

New Zealand Society of Gastroenterology Guidelines on Therapeutic Drug Monitoring in Inflammatory Bowel Disease

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ABSTRACT

The incidence of inflammatory bowel disease (IBD) in New Zealand has increased over the last several decades. The management of IBD has been transformed since the introduction of monoclonal antibody drugs. Other medications used in the treatment of IBD include amino-salicylates, steroids, thiopurines and methotrexate. Therapeutic drug monitoring (TDM) involves the measurement of serum drug levels or active metabolites and anti-drug antibodies. TDM is essential for a personalised approach to the management of patients with IBD and is used to optimise drug efficacy and reduce the risk of toxicity. In IBD, TDM can be used for checking adherence, evaluating drug toxicity, identifying hypermethylators, assessing loss of response and in decisions regarding treatment escalation or de-escalation. Management decisions in patients on a thiopurine are facilitated by checking TPMT enzyme activity and thiopurine metabolite levels. Measurement of drug trough levels and anti-drug antibodies can result in individualised treatment decisions in patients on biologics. In addition to using TDM in patients who fail therapy, proactive TDM can potentially facilitate early treatment decisions, albeit more work is needed in this area. The clinical benefits of reactive TDM are well documented and this has been shown to be cost effective. Studies have shown that combination therapy in patients on a biologic leads to better clinical outcomes. Effective use of drugs in the treatment of IBD is even more imperative in the New Zealand setting due to relatively fewer options of funded treatment, and the limitations on the use of available drugs. This document represents the current guidelines of the New Zealand Society of Gastroenterology on TDM in IBD.

The incidence of inflammatory bowel disease (IBD) in New Zealand has risen substantially in the last five decades.¹⁻⁶ IBD comprises Crohn's disease (CD) and ulcerative colitis (UC) with a small group of patients remaining unclassified (IBDU). The aetiology of IBD is unknown, however it is recognised that environmental factors play a role resulting in an abnormal host immune response to luminal antigens in a genetically susceptible host leading to sustained gastrointestinal and systemic inflammation with resultant bowel wall damage and increased risk of colorectal cancer.^{7,8} Locally effective

anti-inflammatory and systemic immunomodulating medications are typically used in the treatment of IBD. These include amino-salicylate preparations (5-ASA), corticosteroids, thiopurines, methotrexate and monoclonal antibodies.

For many years the thiopurines, azathioprine (AZA) and 6-mercaptopurine (6MP) have been the mainstay of IBD treatment in those with moderate to severe disease, to maintain remission and minimise corticosteroid use. However, many patients are either intolerant or fail to respond to these drugs.

The management of IBD has been transformed since the introduction of monoclonal antibodies or so-called biologic drugs. The two agents publicly funded in New Zealand are infliximab (Remicade®, Janssen, Auckland, New Zealand) and adalimumab (Humira®, AbbVie, Wellington, New Zealand). Both are anti-tumour necrosis factor inhibitors (anti-TNF). However, a number of monoclonal antibodies against other components of the inflammatory cascade are either in development or available for use elsewhere in the world.⁹

Therapeutic drug monitoring (TDM) involves the measurement of levels of drugs or their active metabolites in blood and can also include detection of anti-drug antibodies. TDM is fully funded in New Zealand and can guide clinicians to optimise the drug dosage regimen to increase efficacy and reduce risk of drug toxicity. TDM can also explain treatment failure at times and result in appropriate switching of drug class. Measurement of drug levels in New Zealand is routinely available for AZA, 6MP and anti-TNF drugs. Antibodies to anti-TNF drugs (anti-drug antibodies: ADA) can also be measured. TDM can be undertaken at regular intervals or in specific clinical situations, such as when the drug appears to be failing, as it is based on the understanding that there is a relationship between disease outcomes and adequate drug exposure.

Due to the limited number of biologics available in New Zealand, optimum and effective use of available drugs is of the utmost importance. The executive committee of the New Zealand Society of Gastroenterology (NZSG) identified the need for such a guideline to support clinicians in their management decisions by examining published literature regarding TDM.^{10–15} The guideline took the Australian statement as the framework and adapted this to the New Zealand setting. Literature search focused on studies published regarding treatment options in IBD (specifically infliximab and adalimumab among the biologics as these are available in New Zealand) and the effect of TDM on clinical outcomes. Conflicts of interest—if any—were disclosed by the authors, and disagreements regarding specific guidelines were resolved in light of published literature pertaining to that specific guideline. Clarification has been given in specific sections where there is a

