UK National Survey of Gastroenterologists' attitudes and barriers toward therapeutic drug monitoring of anti-TNF therapy in inflammatory bowel disease

DOI:
10.1136/flgastro-2019-101372

Document Version
Accepted author manuscript

Introduction

The advent of anti-TNF therapy at the turn of the century has revolutionised the practice of inflammatory bowel disease (IBD). The implications of what can be achieved through abrogating immune-mediated tissue damage are significant and a better understanding of relevant outcomes, such as corticosteroid sparing, mucosal healing, reduction in hospitalisation, surgery and improvement in quality of life have re-defined our perceptions around disease control(1-4).

An appreciation of the potential disconnect between symptoms and objective measures of disease activity and evidence that uncontrolled inflammation may lead to progressive intestinal injury and irreversible bowel damage with complications has led to the concept of "treating to target" (T2T). T2T informs the early treatment of patients at high risk for disease progression, to prevent or limit intestinal injury and disability (5, 6). Resolution of symptoms and achieving mucosal healing are now key objectives of meaningful disease control(5, 7, 8). Although the therapeutic armamentarium is expanding, gastroenterologists still have a relatively limited array of biological and novel therapies to choose from, with cost-effectiveness ever more important. It is imperative, therefore, to choose wisely and optimise treatment as accurately as possible (2). The recent approval of biosimilar infliximab and adalimumab driven by the aim of lowering cost and comparable efficacy, safety and immunogenicity to the originator will improve access to these highly effective therapies(9, 10).

It is well-established that anti-TNF therapy is associated with risks of infusion reactions, immunogenicity and loss of response (11). Up to 30% of patients have a primary non-response (PNR) and up to 50% will have secondary loss of response (SLR) to anti-TNF's (12, 13). Both these, may also be influenced by low or

undetectable drug concentrations due to immune (anti-drug antibodies) and non-immune clearance, determined significantly by inflammatory burden, body weight and serum albumin among other factors(12, 14). A growing body of evidence supports the association of higher anti-TNF trough levels with objective therapeutic outcomes during maintenance therapy(15-25), but also through induction(26-29). Taken together, recognised differences in anti-TNF pharmacokinetics, that translate into pharmacodynamic effects through hard end-points such as mucosal healing and potential for treatment failure from PNR and SLR, make it clear that a “one-size fits-all” approach with fixed dosing and schedules, even if practical, is not logical.

Therapeutic drug monitoring(TDM) has been rapidly adopted for anti-TNF dose optimisation and may be defined as “drug concentration measurement with adjustment of the dose and/or dosing intervals in order to achieve and maintain serum concentration within a certain therapeutic range to optimise treatment outcomes(30-33)”. In the case of biologic therapies, anti-drug antibodies are an integral part of this assessment.

TDM is typically performed in a reactive manner wherein serum levels are checked when there is a suspicion of loss of response with confirmed active disease(15-23, 30). It has been shown to be cost-effective compared to empiric dose escalation(24, 34-36). Proactive TDM on the other hand, is performed at pre-defined time-points, irrespective of symptoms and with the aim of preventing “under-dosing” from triggering a flare of disease or indeed even to potentially de-escalate in case of “supra-therapeutic” levels(26-30). The use of TDM, at least reactively, is now supported by international IBD guidelines (31-33, 37-40).

Modern definitions of disease control involving the composite assessment of symptoms, patient reported outcomes with the 'hard' end-point of mucosal healing, make a compelling case for the optimisation of treatment using TDM, particularly when options after anti-TNF may be limited. There are limited data on attitudes, perceptions and barriers to the use of TDM with anti-TNF therapy and virtually no UK-specific data exist.

We conducted a UK nationwide survey on the use of TDM with anti-TNF therapy.

Our primary aim was to describe the proportion of gastroenterologists employing TDM, the clinical setting in which this was used and to identify barriers to the use of TDM in practice. Our secondary aim was to identify the clinical scenarios in which TDM would be used by UK gastroenterologists if all perceived barriers to TDM were removed.

