REVIEW

Anti-TNF drug and antidrug antibody level monitoring in IBD: a practical guide

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Received 25 September 2014

Revised 11 December 2014

Accepted 16 December 2014

Published Online First

21 January 2015

ABSTRACT

The antitumour necrosis factor (TNF) medications, adalimumab and infliximab, play an important role in the management of both Crohn's disease and ulcerative colitis. For those in whom anti-TNF is effective, the therapy is associated with fewer symptoms, improved quality of life and disease and surgery-free survival. Unfortunately, up to 30% of patients will fail to respond to anti-TNF drugs while up to 50% of those who do see an initial response will lose response at some point. The introduction of drug monitoring for anti-TNFs, including drug level and antidrug antibody level testing allows a more personalised management of patients and improves patient outcomes. This article reviews the data for the use of anti-TNF monitoring and presents a 'how to' guide for clinicians.

INTRODUCTION

The inflammatory bowel diseases (IBD), ulcerative colitis (UC) and Crohn's disease (CD), are chronic, relapsing and remitting inflammatory conditions of multifactorial aetiology which is incompletely understood. Genetic, immunological, microbiological and environmental factors have all been implicated in their pathogenesis. There are more than 250 000 sufferers in the UK, and more than 5 000 000 people are afflicted worldwide, with an increasing incidence in developing and developed nations.¹

Treatment regimes differ between the two diseases. For UC, standard care has traditionally included mesalazines and/or corticosteroids to induce remission during acute exacerbations, and mesalazines to maintain remission. Those with more severe disease may require immunosuppressant medications (particularly mercaptopurine and its prodrug azathioprine, as well as methotrexate) to maintain remission.

For CD, it is usual to induce remission with steroids and maintain remission with immunosuppressant therapy for those who relapse off steroids. Despite these treatments, the natural history of the disease veers towards surgery, with 70% of patients with CD and 30% of patients with UC undergoing surgery at some stage.^{2,3}

The antitumour necrosis factor α (TNF α) monoclonal antibody medications adalimumab (ADA) and infliximab (IFX) are efficacious therapies for the induction and maintenance of remission of moderate-to-severe CD and UC.^{4,5} Data consistently show that anti-TNF α medications reduce inflammation and promote improved quality of life and surgery-free survival.⁶

Although anti-TNFs have revolutionised the management of IBD, a number of limitations exist: first, it remains to be seen whether the decreased rates of surgery are a temporary postponement of the inevitable, or a modification of the natural history of the disease leading to long-term surgery-free remission; second, and the focus of this article, 10–30% of patients do not gain any benefit from anti-TNF therapy (primary non-responders) and up to 50% of those who do initially respond will develop loss of response (LOR) with time (secondary non-responders).⁴ While switching drug within the anti-TNF class at the point of LOR may successfully recapture remission, with only a few anti-TNF drugs licensed to treat IBD in Europe, it is desirable to optimise the use of each anti-TNF to avoid treatment failure and preserve medical options.

Until recently, the standard method of dealing with LOR to anti-TNF was to increase the dose of drug. This may be achieved by increasing dose (usually

To cite: Hendy P, Hart A, Irving P. *Frontline Gastroenterology* 2016;**7**:122–128.

doubling) or by decreasing the interval between doses and, at least for IFX, these two strategies have equivalent efficacy, with short-term success in up to two-thirds of patients for both CD and UC.^{7–9} There are, however, concerns regarding the potential increased infection risk with higher drug doses, as well as significant cost implications. For example, in the UK, the cost of a single 5 mg/kg IFX infusion for a patient weighing 75 kg is £1678 British National Formulary (BNF), or £12 584 over 12 months, excluding infusion costs. To double the dose of IFX for just three infusions costs an additional £5034. It is advantageous, therefore, to select only those patients who are likely to gain a significant clinical response.

Recently, tests for anti-TNF drug levels and antidrug antibody levels (ADAb) for both IFX and ADA have become widely available. Research has shown that anti-TNF drug levels predict clinical response (69% remission for detectable IFX compared with 15% with undetectable drug levels), and that the presence of ADAb predict low drug levels, treatment failure and infusion reactions for both UC and CD.^{10–15} Thus, there is significant interest in the use of anti-TNF drug and ADAb testing at the point of LOR to rationalise clinical decision-making.