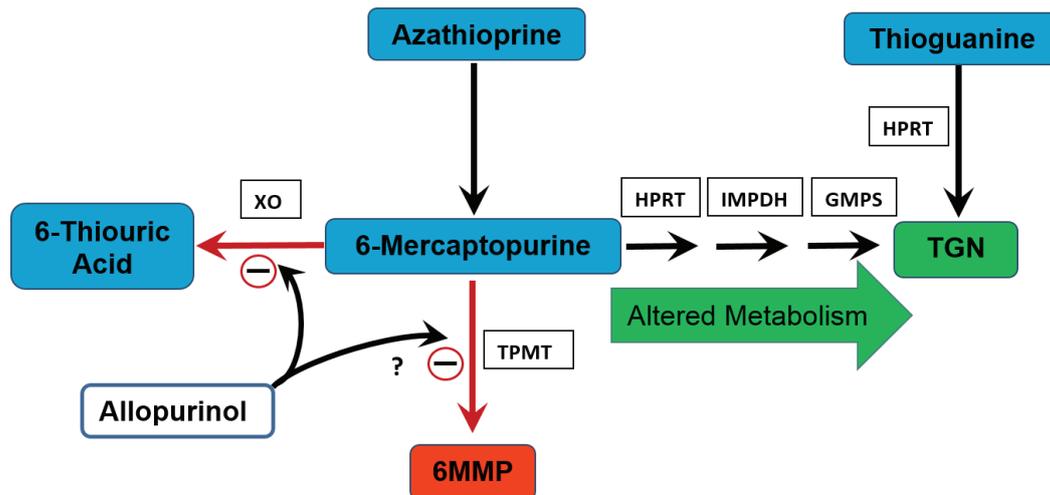
paucity of data. The authors were invited based on their expertise and include adult and paediatric gastroenterologists and a clinical pharmacologist; all with clinical and research interests in inflammatory bowel disease. Feedback was sought from the NZSG executive committee members and integrated. All authors as well as NZSG executive committee members were in agreement regarding these recommendations. These local guidelines have been developed to help the effective use of available drugs keeping in view the availability and funding setting in New Zealand.

Treatment with thiopurines

Thiopurines are thought to specifically target Rac1 activation, which is key for activating CD4-positive T-lymphocytes. The prodrug AZA is metabolised to 6-MP, another prodrug, which is then metabolized by three different pathways as shown in the abridged Figure 1. The main products of each of these three pathways are 6-thioguanine nucleotide (6TGN), 6-methylmercaptapurine (6MMP) and thiouric acid. Thiouric acid is excreted in the urine. 6TGN are the main active metabolites that are thought to be responsible for therapeutic response. Because 6TGN takes time to accumulate in cells, this contributes towards the slow therapeutic onset of thiopurines (10–12 weeks or even longer). However, adequate treatment with thiopurines has been shown to induce remission in 49% of CD and 42% of UC patients with a low rate of loss of response.¹⁶ In addition to the commonly used AZA/6MP, thioguanine (TG) is a non-conventional thiopurine that evades several intermediates in the thiopurine enzymatic pathway and is converted directly to 6TGN nucleotide.¹⁷

Thiopurine side effects can be dose-dependent or dose-independent (idiosyncratic) (Table 1). Up to 50% of individuals treated with thiopurines are reported to have side effects, but this is variable depending on the study. Cessation of thiopurines in 25.6% of patients due to adverse effects was reported in a New Zealand study.¹⁸ There are concerns regarding nodular regenerative hyperplasia (NRH) in patients on TG and the reported rates are 0 to 62%; however, the higher rates reported in earlier studies

Figure 1: Altered metabolic pathway after co-administration of allopurinol with preferential metabolism to TGNs.



Allopurinol inhibits XO and TPMT. Thiopurinomethyltransferase : TPMT. Xanthine oxidase : XO. 6MMP: 6-methyl mercaptopurine. HPRT: Hypoxanthine phosphoribosyl transferase. IMPDH: Inosine monophosphate dehydrogenase. GMPS: guanosine monophosphate synthetase. TGN: thioguanine nucleotides.

may be due to high ($\geq 40\text{mg/day}$) dosing and significant previous patient exposure to other thiopurines. Recent research shows that NRH is rare with thiopurine treatment, including TG, and that the clinical course is often benign and pathology is reversible.¹⁹

Testing for thiopurine methyltransferase (TPMT) enzyme activity is recommended in all patients commencing a thiopurine. One in every 200–300 patients have TPMT deficiency and these patients universally have severe leucopenia with standard dosing. TPMT testing and adjustment of medication dosage markedly reduces this risk. Knowledge of TPMT activity testing is also useful to establish the correct dosage in patients with intermediate or low enzyme activity.^{27,28} Good practise would be to

establish TPMT enzyme activity before initiating thiopurines, however starting at a low dose (eg, 50mg once a day of AZA or 25mg once a day of 6MP) is safe while monitoring for myelosuppression on a weekly basis until TPMT activity results are available. It is noteworthy that blood transfusion within three months prior to TPMT testing can affect TPMT activity testing.²⁹ In these patients, careful dose escalation with weekly monitoring for myelosuppression and repeat TPMT enzyme testing three months after the last transfusion is recommended. TPMT genotype testing can be done in patients with a recent blood transfusion to check their TPMT status.²⁹ However, the genotype test detects a limited number of mutations affecting enzyme activity and is not a substitute for close monitoring.³⁰

Table 1: Side effects of thiopurines.^{18,20–26}

Side-effects of thiopurines	Approximate incidence
Gastrointestinal symptoms	5–24%
Headache	1%
Fatigue or myalgias	7.1%
Allergic reactions	3–6.5%
Myelotoxicity	1.8–3.7%
Infections	1.1%
Hepatitis	3.4–8.8%
Pancreatitis	1.8–6.2%
Nodular regenerative hyperplasia	1.28–1.5% at 10 years
Lymphoproliferative disorder	Standardised incidence ratio of 5.7*
Non-melanoma skin cancer	Standardised incidence ratio of 7.0†

*The absolute risk varies between 1 in 5,000 for patients between 20–30 years old and 1 in 500 for those more than 70 years old.

†Risk increases with age, duration and ongoing use of thiopurines.

