RESEARCH

Utilisation of anti-TNF levels in a UK tertiary IBD centre

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ABSTRACT

Objective To ascertain how anti-tumour necrosis factor (TNF) drug and anti-drug antibody levels testing is used in a 'real-world' setting to optimise inflammatory bowel disease (IBD) treatment.

Design Retrospective cohort study of prospectively collected patient data.

Setting Tertiary IBD centre in London, UK.

Patients All patients at Guy's and St Thomas' Hospitals on anti-TNF who had levels measured between the start of testing in 2012 and October 2014.

Interventions Anti-TNF drug and anti-drug antibody levels as part of routine monitoring.

Main outcome measures Indication for measuring levels and changes in management made as a result of the levels.

Results 330 infliximab levels were carried out in 199 patients and 143 adalimumab levels were carried out in 103 patients. Levels were primarily done in those with evidence of loss of response; 37% of infliximab levels and 52% of adalimumab levels. Levels resulted in a change in management in 26% of patients in infliximab group and 25% of patients in adalimumab group; however, this was greater in those with loss of response, 62% and 61% respectively. Anti-drug antibodies were detected in 7% of patients.

Conclusions Our early experience has demonstrated that measuring anti-TNF drug and anti-drug antibody levels can be useful in the optimisation of IBD management. In an increasing number of patients, particularly those with evidence of loss of response, it allows early decisions to be made regarding changing therapy. It also offers the potential for significant cost-saving by preventing pointless dose escalation in the context of therapeutic levels or when high-level anti-drug antibodies are present.

INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), the two main forms of

inflammatory bowel disease (IBD), are chronic inflammatory conditions of the bowel. Thiopurines are considered the mainstay of treatment for CD and moderate-to-severe UC as steroid-sparing agents, resulting in remission rates of around 40%.¹ However, their benefits are compromised by a slow onset of action, frequent intolerance and occasionally serious side effects. Increasingly, anti-tumour necrosis factor (TNF) agents such as infliximab (IFX) and adalimumab (ADA) are being used in IBD.

The efficacy of anti-TNF agents in CD is clearly established;^{2–7} however, loss of response (LOR) occurs in up to 46% of patients within 12 months of starting therapy⁸ and then at a rate of 10%–15% per year thereafter. It is important that these therapies are optimised and therapeutic drug monitoring is an important aspect of this. For example, measurement of thioguanine nucleotide (TGN) levels to optimise thiopurine treatment has been widely adopted in the UK and has been shown to improve remission rates.⁹ Similarly, measurement of serum drug levels (DLs) for IFX and ADA along with anti-TNF antibody (ATAb) levels is becoming increasingly available. Measuring DLs has been found to guide clinical decisions to improve management in up to 73% of patients.^{10 11}

There is a growing body of evidence to support the use of anti-TNF DLs and ATAbs to optimise anti-TNF therapy.¹² In current clinical practice DLs are more commonly carried out in patients with LOR in association with active inflammation. It has also been demonstrated that performing DLs after completion of induction therapy (at weeks 12–14)^{13–16} and at annual review is beneficial.^{10 17 18} In addition, measurement may be helpful when considering the discontinuation of

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concomitant immunomodulation or considering dose reduction after previous dose escalation or considering withdrawal of anti-TNF.^{17 19}

In this paper we present a single centre, 'real-world' experience of measuring DLs and ATAb levels in patients with IBD. The aim of the study was to identify why measurement of DLs and ATAbs was performed and what subsequent changes in management it facilitated.

METHOD

Guy's and St Thomas' Hospitals is a tertiary centre looking after around 3000 patients with IBD, of whom over 600 patients are on biological therapy. At the time of the study IFX and ADA were used chiefly in patients with CD as directed by the National Institute for Health and Care Excellence guidelines²⁰ and as rescue therapy in patients with acute severe UC. All patients on biological therapy are discussed at two-monthly to four-monthly intervals in our weekly virtual biologics and immunosuppressives clinic (VBIC). DLs are now routinely carried out after standard IFX or ADA induction and at annual reassessment but were originally mainly performed in patients with LOR.

Details of all DLs and ATAb levels performed at our centre since the service began were provided by the ViaPath laboratory at Guy's and St Thomas' Hospitals, London, UK, where these are analysed. Assays were performed using LISA-Tracker (LT) DUO Kits (Theradiag, France) automated on eRobot. As with most ELISAs, ATAbs are generally unable to be detected in the presence of drug; ATAbs are detected only when the DL is <1 µg/mL. Clinical details were obtained from the records of VBIC and supplemented by the results of blood tests, faecal calprotectin, radiology and endoscopic investigations.