Methods

Study design: A 17-question survey (appendix 1), was adapted with permission from a similar study conducted in the USA(41). This was then placed on an online survey tool. The questionnaire was approved by the Chair of the British Society of Gastroenterology (BSG) IBD section and an invitation with a link to complete the same was sent out to over 500 consultants and over 100 higher specialist trainees (Registrar/Fellow) members of the British Society of Gastroenterology between June and October 2018. A link to the questionnaire was also included in the monthly BSG e-newsletter. The invitation with a link to the questionnaire was also distributed via the Royal College of nursing IBD network to over 300 IBD clinical nurse specialists.

The study was registered with and approved by the Research and Innovation department of the Pennine Acute Hospitals NHS Trust.

Participants who did not treat patients with IBD or treating <5 IBD patients per month and/or having no patients on anti-TNF therapy every month were excluded from the study.

Demographic information sought from the participants included their age, sex , their grades (consultant, higher specialist trainee/ registrar, IBD clinical nurse specialist) number of years in practice since specialist qualification or accreditation for gastroenterology (as applicable), and place of work (district general hospital, tertiary centre, university teaching hospital and/or private practice). Additionally, information was collected from respondents regarding the proportion of patients with IBD seen in their clinical practice, numbers of patients with IBD treated personally in a one month period and numbers treated with anti-TNF therapy per month. We also sought details around the use of TDM using a Likert 5-point scales ranging from strongly agree to strongly disagree, to identify levels of agreement or disagreement with potential barriers to using TDM.

Statistical analysis: The data was analysed by using Stata v15. All variables were categorical and expressed as frequencies and percentages. Univariate logistic regressions were used to examine associations between available variables and the outcomes of interest, use of TDM and proactive TDM. Associations were reported as odds ratios, along with their 95% confidence intervals.

Results

Responses were received from 243 participants, of which 237 met inclusion criteria (six clinicians reported treating less than 5 IBD patients per month and were therefore excluded from further analysis). Baseline characteristics of all the participants are depicted in Table 1.

Table 1. Participant demographic and clinical characteristics

Participants	N=237
Gender	
Male	122 (51.5%)
Female	115 (48.5%)
Practice setting	
District General Hospital	123 (51.9%)
Tertiary Centre	41 (17.3%)
Teaching Hospital	103 (43.5%)
Private practice	9 (3.8%)
Grade	
Consultant Gastroenterologist	109 (46%)
Registrar/Fellow (Gastroenterology)	35 (14.8%)
IBD Nurse Specialist (Nurse practitioner)	93 (39.2%)
Age	
25-34	40 (16.9%)
35-44	78 (32.9%)
45-54	93 (39.2%)
55-64	22 (9.3%)

>65	4 (1.7%)
Years (post gastroenterology certification) in practice	
Still in training	30 (12.6%)
<1	9 (3.8%)
1-4	40 (16.9%)
5-9	50 (21.1%)
10-19	68 (28.7%)
>20	40 (16.9%)
% of patients with IBD in individual practice,	
<10%	2 (0.8%)
11-25%	44 (18.6%)
26-50%	51 (21.5%)
>50%	140 (59.1%)
No. of patients with IBD treated per month,	
5-10	10 (4.2%)
11-20	34 (14.3%)
20-30	30 (12.7%)
>30	163 (68.8%)
Patients treated with anti-TNF in a month,	
1-4	34 (14.3%)
5-10	59 (24.9%)

11-20	144 (60.8%)

Practice of TDM: Of all the participants included in the analysis. 96.6% (n=229/237) used TDM in their current practice. Of these 229 participants, 96.9% (n=222) used TDM for secondary loss of response (SLR); 72.5% (n=166) for primary non-response(PNR); 37.1% (n=85) used it before restarting anti-TNF therapy after a drug holiday and 54.1% (n=124) used it proactively. (Fig 1) Amongst those who performed proactive TDM, 52% (n=65) checked drug levels at least once a year. Only 36.7% (n=87) respondents worked in a Trust/practice setting, which had negotiated a free TDM package with their anti-TNF supplier.