Table 2: Dosage of thiopurine depending on TPMT enzyme activity.^{106,107}

TPMT enzyme activity	AZA dose	6MP dose	TG dose
Normal	Start with normal dose (2–3mg/kg/day).	Start with normal dose (1–1.5mg/kg/day).	Start at 0.3mg/kg/day - not exceeding 25 mg/day in adults.
Intermediate	Start with 33–50% of target dose (eg, 1–1.5mg/kg/day).	Start with 33 - 50% of target dose (eg, 0.5–0.75mg/kg/day).	Start with 33–50% of target dose. Consider thrice a week dosing.
Low or absent	Start with 10% of target dose. Alternate days or thrice a week dosing is recommended.	Start with 10% of target dose. Alternate days or thrice a week dosing is recommended.	Start with 10% of target dose. Alternate days or thrice a week dosing is recommended.

Escalate the dose of AZA and 6MP as required allowing time to reach steady state before dose change (two weeks in normal and intermediate TPMT activity; and four weeks in low TPMT activity). Conversion factor of 0.5 can be used for converting AZA dosage to 6MP. TPMT: thiopurine methyltransferase. AZA: Azathioprine. 6MP: 6-mercaptopurine. TG: thioguanine.

Adequate thiopurine dosing

In the 90% of patients with normal TPMT activity, target doses will usually be in the order of 2–3mg/kg for AZA and 1–1.5mg/kg for 6MP, with dose adjustment based on thiopurine metabolite concentrations as below. Some clinicians prefer to start patients on a lower dose and increase over time in the hope of reducing the risk of toxicity and intolerance but evidence for this is poor.³¹ Treatment initiation with 33–50% of the target dose is recommended in patients with intermediate TPMT enzyme activity and at 10% of the target dose in patients with low or absent enzyme activity (Table 2).³¹ After commencing thiopurines, full blood count and liver enzymes should be checked weekly for one month, then monthly for two months and then every three months with ongoing monitoring for adverse effects.

Using thioguanine

Extensive Dutch experience has enabled the following guidelines for use of TG.³² The dose in IBD is 0.3mg/kg/day, not exceeding 25mg/day in adults, adjusted according to thiopurine metabolite concentrations. During the first year, regular blood count and liver function tests are mandatory and 6-TGN levels of 800–1200 pmol/8x10⁸ RBC should be targeted, as compared to the usual

target range of 235–450 pmol/8x10⁸ RBC with AZA or 6MP. TG should be discontinued if liver enzymes, especially alkaline phosphatase, increase two-fold, if the leukocyte count decreases below 1x10⁹/L or platelet count falls significantly. In the past, routine liver biopsies were recommended (due to fear of nodular regenerative hyperplasia). However, liver biopsies are now performed only in cases of suspected liver involvement (increased liver enzymes, decreased platelet count) and/or signs of (non-cirrhotic) portal hypertension (NCPH). As observed in the largest case series (N=111), nodular regenerative hyperplasia was not increased in TG users (6%) and was not associated with clinically relevant liver pathology.³³

Although one early study showed a high rate of nodular regenerative hyperplasia (NRH) and hepatic fibrosis with thioguanine therapy in IBD, subsequent extensive Dutch experience with TG at lower doses of around 0.3mg/kg/day has shown a low incidence of this adverse effect and no clinically significant morbidity.^{33,34} The prevalence of NCPH due to TG and conventional thiopurines is very low in the Netherlands (with over 4,000 IBD patients on TG in 2017).¹⁹ However, treatment with TG should be discontinued in cases of histological proven hepatotoxicity.

Table 3: Interpretation of thiopurine metabolite levels and recommendations for management.^{36–39}

Thiopurine metabolite levels	Interpretation	Management
Indiscernible or negligible 6TGN & 6MMP	Medication non-adherence	Check adherence and educate.
Low 6TGN Low 6MMP	Underdosing or medication non-adherence	Increase dose and monitor after checking adherence.
Low 6TGN High 6MMP (6TGN:6MMP>20)	Thiopurine hypermethylator or “shunter”	Add allopurinol and reduce thiopurine dose to 25–33%.
Normal 6TGN* 6MMP<5700 pmol/8×10 ⁸ RBC.	Adequate dosing	Continue current treatment if quiescent disease or escalate therapy if active IBD.
High 6TGN High 6MMP	Increased risk of adverse events	Decrease dose. Add another drug if active disease.

*Normal range for 6TGN is 235 to 450 pmol/8×10⁸ RBCs. 6TGN: 6-thioguanine. 6MMP: 6-methyl mercaptopurine. RBC: red blood cells. IBD: inflammatory bowel disease.

Monitoring of thiopurine metabolites

Ongoing disease activity while on a thiopurine can be due to primary non-response, loss of response, medication non-adherence, underdosing or altered metabolism with preferential production of the hepatotoxic 6MMP at the expense of low concentrations of the therapeutic 6TGN (Table 3). Underdosing and medication non-adherence are important causes of ongoing active disease in patients on thiopurines.³⁵ Active disease can be present in symptomatic as well as asymptomatic patients and should be confirmed with endoscopy, radiology or biochemical indices or a combination of these.

