RESEARCH

Reassessment of Crohn's disease treated with at least 12 months of anti-TNF therapy: how likely is treatment withdrawal?

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ABSTRACT

Objective To assess methods of disease reassessment and rates of treatment withdrawal in patients with Crohn's disease (CD) treated with biologics and to report retrospective risk stratification for treatment withdrawal as suggested by the STORI trial in the context of this cohort.

Design A retrospective observational cohort study of all patients with CD treated with antitumour necrosis factor (anti-TNF) therapy for >12 months in 2011.

Setting Tertiary care.

Patients Patients with CD treated with anti-TNF therapy.

Main outcome measures Method and outcome of reassessment and whether patient was withdrawn from therapy; also, whether patients met low-risk criteria for withdrawal as identified by the STORI trial, and outcome of those meeting low-risk criteria.

Results 73 patients (infliximab n=48, adalimumab n=25) underwent disease reassessment. Nine patients were deemed to have achieved remission and were withdrawn from treatment: 6 (67%) maintained remission at 12 months, three patients relapsed and were successfully retreated. 52 patients had sufficient data available for STORI criteria to be applied retrospectively. 37% (19/52) fulfilled low-risk criteria for withdrawal—of these, 26% (5/19) were withdrawn from anti-TNF therapy and three had sustained clinical remission at 1 year. Reasons for non-withdrawal included ongoing endoscopic activity (n=8), radiological activity (n=2) and clinical concern due to previous disease behaviour (n=4).

Conclusions Relatively few patients were deemed in sufficient depth of remission to warrant a trial of withdrawal of anti-TNF therapy.

Many patients were not withdrawn, despite meeting STORI low-risk criteria, due to ongoing disease activity highlighting the limitations of applying such criteria in a 'real world' setting.

INTRODUCTION

Antitumour necrosis factor (anti-TNF) α antibody therapy (infliximab (IFX) and adalimumab (ADA)) is increasingly used in the management of Crohn's disease (CD). It is effective at inducing and maintaining steroid-free remission and mucosal healing (MH).^{1–3} However, anti-TNF therapy is also expensive, costing in the region of €10 000–15 000/patient/year. This represents a significant portion of the healthcare costs of patients with CD, being as high as 64% in one recent study.⁴ Constructing a robust pharmacoeconomic model of anti-TNF therapy use in CD is difficult and the cost-effectiveness of long-term treatment beyond 4 years has been questioned by some.⁵ Accordingly, in the UK, the National Institute for Health and Care Excellence (NICE) guidance (TA187) recommends that all patients have their disease reassessed on a yearly basis and those with evidence of ongoing disease continue therapy, while those in remission, although remission is not defined, should be considered for withdrawal.^{6–9}

Over recent years, treatment goals have moved towards harder endpoints of MH combined with clinical remission with the aim of altering the course of the disease and, potentially, reducing hospital admission and surgery. Although high quality evidence supporting this concept is lacking, it is biologically attractive and worthy of the investment in research

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activity it is receiving.¹⁰ However, besides the goal of 'deep remission', other important issues arise as a result, including how best to maintain remission; this is particularly pertinent in patients receiving anti-TNF therapy. Initial data from the study of infliximab discontinuation in Crohn's disease patients in stable remission on combined therapy with immunosuppressors (STORI) trial of infliximab discontinuation suggest that a small proportion of patients in clinical remission can discontinue anti-TNF therapy with a low likelihood of relapse.¹¹

In every day practice, little is known about the factors permitting successful withdrawal of anti-TNF therapy. NICE mandates yearly reassessment of patients on anti-TNF therapy, which results in collection of informative data and creates a useful resource with which to study anti-TNF therapy withdrawal. In this paper, we describe a tertiary referral experience of yearly disease reassessment and the numbers of patients suitable for anti-TNF therapy discontinuation, and the factors leading to discontinuation or continuation of therapy in suitable patients. In addition, we use this opportunity to assess the proportion of our heterogeneous cohort of patients assessed to be at low chance of relapse using parameters derived from the STORI trial (table 1). Finally, we report the results of withdrawal of treatment in the patients who discontinued anti-TNF therapy.