This article discusses the ‘how, when and why’ of drug and ADAb testing in order to act as a practical guide to their use based on current knowledge.

HOW

Available assays

It is important to have an understanding of the differences between the available assays used to assess drug and ADAb levels as this will aid interpretation of test results.

ELISA

ELISA is the cheapest, most widely available and easiest to use of the assays. Most available study data are drawn from trials using the ELISA assay. Because of these attributes it is, in practice, the only commercially viable option for physicians in the UK.

The patient's serum is applied to a plate impregnated with a capture moiety. For anti-TNF α drug level testing (whether IFX or ADA) the capture moiety is usually TNF α , while for ADAb levels the capture moiety is usually the drug itself (ie, IFX is the capture moiety when assessing for antibodies to IFX and ADA is the capture moiety when testing for antibodies to ADA). IgG, bound to a colour-producing enzyme (horseradish peroxidase), is then added and binds to the complex in solution (ie, for drug level testing the complexes will be TNF α -drug, while for ADAb testing the complexes will be drug-ADA). For each complex that the IgG binds to, the linked enzyme will catalyse a colour change. Using luminosity to calculate the colour intensity, it is possible to calculate the concentration of the target molecule.

A weakness of the ELISA assay, in some laboratories, is that if the patient has circulating drug this will act as a direct competitor to the capture moiety (ie, plate-bound drug) for binding ADAb. Thus, absence of ADAb can only be reliably confirmed in the absence of detectable drug. Some laboratories are, however, able to overcome this limitation (eg, Immundiagnostik), and give reliable ADAb levels in the presence of drug.

Several CE marked commercially available ELISA kits are available in the UK as well as assays developed in-house. There are almost no data available comparing the kits.

IFX monitoring should be performed as trough levels, while ADA monitoring may be performed at any time in the drug cycle (see [table 1](#)).

It is important to be aware that although many laboratories present ADAb levels as positive or negative, this reflects ADAb levels above or below a predefined cut-off determined by their clinical relevance. Other laboratories give numerical results for ADAb levels. Higher ADAb levels are more likely to be associated with low drug levels and LOR. Lower ADAb levels are more likely to be ‘transient antibodies’ which may disappear on later testing and are less likely to have a clinically detrimental effect.¹²

Radioimmunoassay and homogenous mobility shift assay

Radioimmunoassay overcomes the problem of false-positive ADAb tests in the presence of detectable drug level by using liquid chromatography. The chromatography channels are lined with antihuman γ light chains which will bind to the ADAb, but not to the drug itself (which is comprised of κ light chains). Homogenous mobility shift assay is another fluid phase test capable of detecting ADAb in the presence of circulating drug. Both of these tests are limited by availability and cost, and in fact ELISA has been shown to be at least as good as these more expensive techniques at detecting ADAb in the absence of drug which probably represents the most important clinical scenario. Where drug and ADAb levels are available in the UK it is usually an ELISA test assay which will be used.

WHEN AND WHY

This section (summarised in [table 3](#)) covers the different clinical scenarios in which drug level monitoring may be undertaken. Evidence levels for the

Table 1 The timing of drug and antidrug antibody (ADAb) testing related to the stage of the treatment cycle

Drug	When to test	Rationale for timing
Infliximab	Trough level—ideally immediately before the next dose is due	Optimises detection of ADAb. Majority of published data relate to trough levels
Adalimumab	Any time—not necessary to perform trough levels	The every other week regime, and bioavailability from subcutaneous administration give a more steady level

recommendations given are provided (Oxford Centre for Evidence-based Medicine—Levels of Evidence (March 2009)).

LOR—✓ PERFORM (evidence level 1B)

The use of drug and ADAb levels can help establish aetiology of LOR and hence guide appropriate onward therapy. Testing drug and ADAb levels in this scenario has been shown to be both clinically useful and economically advantageous.^{16 17} When a patient on anti-TNF therapy develops symptoms, it is important first to establish that the symptoms are caused by active inflammation, rather than non-inflammatory conditions such as irritable bowel syndrome, small intestinal bacterial overgrowth or bile salt malabsorption (see [figure 1](#)). Assessment of disease activity with blood and/or faecal inflammatory markers together with endoscopic and radiological evaluation is mandatory when LOR is suspected.