The correlation between weight-based dosing and 6TGN levels is not strong.⁴⁰ In addition there is ethnic variability in 6TGN levels likely due to differences in thiopurine metabolism, which is an area of ongoing research.^{41,42} Hence routine monitoring of thiopurine metabolites is now often recommended in all IBD patients whether they have active disease or are in remission, with the latter to help reduce the risk of disease flare.⁴³ Monitoring of thiopurine metabolites is also helpful in identifying underdosage, non-adherence and those with unconventional thiopurine metabolism.^{43,44} However there are no randomised controlled studies supporting routine thiopurine TDM in IBD. In patients with active IBD or those with adverse effects suspected to be secondary to thiopurine toxicity, metabolite testing

helps guide subsequent treatment decisions (Figure 2). Frequency of response to thiopurines has been shown to be around 78% in patients with 6TGN levels higher than 235 pmol/8×10⁸ RBCs and can result in steroid-free remission in approximately 65% of patients on thiopurines compared with 41% response in those with concentrations <235 pmol/8×10⁸ RBCs.⁴⁴

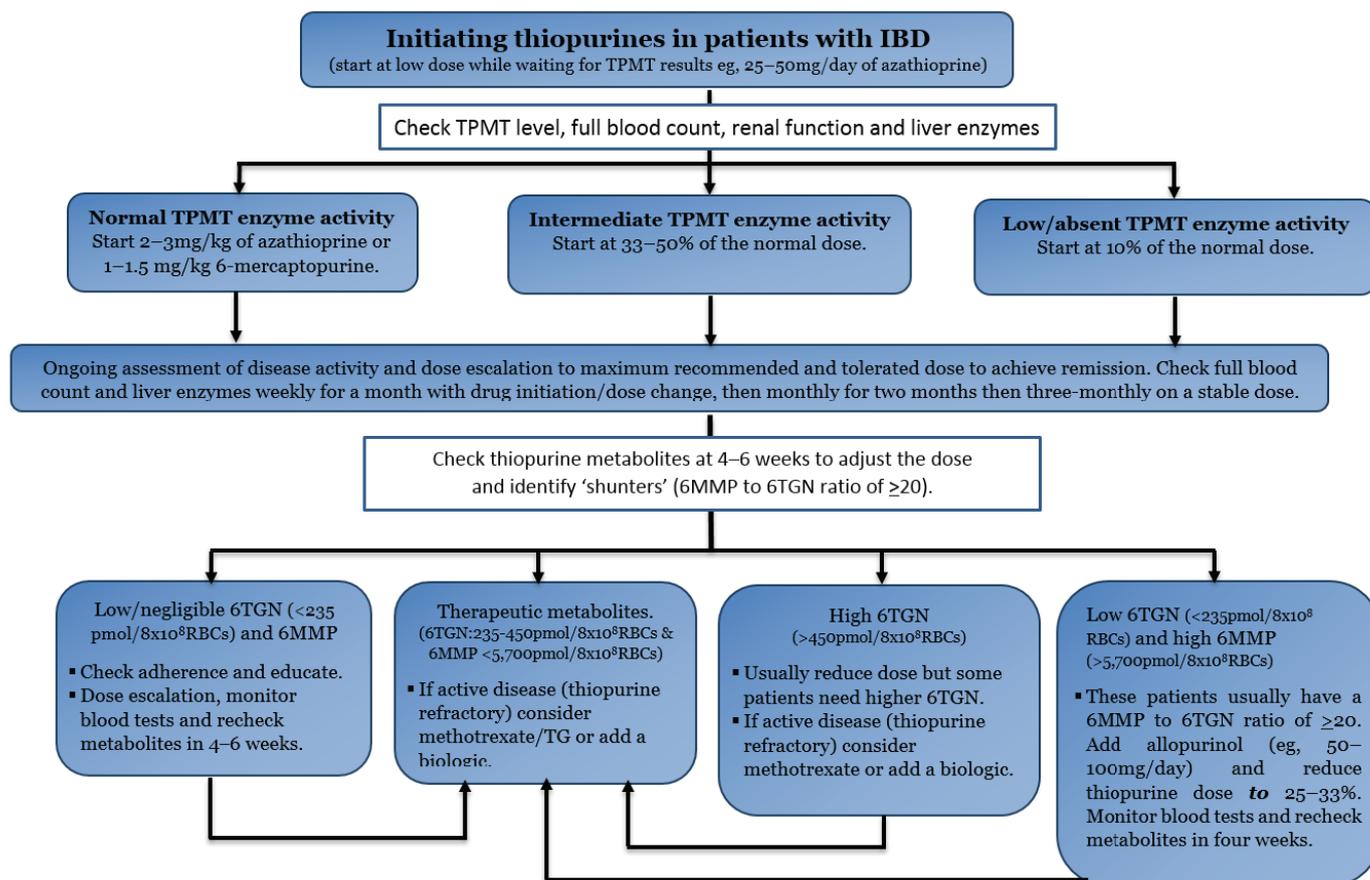
Low TGN levels indicate medication non-adherence, underdosing or thiopurine hypermethylation (Table 3). In contrast, TGN levels greater than 450 pmol/8×10⁸ RBCs are associated with a higher risk of leukopenia and myelotoxicity.⁴⁰ 6MMP is a potentially toxic metabolite and is associated with hepatotoxicity, especially at levels of greater than 5,700 pmol/8×10⁸ RBC.⁴⁵ High 6MMP has also been associated with myelotoxicity.⁴⁶

Patients who are intolerant to AZA can often be successfully switched to 6-MP or thioguanine.^{47–49} Patients can tolerate and respond to TG even if they have previously experienced pancreatitis secondary to AZA or 6-MP.⁵⁰

Thiopurine hypermethylators or ‘shunters’

About 18% of patients with normal TPMT activity can have altered drug metabolism with thiopurine hypermethylation. These patients (also known as ‘shunters’) metabolise AZA or 6-MP preferentially to the toxic metabolite 6MMP instead of 6TGN (Figure 1). Hence the level of 6TGN is low and that of

Figure 2: Algorithm for initiation and monitoring of treatment with thiopurines in patients with inflammatory bowel disease (IBD).