METHODS

Setting and case identification

Guy's and St Thomas' Hospitals NHS Foundation Trust, London, is a tertiary referral centre providing a specialist inflammatory bowel disease (IBD) service with a multidisciplinary virtual biologics clinic forming the basis of follow-up of patients treated with anti-TNF therapy.¹² Disease reassessment was individualised according to clinical assessment, patient wishes, and previous disease course and was agreed by the multidisciplinary team.

We identified all patients with CD treated with anti-TNF therapy from departmental databases. Retrospective case note review was performed and

patients were included if they had received biological therapy for at least 12 months by 31 December 2011 and were re-evaluated in 2011. Age, gender, duration of treatment and disease phenotype at diagnosis (Montreal classification) were recorded.¹³ Patients who moved out of area in 2011, prior to their reassessment date, were excluded.

Definition of reassessment

Reassessment was defined as having undergone one or more of the following investigations aimed at assessing disease activity: endoscopy, examination under anaesthesia (EUA) of rectal and/or perianal CD, small bowel or fistula protocol MRI, or faecal calprotectin (FC) testing.

Endoscopy

Endoscopic findings were recorded as MH, inflammation $\pm$ aphthous or superficial ulceration, or inflammation with deep ulceration. Formal scoring was not possible in view of the retrospective nature of the study as scoring systems are not used in our routine practice.

Magnetic resonance enterography

Small bowel disease was assessed by magnetic resonance enterography (MRE) using an activity score based on that of Girometti *et al*,¹⁴ taking into account the following parameters: bowel wall thickness, relative mural enhancement and motility.¹⁵ Disease activity was classified into four different categories as follows: A1=Inactive (0–2), A2=Mild activity (3–6), A3=Moderate activity (7–9) and A4=Severe activity (10–12).

Assessment of perianal disease: pelvic MRI and EUA

Pelvic MRI results were reviewed and disease activity was noted as ongoing (ie, unchanged or worse activity), improved or resolved. For EUA, findings were also recorded as ongoing, improved or resolved.

Other parameters

White cell count, CRP and haemoglobin at time of reassessment were available for all patients and recorded. Where performed, FC was recorded.

Definition of remission

Decisions on continuation or withdrawal of therapy were taken on clinical grounds, in accordance with NICE guidance, at the time of reassessment by the multi-disciplinary IBD team. The accepted definition of remission in the clinical setting was if, of the investigations undertaken, MH was present on endoscopy, MRE was scored as A1, fistula resolution was demonstrated on pelvic MRI and/or EUA, FC <80 μ g/g and CRP <5 mg/L. For the purposes of this study, we also retrospectively applied STORI criteria to identify which patients were at low risk of relapse (score ≤ 2) (table 1).¹¹

Table 1 High-risk groups for withdrawal of antitumour necrosis factor therapy (adapted from STORI trial¹¹)

Risk factor	Score
Male sex	1
No previous surgical resection	1
Leucocyte count $\geq 6 \times 10^9/L$	1
Hb ≤ 14.5 g/dL	1
FC ≥ 300 μ g/g	1
CRP ≥ 5	1
Score ≤ 2 associated with 15% risk of relapse at 1 year	

CRP, C-reactive protein; FC, faecal calprotectin; Hb, haemoglobin; STORI, study of infliximab discontinuation in Crohn's disease patients in stable remission on combined therapy with immunosuppressors.

Statistics

Statistics were performed using Fisher's exact test in SPSS V.21.