A univariate analysis of independent factors associated with TDM suggested that clinicians working at a teaching hospital were more likely to use TDM compared to clinicians at a district general hospital (OR 2.6, 95% CI 0.71-9.8).. Clinicians practicing for >20 years were more likely to check TDM than less experienced clinicians (OR 4.1, 95% CI 0.4-41.8). Clinicians with a large volume IBD practice (>50% IBD patients per month) were more likely to check TDM than those seeing fewer IBD patients (OR 45.6, 95% CI 7.5-275). IBD clinical nurse specialists (CNS) and gastroenterology specialist registrars (SPRs) used TDM more often, when compared to consultants (OR 2.6, 95% CI 0.69-10 & OR 1.5, 95% CI 0.3-7.2 respectively) (Table 2) Proactive TDM (Table 3), was more likely to be used by clinicians working in a tertiary care setting (OR 2.25, 95% CI 0.84-6.05), clinicians managing a proportion of >50% IBD patients per month (OR 10.8, 95% CI 1.2-90)

and clinicians with 5-9 years of experience in practice (OR 2.6 & CI 1.04-6.42) and IBD CNS (OR 1.2, 95% CI 0.7-2.1).

Table 2. Univariate analysis comparing factors related to TDM use		
Variable	OR	95% CI
Practice setting		
Tertiary hospital	1	
Teaching Hospital	2.6	0.71-9.8
Private practice	0.16	0.01-1.8
Grade		
Registrar (gastroenterology)	1.5	0.3-7.2
IBD Nurse Specialist	2.6	0.7-10
Years in practice		
<1	0.83	0.07-9.1
1-4	0.52	0.12-2.2
5-9	2.53	0.4-16.1
10-19	3.41	0.5-21.5
>20	4.14	0.4-41.8
% of patients with IBD		
11-25%	7.8	1.5-41.4
26-50%	11.7	2.1-65.7
>50%	45.7	7.6-275.4

Table 3. Univariate analysis comparing factors related to proactive TDM use		
Variable	OR	95% CI
Practice setting		
Tertiary hospital	2.25	0.8-6.1
Teaching Hospital	1.1	0.61-1.9
Private practice	1.2	0.07-19.8
Grade		
Registrar (gastroenterology)	0.5	0.2-1.05
IBD Nurse Specialist	1.2	0.7-2.12
Years in practice		
<1	0.83	0.18-3.9
1-4	2.02	0.8-5.16
5-9	2.58	1.04-6.4
10-19	1.5	0.63-3.5
>20	2.13	0.83-5.5
% of patients with IBD		
11-25%	4.8	0.5-42.8
26-50%	4.5	0.5-39.5
>50%	10.8	1.3-90.3

The main barriers for TDM use reported by the respondents were time lag in receiving results (49.8%, n=118) and lack of clinical guidelines recommending TDM (46.4%, n=110). A third of the respondents (29.9%, n=71) felt that the cost of TDM was a barrier for use in their practice. Respondents mostly disagreed or strongly

disagreed that uncertainty about availability of the test in their hospital/practice (77.2%, n=183) was a barrier for TDM use. Similarly, a majority of the respondents did not consider lack of overall knowledge of TDM (70.5%, n=167), lack of knowledge on interpretation and use of TDM (70%, n=166), TDM being cumbersome and/or time consuming (68.4%, n=162) and lack of a good evidence base for use of TDM (59.5%, n=141) as barriers in its use. (Fig 2)

If all barriers to TDM use were removed, 7 out of the eight respondents currently not practicing TDM would perform it more frequently. Amongst them 85.7% (n=6) would check TDM for SLR, 71.4% (n=5) for PNR, 57.1% (n=4) when restarting after a drug holiday and 71.4% (n=5) would check it proactively. (Fig 3) 85.7% (n=6) of these would check TDM proactively at once a year if all barriers were removed.

Discussion

There is substantial variation in anti-TNF drug exposure and response to treatment, underscoring the role of treatment optimisation based on TDM. Consequently, TDM has emerged as the new standard of care for optimising anti-TNF therapy in IBD, with reactive TDM being endorsed for assessment of PNR and SLR by recent international guidelines (31, 32, 37-40, 42). There is a dearth of literature on clinicians' attitudes, perceptions and barriers to the use of anti-TNF TDM, with virtually no data from the UK(41). This is the first UK National survey on TDM among clinicians treating IBD patients with anti-TNF therapies.