TPMT: thiopurine methyltransferase. 6MMP: 6-methyl mercaptopurine. 6TGN: 6-thioguanine. TG: thioguanine.

6MMP in these patients is high. These preferential 6MMP producing patients typically have a ratio of 6MMP to 6TGN of >20 .⁵¹ This ratio can be corrected by the addition of allopurinol 50–100mg daily and reduction of the thiopurine dose to 25–33% of baseline.^{52,53} For example, a 75kg patient may receive 100mg allopurinol and 50–100mg AZA. After commencement of allopurinol, it is recommended that thiopurine metabolites should be rechecked in approximately four weeks and the dose of AZA or 6-MP should be adjusted accordingly. At least fortnightly monitoring of full blood count is recommended in this interim period. There is some evidence to suggest that the mechanism for allopurinol correcting the 6TGN/6MMP ratio is via indirect inhibition of TPMT.⁵⁴

Treatment with biologics

Biologic or monoclonal antibody drugs are protein-based treatment modalities, usually IgG molecules, that bind to their antigen with high specificity. Anti-TNF α antibodies have been used in the treatment of IBD since the late 1990s and were introduced in New Zealand in the early 2000s. TNF- α is a cytokine that plays a key role in mediating inflammation in a number of autoimmune diseases. It is produced as a transmembrane molecule and after proteolytic cleavage of this molecule, the soluble TNF- α is released. Anti-TNF α antibodies prevent the interaction of TNF α with its receptor and thus inhibit its effector functions in inflammation. Infliximab is a chimeric

antibody while adalimumab is a fully humanised IgG1 kappa antibody. Infliximab and adalimumab act against transmembrane, soluble and receptor-bound TNF- α . Anti-TNF antibodies bind to TNF and form complexes. The rate and mode of clearance of these complexes is not entirely clear. At least some clearance is achieved by uptake via antigen presenting cells and this is likely to play a major role in immunogenicity and the formation of anti-drug antibodies (ADA).⁵⁵ Approximately 10–30% of patients treated with anti-TNF agents for IBD have primary non-response (14 and 12 weeks after induction with infliximab and adalimumab respectively) while secondary non-response occurs in approximately 23–46% patients by 12 months.^{56–58}

Anti-drug antibodies

ADAs can be directed against the antigen binding or Fab portion of the monoclonal antibody or against the Fc portion. Those directed against the Fab portion are likely to be neutralising antibodies as they will inhibit binding of the monoclonal antibody with its target and at the same time increase its clearance via the immune system. Antibodies directed against other portions of the monoclonal antibodies are generally not neutralising as the drug can still bind to TNF- α but the ADAs can cause increased immune-mediated drug clearance.

The results of different quantitative assays of ADAs are often not comparable and if repeated testing is required this should be undertaken using the same assay. In addition, the units of measurement used in assays are not uniform. Available reports indicate a possible different management approach to patients with low level and transient ADAs compared to those with high and sustained ADAs.^{59,60} In one cohort study, it was reported that among patients developing ADAs to infliximab, 72% had sustained ADAs while 28% had transient ADAs. Dose escalation of infliximab resulted in a response in approximately 70% patients with transient ADAs compared with just 16% with sustained ADAs ($p=0.0028$).⁶⁰ If detected on testing, consider repeating antibody titres eight weeks later, as these (especially against infliximab) can be transient and disappear on repeat testing.

However, the results of this single study need to be validated and further data is needed before repeat antibody testing is routinely recommended. Transient antibodies are not associated with loss of response to anti-TNF α agents or lack of response to dose escalation. Depending on the assay used (and hence the different units of measurement), infliximab ADA levels greater than 9.0U/ml and 9.1ug/ml have been found to be closely related (90% specific) with an unsuccessful result from dose escalation.^{60,61} In New Zealand, the ADA assay has recently been changed from an ELISA to a homogeneous mobility shift assay (HMSA), which is not drug concentration-dependent and the result will likely be reported as absent, low or high antibody titre.⁶²

Drug levels of biologics and recommendations for management

While there are no prospective randomised controlled trials showing benefit of TDM-based biologic dosing compared with clinically-based dose optimisation, TDM of biologics can be very helpful in guiding treatment especially in patients with secondary loss of response. There is a wide range of measured concentrations of these drugs and clearance is related to the severity of disease, disease phenotype, patient's body mass index and gender as well as differences in pharmacokinetics and drug clearance due to multiple mechanisms, which could be immune mediated or non-immune mediated.⁶³ These drugs are unique in that the severity of disease is strongly associated with drug clearance, hence larger doses are required in severe disease.⁶⁴ Patients with active disease on anti-TNFs can have mechanistic failure (blocking TNF is not working) or pharmacokinetic failure due to increased drug clearance, which can be immune or non-immune mediated. Consequently, patients can be divided into three groups (Table 4). Patients with mechanistic failure are not likely to benefit from other treatment options which have the same mechanism of action or are within the same class. This drug failure is likely due to the disease being driven by pro-inflammatory mediators that are not targeted by that specific drug.