Once inflammatory LOR has been confirmed, drug and ADAb levels should be assessed. Patients found to have subtherapeutic drug levels in the presence of positive ADAb have probably developed immunogenicity to the anti-TNF, suggesting that the most effective next step is to switch to a different anti-TNF (see [table 2](#)). Another option is to add an immunomodulator (IM) if the patient is on monotherapy, as this can sometimes make the antibodies disappear. If the patient is already on an IM, there is anecdotal evidence to suggest that changing the IM can also be effective. For patients on thiopurine therapy, therapeutic thiopurine metabolite levels should be targeted as this has been shown to promote primary response and maintenance of response (abstract 343 DDW

2014). These strategies may be particularly important if the patient is already on their second anti-TNF.¹⁸ Those patients with low anti-TNF drug levels and absent ADAb have non-immune mediated LOR and should receive dose escalation of anti-TNF, which is effective in up to 85% of patients with IBD on IFX and 67% on ADA (in contrast to the 21% and 12% with positive ADAb who benefit from dose escalation while on IFX and ADA, respectively).^{19 20}

Patients with active disease and therapeutic drug levels do not respond well to dose escalation or switching within class, as their levels are already optimal and their disease is not fully anti-TNF responsive.¹⁹ Higher drug doses in this situation add risk without clear benefit. For such patients an individual decision should be made regarding continuation of anti-TNF therapy, based on the magnitude of ongoing response to anti-TNF therapy, alternative options available and patient preference.

It is important to note that [table 2](#) gives guidance for management at the time of LOR. The presence of ADAb in the absence of LOR to anti-TNF is more controversial; in some cases it is inappropriate to change therapy, as this may merely represent ‘transient antibodies’ which can disappear without having caused any detectable clinical effect. Alternatively, in the presence of low drug levels and high ADAb, continuing therapy may be regarded as pointless, even in a patient who is in remission.

After induction—✓ PERFORM (evidence level 2B)

Several authorities suggest monitoring drug and ADAb levels at 12–14 weeks after initiation of anti-TNF therapy.^{12 21–24} It is known that low drug levels at 14 weeks predict development of ADAb and, later, LOR.²⁵ Such patients should be followed closely and have further drug monitoring performed. As yet, however, there is no evidence to show that intervening to increase drug levels after induction improves outcome.

Patients in stable response—✓ PERFORM (evidence level 2B)

There are also data suggesting that adjusting drug dose to achieve levels within an optimal target range, even in the absence of LOR, can be clinically beneficial. The Trough level Adapted infliximab Treatment trial (TAXIT), a randomised controlled trial (RCT), studied the clinical utility of monitoring drug levels. Consecutive patients with IBD on anti-TNF received dose optimisation (either to increase or decrease drug levels) to achieve an anti-TNF drug level within 3–7 µg/mL. Dose escalation for patients with drug level <3 µg/mL resulted in a significant drop in C reactive protein (CRP) and Harvey-Bradshaw index (HBI). Dose reduction for patients with drug level >7 µg/mL did not adversely affect CRP, HBI or Mayo score but did reduce cost.^{21 26} There was no benefit in continuing to dose to target during the maintenance phase of

Figure 1 Different aetiologies of apparent LOR to anti-TNF medication (LOR, loss of response; TNF, tumour necrosis factor; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; BSM, bile salt malabsorption; SIBO, small intestinal bacterial overgrowth).

Table 2 Interpretation of drug and ADAb levels taken at LOR

	Detectable ADAb	Undetectable ADAb
Subtherapeutic drug levels	Insufficient anti-TNF bioavailability due to induced immunogenicity <i>Action</i> —Switch to a different anti-TNF ± add immunomodulator	Insufficient anti-TNF bioavailability due to non-immune mediated pharmacokinetics <i>Action</i> —Intensify anti-TNF treatment by increasing dose or decreasing frequency
Therapeutic drug levels	Consider: non-functional ADAb; false positive test <i>Actions</i> —Do not escalate dose of anti-TNF, and consider discontinuation <i>Consider</i> : alternative anti-TNF; optimise conventional immunosuppressant; glucocorticoid; surgery	Consider: inhibition of TNF- α is ineffective due to non-TNF driven disease <i>Actions</i> —Do not escalate dose of anti-TNF, and consider discontinuation <i>Review clinical condition and consider</i> : alternative anti-TNF (unlikely to be successful); alternative non-anti-TNF biological (vedolizumab) optimise conventional immunosuppressant; glucocorticoid; surgery

ADAb, antidrug antibody; LOR, loss of response; TNF, tumour necrosis factor.

the study (the primary end point) and it is, therefore, unclear how frequently testing should be performed in patients in stable response, but a pragmatic approach would be to do so once or twice a year.