IFX DLs were measured at trough (the lowest level just before the next scheduled dose), whereas ADA DLs were taken at any point in the treatment cycle. The therapeutic cut-off for IFX DLs was taken as

>2 µg/mL based on data specific to this assay. The therapeutic cut-off for ADA DLs was >5 µg/mL.²¹

RESULTS

IFX drug and anti-drug antibody levels

A total of 330 DLs were measured in 199 patients from May 2012 to October 2014. The median DL was 3.2 µg/mL (IQR 1.6–5). A total of 87 DLs (26%) in combination with other markers of disease activity (patient symptom scores, blood results, faecal calprotectin, endoscopy and radiology investigations) resulted in a change in management. The most common indication for DL testing was LOR (37%) and it was for this indication that DLs contributed to the greatest proportion of changes in management (62%). Indications for performing DLs and the percentage of each indication that contributed to a change in management can be seen in [table 1](#).

Of the 87 DLs that contributed to a decision to change management, 42 (48%) had a dose increase either from 5 to 10 mg/kg eight weekly or from 5 mg/kg eight weekly to 5 mg/kg six weekly. The mean DL prior to dose escalation was 1.4 µg/mL and post-dose escalation was 3.4 µg/mL. A total of 14 patients (16%) had a decrease in their dose, from either 10 to 5 mg/kg eight weekly or from 5 mg/kg six to eight weekly. The mean DL prior to dose de-escalation was 6.1 µg/mL and post-dose de-escalation was 3.2 µg/mL. A total of 14 patients (16%) stopped IFX due to clinical remission and 17 (20%) switched to another anti-TNF due to ATAb detection or symptoms and clinical markers suggestive of LOR despite therapeutic DLs.

A breakdown of the results for each testing indication is shown in [figure 1](#).

ATAbs were detected in 22 tests (7%) from 19 patients, all of whom had undetectable DLs. The mean ATAb was 142 U/mL (range 11–200 U/mL). Six of these patients (32%) had prior exposure to IFX with a 'drug holiday' of over 6 months. The presence of ATAbs resulted in a change in management in all cases, either by switching to a different biological

Table 1 Indications for measuring DLs and the percentage of each indication that contributed to a change in management for both IFX and ADA

Indication for performing DLs	No. of IFX DLs performed (total=330)	No. of IFX DLs that contributed to a change in management (total=87)	No. of ADA DLs performed (total=143)	No. of ADA DLs that contributed to a change in management (total=36)
Loss of response	122 (37%)	54 (62%)	74 (52%)	22 (61%)
After standard induction therapy (weeks 12–14)	32 (10%)	4 (5%)	5 (3%)	1 (3%)
Annual reassessment	97 (29%)	8 (9%)	38 (27%)	2 (6%)
After a change in dose of anti-TNF	57 (17%)	12 (14%)	5 (3%)	1 (3%)
Consideration of withdrawal of anti-TNF	10 (3%)	4 (5%)	3 (2%)	1 (3%)
Consideration of dose reduction of anti-TNF	10 (3%)	5 (6%)	17 (12%)	9 (25%)
Consideration of withdrawal of concomitant immunosuppression	2 (<1%)	0	1 (<1%)	0

ADA, adalimumab; DL, drug level; IFX, infliximab; TNF, tumour necrosis factor.

Figure 1 Flow diagram showing the indications for checking infliximab (IFX) levels and subsequent change in management. ATAb, anti-tumour necrosis factor antibody; LOR, loss of response; Tx, treatment; W/d, withdrawal.

therapy or optimising concomitant immunosuppressive therapy. Eleven patients (58%) were switched to ADA, all of whom responded, with a minimum follow-up of 6 months. One patient was switched out of class to vedolizumab (which became available for routine use at the end of the study period) because of prior LOR to ADA and achieved clinical remission. Three patients stopped biological treatment, one continued on IFX at their request and one had IFX dose escalation to 10 mg/kg eight weekly, both these patients had a thiopurine added as concomitant immunomodulation.

