical remission who have high risk features, sub-therapeutic drug trough levels and undetectable anti-drug antibodies should have optimization or addition of an immunomodulator and/ or dose escalation
4e. Patients in clinical remission who have high risk features, with sub-therapeutic drug trough levels and low titres of anti-drug antibodies should have an immunomodulatory added/ optimised and/ or dose escalation.
4f. Patients in clinical remission who have high risk features, with undetectable drug trough levels and persistently high titres of anti-drug antibodies, should be considered for switching within or out-of-class.
5. Target drug trough levels
5a. In patients with luminal disease we generally recommend a steady state trough infliximab level between 3 and 8µg/mL
5b. In patients with luminal disease we generally recommend a steady state adalimumab trough level between 5 and 12 µg/mL.
5c. In certain situations higher or lower trough levels than the above ranges may be appropriate.
6. Anti-drug antibodies

6a. When interpreting anti-drug antibodies, quantifying titres is clinically more useful than positive/ negative status.
6b. When interpreting anti-drug antibodies, repeat testing is useful to determine if antibodies are transient or persistent before acting on a result, particularly for patients that meet criteria for clinical remission.
6c. There is insufficient evidence to recommend a drug-tolerant assay for anti-drug antibody detection
7. TDM for non-anti-TNF biologics and future therapies
7a. There is emerging evidence that trough levels of non-anti-TNF biological agents may be relevant to clinical endpoints. However, more longitudinal data are required before routine use of therapeutic drug monitoring to guide clinical decision making on the use of non-anti-TNF biological agents.
7b. Data on therapeutic drug monitoring should be available at time of registration for all future therapies (consensus not reached).

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