In practice, it may be difficult to convince a commissioning body to fund an expensive escalation of treatment in somebody yet to develop LOR. Any business case suggesting dose modification based on drug levels in the absence of LOR must stress the significance of the cost savings made by reducing the dose for those with supraoptimal levels and by withholding drug from those patients who are responding despite having absent drug levels. In the TAXIT study, 26% of participants had dose reduction while 30% required dose escalation and so cost of therapy to the commissioning group would be neutral, even before cost savings from better disease control are factored in (not to mention improved quality of life and economic output of the patient).

Annual reassessment—✓ PERFORM (evidence level 5)

In the UK, as mandated by National Institute for Health and Care Excellence (NICE), patients on anti-TNF therapy have yearly assessment of disease activity, including a combination of clinical, radiological, endoscopic and biochemical assessments (as appropriate). These investigations help to assess whether the drug is still effective and whether it should be continued, or whether a trial of withdrawal should be considered. As part of this assessment, it is probably reasonable to check drug and ADAb levels as the results may aid the clinical decision-making, although there are no data to support this.

At the time of withdrawal—X NOT INDICATED (evidence level 2B)

Some have advocated testing drug and ADAb levels at the point of withdrawal of anti-TNF therapy to help establish whether future reintroduction might be successful and safe. However, those patients who do require further anti-TNF should have levels checked at the point of or after reinitiation (see below). Additionally, in practice we cannot predict which patients will require reinitiation, and sending levels on

those who will not be restarted on anti-TNF may be considered wasteful.²⁷

Reinduction following a drug holiday—✓/X further data required/case by case basis (evidence level 2B)

While it is known that reinduction with anti-TNF can be safe and effective following a period of discontinuation, it is worth remembering that restarting anti-TNF is associated with a significant risk of infusion reactions, and induction of ADAb is common.^{24–28} ADAb may be reduced by concomitant steroid administration, and regular, rather than ad hoc, dosing²⁹ as well as by concomitant use of IMs. Since ADAb may be predictive of infusion reactions in other circumstances, it has been suggested that performing ADAb levels prior to reinduction of anti-TNF may be useful in helping to predict both non-response (and thus allowing a different regime to be chosen) as well as infusion reactions (allowing the option of a slow infusion). However, data regarding this are conflicting. One prospective cohort study demonstrated that IFX ADAb rarely persists beyond 1 year, and that for both IFX and ADA the presence of ADAb predicts neither treatment failure nor infusion reactions.²⁷ A second prospective cohort study found that undetectable ADAb did predict a safe reinitiation of therapy.³⁰

Prior to administration of live vaccine to offspring exposed in-utero—✓ PERFORM (evidence level 5)

Both IFX and ADA are IgG1 molecules and thus readily cross the placenta, especially late in the second and during the third trimester when the transfer is by active transport. For expectant mothers with IBD, the European Crohn's and Colitis Organisation (ECCO) consensus statement recommends "timing of the last dose of anti TNF therapy should be as early in the third trimester of pregnancy as possible," to minimise placental transfer (although recent outcome data from the Pregnancy in IBD And Neonatal Outcomes (PIANO) registry are reassuring³¹). A cohort study following neonates with in utero exposure to anti-TNF demonstrated that drug is detectable in the infant (cord blood and/or peripheral blood); and, for ADA and IFX, that the infant drug level is higher than the maternal level on the day of delivery.^{32–33} Drug levels

were detected in all infants in the study (21/21), with the longest interval between last dose and delivery being 13 and 8 weeks for IFX and ADA, respectively, and with drug detectable for up to 7 months postdelivery.