A total of 15 patients (79%) with detectable ATAbs were taking concomitant immunomodulation (two methotrexate, 13 thiopurines), of whom 8 (53%) receiving thiopurines had sub-therapeutic TGN levels (<235 pmol/mL 8×10^8 RBC). The two patients who had a thiopurine added achieved clinical remission. In both patients the levels of ATAbs decreased and one had complete resolution of ATAb.

ADA drug and drug-antibody levels

A total of 143 DLs were measured in 103 patients from October 2012 to October 2014. The median value was 5 µg/mL (IQR 4.6–7.3). A total of 36 DLs (25%) in combination with other markers of disease activity resulted in a change in management. Again, most DLs were done in patients with LOR (52%) and it was in this indication that the DLs contributed to the greatest proportion of changes in management (61%). Other indications for testing and the percentage of each indication that contributed to a change in management can be seen in [table 1](#).

Of the 36 DLs that contributed to a decision to change management, 16 (44%) resulted in a dose increase from every other week to weekly ADA. The mean DL prior to dose escalation was 3.3 µg/mL and post-dose escalation was 7.4 µg/mL. A total of 10 patients (28%) had a decrease in their dose back to every other week ADA. The mean DL prior to dose de-escalation was 5.8 µg/mL and post-dose de-escalation was 5 µg/mL. Four (11%) stopped ADA and five (14%) switched to IFX due to ATAb detection or symptoms along with clinical markers suggestive of LOR despite therapeutic DLs. One patient (3%) had a concomitant immunomodulator started.

A breakdown of the results for each testing indication is shown in [figure 2](#).

ATAbs were detected in only two patients (1%) both with undetectable DLs. The mean ATAb was 87 U/mL (range 14–160 U/mL). One patient (14 U/mL ATAb) stopped all biological treatments due to recurrent infections and the other patient was lost to follow-up shortly after the levels were tested.

DISCUSSION

The importance of anti-TNF DLs was first highlighted in 2006 when it was identified that higher rates of clinical remission and mucosal healing were seen in patients with CD that had detectable trough levels to IFX independent of ATAb formation.²² This was demonstrated again in an acute UC cohort where undetectable DLs predicted an increased risk of colectomy.²³ It is worth noting, however, that there is significant interpatient variability in DLs²⁴ and that the lack of standardisation between different assays means

Figure 2 Flow diagram showing the indications for checking adalimumab (ADA) levels and subsequent change in management. LOR, loss of response; Tx, treatment; W/d, withdrawal.

there is a variation in the reported optimum DL related to clinical efficacy.

Trough IFX DLs of around 2–3 µg/mL have been found to be a therapeutic cut-off using a number of different assays.^{25–27} Levels below this are associated with an increased likelihood of non-response and levels above this are associated with clinical remission and sustained response to IFX.^{18 28}

In comparison with IFX, there are less data on monitoring ADA drug and ATAb levels; however, there is a growing literature on the subject. Six studies included in a meta-analysis of 536 patients with CD showed that ADA DLs were inversely related to disease activity.²⁹ Patients with DL above 4.8–5.9 µg/mL were twice as likely to be in clinical remission as those with levels below that.

ADA levels in our unit are taken at any time point during the treatment cycle due to the logistical difficulties of getting a true trough sample and the limited data to suggest that DLs vary significantly throughout the cycle.³⁰

The incidence of ATAb development in IFX has been reported to be as high as 24% and even higher in episodic treatment regimens.^{22 28} The presence of ATAbs is clinically relevant because it is associated with an increased risk of infusion reactions along with reduced response to treatment.^{22 31–34} In most ELISA assays, including the one we use, ATAbs are only detectable in the absence of drug. Thus, assays that can detect ATAbs in the presence of drug will report higher proportions of patients with ATAbs although

the significance of these antibodies in the presence of drug is less clear.

The use of concomitant immunosuppression has been shown to reduce the formation of ATAbs in IFX in a number of trials^{31–33 35} and is associated with higher trough levels.²⁷ Previously the same benefit has not been consistently demonstrated in patients on ADA,²⁹ however, a recent study does indicate that patients on combination therapy have higher DLs.³⁶ Antibodies were detected in 2.6% of patients in the initial ADA maintenance trial (CLASSIC II),³⁷ although subsequent studies describe the prevalence of antibodies as being between 0.04% and 35%.²⁹ Again, this range may in part be explained by the different assays being used. In our cohort the development of ATAbs was 7% in patients on IFX and 1% in those on ADA.