Table 4: Interpretation of drug trough levels and anti-drug antibodies in patients with active IBD on anti-TNF agents.

	Drug trough levels	Anti-drug antibodies
Mechanistic failure	Acceptable	Variable
Immune-mediated pharmacokinetic failure	Low	High
Nonimmune-mediated pharmacokinetic failure	Low or absent (check drug adherence)	Undetectable

There is ongoing debate regarding proactive versus reactive TDM in patients in clinical remission. Retrospective studies have shown that proactive TDM in patients on anti-TNF agents in clinical remission result in lower hospitalisations, operative interventions, lower rates of immunogenicity and lower rates of drug discontinuation.^{69,70–72} The TAILORIX study compared proactive TDM and clinical dose escalation in patients receiving infliximab for Crohn's disease and found no difference in outcomes at one year.⁶⁹ However, a large proportion of patients in the clinical arm had dose escalation, which could have had an effect on the study results. The TAXIT study did not find a significant difference in clinical remission measured at a single point in time (at one year) between clinically-based dose changes compared to proactive TDM-based dose changes.⁷⁰ However the dosage of both groups in the TAXIT study was optimised to a target trough level based on TDM before randomisation, which could affect the primary outcome. And notably a significantly higher proportion of Crohn's disease patients attained remission after initial dose optimisation via TDM to a target trough level. In addition, the risk of disease flares in the proactive TDM group was less than those in the clinically-based dosing group. While the primary outcome of disease remission measured at a single point in time was not met in this trial, significant information was gained regarding the benefits of proactive TDM.⁷¹ Proactive TDM in patients with IBD in remission can result in no change in dosage, dose escalation or dose de-escalation. Dose de-escalation will result in cost-savings, and patients needing dose de-escalation is not a negligible proportion as the TAXIT study showed that 26% of patients had dose de-escalation. Although currently the evidence is limited and further prospective studies

are needed, proactive TDM and individualised management of patients is logical, especially in the funding environment in New Zealand, and can help clinicians use the available drugs effectively. It has to be noted that the benefits of proactive TDM mainly come from retrospective studies and the two prospective studies regarding this had some limitations as discussed above. In patients with disease remission on an anti-TNF agent, periodic TDM is recommended, especially if it is likely to change management (Figure 3). TDM is also recommended in patients after induction as well as before drug cessation or a drug holiday.^{65,72} Currently dose escalation in certain situations for both CD and UC is funded and these guidelines should be implemented in that context. In cases of presumed disease remission and TDM indicating the need for dose escalation, a careful reassessment should be done to ensure disease remission. Undetectable or low trough levels are associated with low risk of relapse after cessation of therapy in selected patients.⁷² A steady state trough level of 3–8ug/ml and 5–12ug/ml is recommended for infliximab and adalimumab respectively. However, it is also recognised that patients with a severe disease phenotype, such as perianal or fistulising disease, may require higher concentrations. Reduction in anti-TNF α dose is recommended in patients in clinical remission who have supra-therapeutic trough levels, without any deterioration in outcomes but resulting in significantly increased cost-effectiveness.^{10,73,74}

In patients with active IBD (supported by endoscopy, radiology or biochemical indices) and suspected nonimmune-mediated pharmacokinetic failure (subtherapeutic anti-TNF drug level and negative ADA), the initial recommended step is to review medication adherence and then escalate the dose with consideration of adding an

immunomodulator (IMM)—if not already utilised.^{61,75} Repeat TDM within 4–8 weeks is recommended. Failing this, a switch within the same class (anti-TNF) or to a different class may be required. It is important to confirm active disease in symptomatic patients with relevant investigations as a significant proportion of IBD patients have symptoms due to irritable bowel syndrome (IBS). Studies show a range of prevalence of IBS in IBD patients with a pooled prevalence of 30.9%.^{76–80}

In patients with active IBD and immune-mediated pharmacokinetic failure (subtherapeutic anti-TNF drug level, positive ADA), consider rechecking ADA in eight weeks to detect transient ADA.⁶⁰ Dose escalation of anti-TNF α and IMM can be added in these patients, especially if the ADA titre is available and low.⁶¹ Transient ADA can develop randomly at any point during treatment, while persistent and clinically significant ADA usually appear during the first year of therapy.⁸¹ Changing or therapy escalation in patients with possible transient ADA should be individualised and weighed against close monitoring and repeated antibody testing depending on disease severity. In primary loss of response with immune-mediated pharmacokinetic failure, switching within the same class and addition of an IMM is recommended, especially if ADA titre is available and high.¹⁴ A drug of a different class can be used in primary non-response but currently there are no funded options available in New Zealand.⁶¹ In secondary loss of response with immune-mediated pharmacokinetic failure, switching within the same class is recommended initially along with the addition of an IMM.¹⁴ A drug of a different class can be used if there is no response to the initial switch.⁶¹

Patients have a mechanistic failure (regardless of ADA status) if they have active disease while on maintenance anti-TNF therapy with adequate drug concentrations (infliximab more than 5 μ g/ml and adalimumab more than 7.5 μ g/ml). This type of secondary loss of response has been observed in 30% of patients with IBD.^{60,61,75} Switching to a drug of a different class is recommended in these patients, as it is assumed that the inflammation in these

patients is primarily mediated by cytokine(s) not inhibited by the initial biologic. In this group of patients, addition of an immunomodulator is recommended, especially in those with ADA when switching to a different biologic.⁸² The management of these patients can be challenging due to the limitations of funded biologics in New Zealand currently. Detailed discussion regarding options including involvement in clinical trials of a different class of agent should be undertaken if available.