We found that the majority of respondents (96.6%) reported using TDM in their practice with 96% employing TDM for assessment of SLR and 72% for PNR. This resonates with findings from a recent a US study wherein 87% of gastroenterologists

(GI's) utilised TDM for SLR and 66% for PNR respectively(41). Practice in an academic setting (teaching hospital or tertiary centre), clinicians with over 20 years' experience in treating IBD, seeing a large number of IBD patients (>50% in their practice) and seeing IBD nurse specialists was associated with greater use of TDM. In contrast, low volume IBD practice and solo private practice was associated with less TDM use.

Only 54% in comparison reported using proactive TDM which was higher than that reported in a US survey by Grossberg et al.(41). All predictors of reactive TDM held true for proactive monitoring, with the only difference being clinicians within 5-9 years of practice since speciality certification utilising it more than other subset categories. This is likely a reflection of the growing body of evidence in recent years demonstrating the merits of proactive TDM during maintenance therapy with improved outcomes(26, 28, 29, 43).The TAXIT trial demonstrated that proactive TDM was associated with less undetectable concentrations and relapse compared to clinically based dosing(26). Proactive TDM has also been associated with less treatment failure, lower rates of IBD-related hospitalisation or surgery, risks of anti-drug antibodies and serious infusion reactions as compared to reactive testing(43).Indeed, proactive TDM was also shown to be associated with longer duration of drug survival and fewer IBD-related hospitalisations compared to reactive TDM(44).Arguably, proactive TDM may be more compelling during induction when the disease may be most active and drug clearance at its highest(27, 33, 40, 45).A post-hoc analysis of the TAILORIX trial (27) demonstrated that higher infliximab concentrations were associated with early endoscopic remission at week 12(45). These data make a strong case for the use of proactive TDM, but more robust data may be needed to translate into consensus/guideline recommendation.

We explored the limitations or barriers to the wider acceptance and use of TDM. The main barriers for TDM use in our survey were time lag from serum sampling to receiving results, perceived lack of clinical guidelines recommending the use of TDM, and high cost of the test as reported in the study by Grossberg et al.(41) Furthermore, our survey respondents, who were not using TDM, would use TDM more frequently if all barriers were removed.

Our respondents (70%) did not report a lack of knowledge of TDM or its interpretation as being a limitation to its use, similar to the US survey(41). A recent UK study exploring understanding and interpretation of TDM using TDM based clinical scenarios, however, demonstrated marked heterogeneity in its practical use, understanding and interpretation(46). This makes sense when one acknowledges that TDM is a relatively newer concept albeit integrated through evidence into standard of care and that its use may still be limited by experience and awareness of various assays and the heterogeneity therein. It also makes a compelling case for a more robust approach through multidisciplinary care provided by experienced IBD clinicians. It is possible that population pharmacokinetics will identify parameters and sources of variability with dosing and enable clinicians to apply individual dosing using a dashboard system (47, 48) to calculate the exact dose a patient should receive and at what time to maintain optimal drug concentrations(47, 48). Meanwhile, “point of care” assays may be able to rapidly measure trough concentrations enabling efficacy through speedy and accurate dose optimisation (30, 49). Reassuringly, TDM has been shown to be cost-effective compared to empiric dose escalation(24, 34-36).

A major strength of our study is the inclusion of respondents with a wide variation of clinical experience, representing the “real-world” UK practice of IBD. Despite our

wide reach through national organisations only a quarter of the total membership responded reflective of most survey-based studies(41). We must acknowledge an element of selection bias as it is entirely plausible that our respondents were clinicians with a particular interest in IBD. Consequently, there may be an over-estimate of the use of TDM within this study compared with that of more “general” gastroenterologists.

In conclusion we found that TDM is already being used widely in current clinical practice in the UK, mainly in the reactive setting but over just 50% of clinicians using it proactively as well. Significant barriers to TDM use were time lag, perceived lack of clinical guidance and high cost of the test. Validation of point of care testing, lower cost assays and wider dissemination of guidance with updated recommendations to TDM use may further optimise treatment with anti-TNF therapies. Dashboard systems and novel approaches using population pharmacokinetics may serve to optimise drug exposure through predictive modelling. Finally, published literature so far only has limited data on the use of TDM in resource rich settings. Further exploration on TDM use in developing countries with limited biological choices make a compelling argument for optimisation of available therapies and is worthy of exploration. Therapeutic drug monitoring of biological therapies is a science in evolution with exciting implications for clinical research.

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