In two of our patients with low DLs and positive ATAbs, a thiopurine was started. Both had a reduction in ATAbs and one had complete resolution. This has also been reported in other retrospective cohorts.³⁸ The intensity of immunosuppression needed to prevent ATAb formation is unclear and may be lower than the accepted therapeutic range of TGN of 235–450 pmol/mL 8×10^8 RBC.³⁹ Out of 13 of our patients with antibodies who were taking thiopurines, 8 had subtherapeutic TGNs. It is also worth noting that, in general, initiating concomitant immunosuppression prior to the induction of IFX is more beneficial in reducing the risk of antibodies than once treatment is established.⁴⁰

Importantly, there is potential for significant cost-savings by using DLs and ATAbs compared with 'blind' intensification of dosing (€6038 vs €9178 in an IFX cohort $p < 0.001$).⁴¹ From our IFX cohort, blind intensification following LOR would have led to 50 patients receiving IFX dose escalation with a low likelihood of benefit but at significant cost.

There is a rationale in terms of clinical and cost benefit in measuring DLs and ATAbs in patients who have LOR, after standard induction and at annual reassessment,¹⁷ although the evidence supporting this is relatively limited at the moment. Nevertheless, in our cohort, DLs in patients experiencing LOR aided the decision to change management in over 60% of cases. In these patients we were able to make an early decision whether to escalate therapy, switch to another anti-TNF, switch out of class or optimise a concomitant immunomodulator, enabling the recapture of response in a large proportion of patients.

A number of treatment algorithms have been proposed to optimise anti-TNF treatment, based on therapeutic drug monitoring.^{10 12 42} In essence, it is recommended that patients with active disease who have low DLs with either low or absent ATAb levels should have their anti-TNF therapy intensified. It may also be appropriate to consider adding, changing or optimising concomitant immunomodulation in these patients. Patients with low DLs and high ATAb levels will normally respond to a change of drug within the class whereas those with therapeutic DLs are more likely to respond if switched out of class.

It must be acknowledged, however, that the use of DLs and ATAbs needs to be interpreted carefully in the clinical context of each patient. Indeed, the cut-offs proposed for a therapeutic level of IFX or ADA can only be viewed as a guide. The levels transfer poorly between different platforms used to measure them and a therapeutic level may vary from patient to patient, for an individual patient at different times and also in different clinical scenarios. Undoubtedly, further research is needed to clarify the role of therapeutic drug monitoring for anti-TNF therapies (and other biological treatment) in IBD.

CONCLUSION

The measurement of anti-TNF DLs and ATAbs remains an important area of interest within IBD and has the potential to significantly improve the efficacy of anti-TNF treatment. In the first 3 years that testing was available to us we carried out in excess of 330 IFX DLs and 143 ADA DLs, which aided the decision to change management in 26% of our patients on IFX and 25% of our patients on ADA. The highest proportion of levels were carried out in patients with LOR and this resulted in the greatest change in management, 62% in the IFX group and 61% in the ADA group. Our 'real world' study highlights that the measurement of DLs and ATAbs is helpful in the

optimisation of anti-TNF treatment in IBD although further research is needed before routine testing and algorithm-driven management becomes standard of care.

Significant of this study

What is already known on this topic?

- ▶ The anti-tumour necrosis factor (TNF) agents infliximab and adalimumab are increasingly being used in the treatment of Crohn's disease and ulcerative colitis.
- ▶ The majority of patients respond to induction therapy, but up to 46% of patients lose response within 12 months of starting treatment.
- ▶ Therapeutic drug monitoring by way of quantifying anti-TNF and anti-drug antibody levels has been shown to alter management of patients in up to three-quarters of cases.

What this study adds?

- ▶ In a 'real-world' setting measuring anti-TNF and anti-drug antibody levels contributed to the decision to change management in around 25% of patients but this increased to over 60% in patients with evidence of loss of response to therapy.

How might it impact on clinical practice in the foreseeable future?

- ▶ Anti-TNF levels are becoming increasingly available for use in routine clinical practice.
- ▶ Levels facilitate early decisions to be made regarding escalation or change in therapy and as a result have the potential to be cost-saving.
- ▶ Measuring levels should be considered in all patients with evidence of loss of response to anti-TNF therapy to assist in decisions regarding changes in management in this complex group of inflammatory bowel disease patients.

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Competing interests None declared.

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