Ideally, samples for drug trough levels should be taken within 24 hours prior to the scheduled dose, especially for infliximab where there are large differences in concentration over the eight-week dosing interval. This is a little less critical for adalimumab where there is only about a 50% difference between peak and trough concentrations over the two-week dose interval.

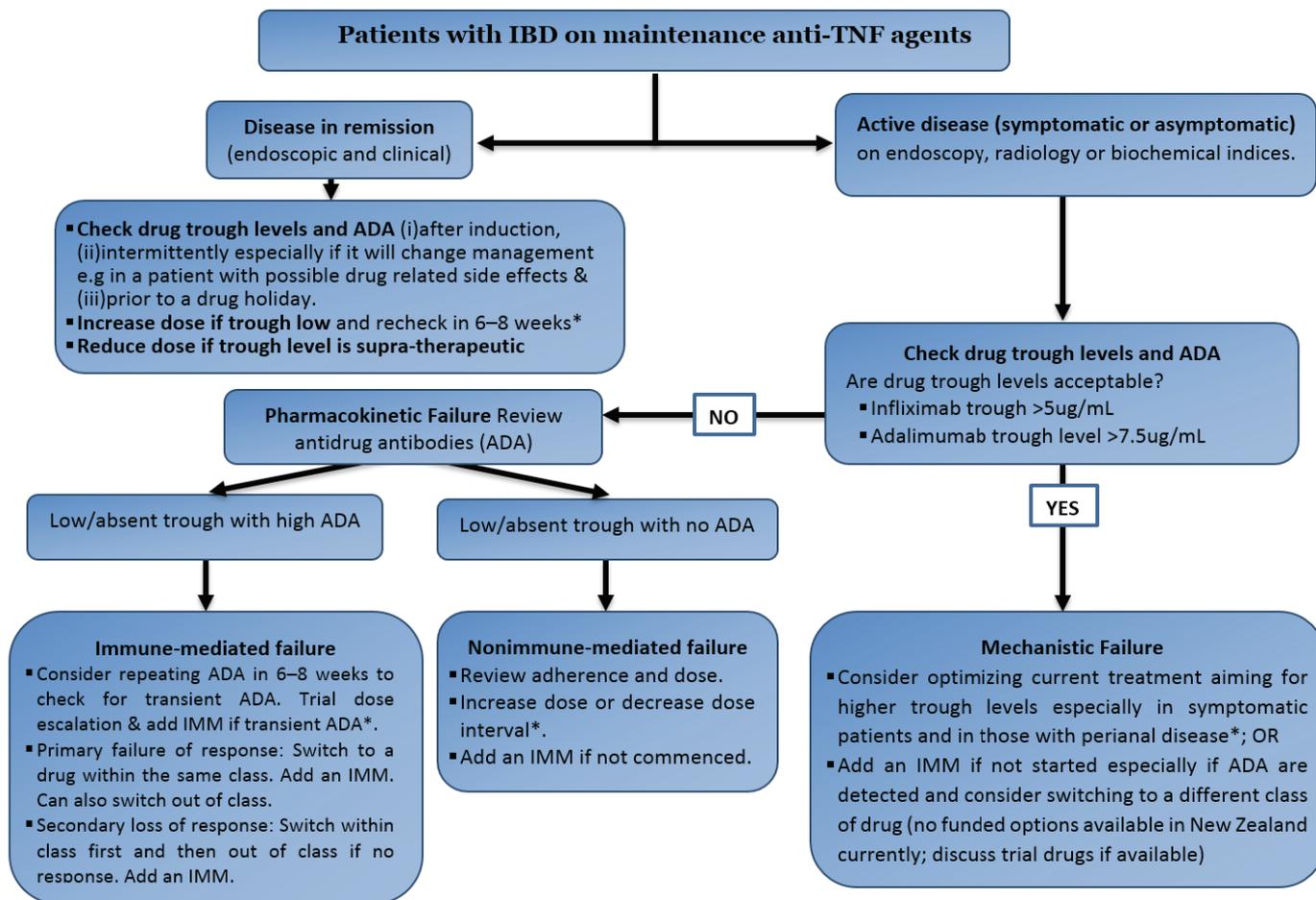
It is important to note that dose escalation of infliximab and adalimumab should ideally be continued based on TDM, however, there are limitations on funded dose escalations. Dose escalation of infliximab to 10mg/kg every eight weeks for three doses or equivalent is currently funded.⁸³ A second re-induction of infliximab can be done 16 weeks after the first one. For adalimumab, a maintenance dose of 40mg every two weeks is currently funded.⁸⁴ Increasing dosage or shortening dosage interval is currently not funded and additional doses can be negotiated with the pharmaceutical company on a case by case basis.

Testing assays

Multiple assays are available currently for testing the concentration of drugs as well as the titres of anti-drug antibodies. There is some consensus and agreement among different assays available for testing infliximab trough levels.⁸⁵ However, there is more variability among different assays for measurement of the trough levels of adalimumab.⁸⁶

ADA detection can be affected by the presence of the drug when using drug-sensitive assays like enzyme-linked immunosorbent assays (ELISA) or radioimmunoassays (RIA).⁸⁷ Drug-tolerant assays like the electrochemiluminescence and HMSA assays are more resistant to this effect

Figure 3: Algorithm for therapeutic drug monitoring and management of patients with inflammatory bowel disease (IBD) on anti-TNF agents.