Live vaccines should not be administered to neonates exposed to anti-TNF in utero for at least 6 months postpartum. There has been a case report of an infant death from disseminated 'BCG' after *Bacillus Calmette-Guérin* (BCG) vaccination following in utero IFX exposure. For those offspring exposed to anti-TNF in utero, live vaccines should be withheld until at least 6 months, at which point absence of drug can be confirmed by anti-TNF level testing. A negative level at this point would allow live vaccination to be performed, while a positive drug level should prompt further postponement of the live vaccinations until a negative test is performed. It is reasonable to test every 3 months in this situation.³⁴ The scheduled live vaccines for neonates in the UK are BCG at birth (high-risk populations) and rotavirus at 2 months (all infants).

When considering IM withdrawal—✓/X CASE BY CASE BASIS (evidence level 5)

Dual therapy with anti-TNF plus IM leads to higher anti-TNF levels than does monotherapy alone.^{35–36} However, an open label RCT, albeit likely underpowered, concluded that there is no clear benefit to continuing dual therapy beyond 6 months. Nevertheless, it was noted that patients on dual therapy had higher trough IFX levels and lower CRP. These modest benefits must be weighed against the potential adverse sequelae of combined immunosuppression.³⁷

Before considering stepping down from dual IM/anti-TNF therapy to anti-TNF monotherapy it is usual to ensure clinical remission by performing endoscopy, imaging and blood and stool markers.³⁸ It has been proposed that additionally testing anti-TNF drug and ADAb levels at this point may be beneficial in helping to predict those patients who will remain in remission after stepping down to anti-TNF monotherapy. A recent retrospective study has shown that patients with detectable anti-TNF levels at the point of step down from dual to monotherapy have a better clinical outcome than those with undetectable drug levels.³⁹ For those patients in remission, and with optimal drug levels and absent ADAb, it would be reasonable to discontinue IM. For those patients in remission, but with positive ADAb (low titres), or low drug levels, the potential risk of ADAb levels increasing in the absence of the usual suppression from the IM and impacting on drug level and disease control must be considered. Finally, in the absence of detectable drug levels, it may make more sense to consider stopping anti-TNF therapy rather than the IM. There are few data to support or refute this hypothesis, however (table 3).

Table 3 Summary of the suggested time points to perform anti-TNF drug and ADAb levels

When to perform	Yes	No	Maybe
LOR	✓		
After induction	✓		
Yearly	✓		
After drug cessation		✓	
Before reinitiation			✓
Step down from anti-TNF+IM to anti-TNF monotherapy			✓
Neonate exposed in utero prior to live vaccination	✓		

ADAb, antidrug antibody; IM, immunomodulator; LOR, loss of response; TNF, tumour necrosis factor.

THE BUSINESS CASE FOR PERFORMING ANTI-TNF AND ADAB LEVELS

The business case presenting the advantages of drug level testing over blind empirical dose escalation is a strong one. The only 'new' cost to the CCG is £45–£85 for each individual test. This cost is offset many times over by the £5034 saved for each patient able to avoid unnecessary dose escalation. A recently published Danish RCT compared standard dose escalation of anti-TNF at the point of LOR with management dictated by results of drug and ADAb levels and found that the latter were associated with significant cost savings of €3140 per patient, and a trend towards clinical superiority.¹⁶

CONCLUSIONS

Drug and ADAb monitoring for patients on anti-TNF is an emerging technique which is gaining popularity. It provides additional mechanistic information to aid

Significance of this study

What is already known on this topic

- ▶ Presence of antidrug antibody (ADAb) correlates with lower antitumour necrosis factor (TNF) levels.
- ▶ Lower drug levels predict loss of response and increased disease activity whereas higher levels predict remission.
- ▶ Patients with ADAb are unlikely to benefit from anti-TNF dose escalation.
- ▶ Measurement of drug and ADAb levels is clinically useful in patients losing response to treatment and in patients in stable remission.

What are the current knowledge gaps?

- ▶ The clinical benefit of measuring drug and ADAb levels in other clinical scenarios.
- ▶ Correlation between serum and tissue anti-TNF levels.
- ▶ Clinical relevance of 'high' anti-TNF levels.

onward management decisions at a number of different clinical junctures. The most important of these is at the point of LOR where it may help differentiate those patients who will benefit from anti-TNF dose escalation from those who would not, allowing timely and cost-effective therapy. Knowledge of the technical profile of the most widely used assay in clinical practice, the ELISA test, will help clinicians understand the limitations of the test.

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Contributors PH wrote the article. AH and PI contributed to and oversaw the article.

Competing interests None.

Provenance and peer review Not commissioned; externally peer reviewed.

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