ADA: anti-drug antibodies. IMM: immunomodulator.

* Dose escalation of infliximab to 10mg/kg every eight weeks for three doses or equivalent is currently funded. Dose escalation of adalimumab is not funded but can be negotiated with the pharmaceutical company on a case-by-case basis.

compared with an ELISA. The HMSA assay will detect antibodies in more patients and will ultimately provide better information for clinicians.

One of the important aspects of TDM is the timing of results once testing is done. In the current setting results are not available immediately and any dose optimisation based on TDM can be delayed. Point-of-care testing provides an opportunity to have TDM results immediately available and acted upon.^{88,89} No data from large prospective studies regarding point-of-care testing is available at present.

Combination therapy

Combination therapy with an IMM (thiopurine or methotrexate) and a biologic results in a significantly higher rate of steroid free remission and mucosal healing; and lower rates of secondary loss of response.⁹⁰⁻⁹² Combination therapy results in higher biologic concentrations, at least in part due to a significantly lower rate of formation of ADA as well as a lower titre of ADA if formed.^{13,90} In patients on biologic monotherapy, the addition of an IMM can result in improving response to the biologic by reducing or eliminating ADAs.⁹⁰ There is

no increased risk of infection with combination therapy.⁹³ Patients being treated with adalimumab have a lower rate of developing ADA compared to those on infliximab.^{94,95} Combination treatment with adalimumab and an IMM leads to increased biologic drug concentrations and lowers immunogenicity, but increased clinical efficacy has not yet been determined.⁹⁵

In patients being started on infliximab, combination therapy with an IMM is recommended. There is data showing that low-dose AZA is sufficient to achieve the immunologic benefits of preventing antibody formation in combination therapy.⁹⁶ Data regarding a lower dose of IMM in combination therapy is not conclusive, and monitoring of thiopurine metabolites is still useful in cases of treatment failure, monitoring of treatment adherence, detecting hypermethylators ('shunters') and investigating drug toxicities.

It has been shown that adding a thiopurine to a biologic is beneficial in preventing the formation of ADA even in patients with no previous response to a thiopurine.⁹⁷ The optimum treatment duration of an IMM in combination with a biologic for the prevention of ADA is yet to be determined but continuing the IMM or biologic (in combination therapy) for one year is recommended, keeping in view the possible risks of combination therapy and the clinical benefits.¹³ The small increased risk of malignancy with combination therapy (while using a biologic and/or a thiopurine) should be considered when continuing treatment beyond one year.^{13,98}

Methotrexate can be added to a biologic instead of a thiopurine in cases of intolerance to thiopurines. There is currently no consensus about the optimal dose of methotrexate in this setting. Further studies are ongoing in this area, including the COMBINE study (Clinical Outcomes of Methotrexate Binary treatment with INfliximab or adalimumab in practiceE).⁹⁹

The use of combination therapy is also important in children and adolescents, as discussed in a recent clinical report.¹⁰⁰

However, aspects such as age and gender, and the consideration of EBV testing in adolescence require an individualised approach in the paediatric population. Combination therapy could be initiated early in patients with risk factors for aggressive disease in the paediatric population including older age (6–17 years old compared with younger patients), female sex, ileocolonic or ileal disease, perianal disease, fistulising disease, steroid dependence or refractoriness, previous surgery and growth failure.^{100,101}

Cost effectiveness of TDM

TDM has been shown to result in cost savings without any adverse effect on clinical outcomes in a systemic review of multiple studies involving patients with IBD and rheumatoid arthritis.¹⁰² A more recent meta-analysis supports the cost-effectiveness of TDM in IBD with the effect more evident for reactive TDM.¹⁰³ Better clinical outcome due to reactive TDM can result in fewer disease-related complications and need for surgery. Furthermore, TDM results in dose de-escalation in a number of patients resulting in cost savings. The benefits of reactive TDM are well recognised and it is currently recommended in international guidelines.^{10,12,104} There are no prospective controlled studies showing cost-effectiveness of proactive TDM, however retrospective data has suggested some benefit.¹⁰⁵ The limited options of biologics available in New Zealand for IBD can make disease treatment difficult, especially in cases of mechanistic failure of an anti-TNF agent. Additionally, consideration of surgical intervention is potentially done earlier due to limited availability of biologic drugs. Currently there is no local data regarding cost-effectiveness of TDM, however international data can be extrapolated to the scenario in New Zealand. The judicious and effective use of funded medications for IBD in New Zealand is even more important due to relatively fewer options available and the limitations on their funded use. TDM in the New Zealand setting can help clinicians get the most out of the available drugs and provide individualised care to their patients.

Conclusion

TDM is now an essential component in the management of IBD patients and the cornerstone of individualised treatment. TDM is used to optimise drug efficacy and reduce the risk of toxicity. In IBD, TDM is also indicated for checking adherence, evaluating

drug toxicity, identifying hypermethylators, assessing loss of response and in decisions regarding treatment escalation or de-escalation. In addition to using TDM in patients who fail therapy, proactive TDM can facilitate early treatment decisions and has been shown to lead to better outcomes.

Competing interests:

Dr Day reports personal fees from Abbvie and Janssen outside the submitted work.

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