RESULTS

Group characteristics

A total of 91 patients fulfilled the inclusion criteria (IFX $n=55$, ADA $n=36$) and 80% (73/91) had their disease reassessed (48 IFX, 25 ADA) (table 2). The median time on anti-TNF therapy was 25 months (range 12–108) and most patients (62/73) were treated with concomitant immunomodulation. The majority of the patients

Table 2 Demographic details, disease activity scores and inflammatory markers of patients reassessed after 1 year of antitumour necrosis factor (anti-TNF) therapy

Sex (M:F)	40:33	
Age: years (median (range))	32	(17–61)
Time on anti-TNF therapy at reassessment: months (median (IQR))	25	(19–35)
Treatment:		
Anti-TNF therapy		
Infliximab to adalimumab	48:25	
Concomitant immunosuppression (n (%))		
Azathioprine	41	(56)
Mercaptopurine	12	(16)
Methotrexate	6	(8)
Tioguanine	2	(3)
Mycophenolate mofetil	1	(1)
None	11	(15)
Disease distribution: Montreal classification (n (%))		
Location		
L1	10	(14)
L2	18	(25)
L3	38	(52)
L1+L4	3	(4)
L2+L4	0	(0)
L3+L4	4	(5)
B1	14	(19)
B1p	17	(23)
B2	24	(32)
B2p	10	(14)
B3	6	(8)
B3p	2	(3)
Harvey Bradshaw Index (n=48) (median (IQR))	3	(2–6)
Previous resection, n (%)	37	(51)
Laboratory results (data available for all patients except FC; n=22) (median (IQR))		
Haemoglobin g/dL	13.4	(12.4–14.4)
White cell count $\times 10^9/L$	5.7	(4.4–7.1)
CRP mg/L	<5	(<5–5)
FC	92	(27.5–183.5)

B1, non-stricturing/penetrating; B2, stricturing; B3, penetrating; FC, faecal calprotectin; L1, terminal ileum; L2, colon; L3, ileocolon; L4, upper gastrointestinal tract; p, perianal disease.

had ileocolonic disease (58%) and a significant proportion had perianal involvement (40%).

Mode of reassessment

In all, 45% (33/73) of patients were reassessed using >1 investigation, although the number receiving four investigations was small (2/73; 3%) (figure 1). In total, 119 investigations were undertaken. Endoscopic evaluation was undertaken in 66% (48/73) and MRE in 47% (34/73), at least one of these investigations being used in 85% (62/73) of patients (figure 2). Other methods of reassessment included pelvic MRI 19% (14/73) and EUA in 7% (5/73). FC was used in 32% (23/73).

Outcome of reassessment

Endoscopy

Endoscopy revealed MH in 25% (12/48), ongoing inflammation in 40% (20/48) and deep ulceration in 35% (16/48). MH was more likely in patients with B1 disease (45%; 9/20) compared with B2/3 disease (11%; 3/28, $p=0.016$). However, while colonic disease location (L2–46%; 6/13) was more frequently associated with MH than other disease location (L1/3–17%; 6/35), this was not significant $p=0.061$.

Radiological reassessment

Remission (defined as a score of A1) was found in 47% cases (16/34) undergoing MRE. Radiological remission was not significantly associated with either disease behaviour or location.

Fourteen patients underwent pelvic MRI to assess fistulising disease. Five patients had ongoing disease evident on pelvic MRI, five demonstrated improvement but not resolution of disease and four patients had healed fistulae. Three patients underwent EUA without pelvic MRI, one demonstrated fistulae, one demonstrated abscess and one demonstrated resolution of disease.

Withdrawal and outcome

At the time of reassessment, 11 patients were considered suitable on clinical grounds for a trial of withdrawal

Figure 1 Number of modalities used in reassessment (n=73).

Figure 2 Frequency of use of reassessment techniques.

(table 3). Of these patients, nine were withdrawn, and within 1 year, six remained in clinical remission off anti-TNF therapy (table 3: pts 1–5 and 7). Two patients decided against maintenance therapy with an immunosuppressive agent after withdrawal, for personal reasons. One of these patients (pt 6) relapsed after 11 months and was successfully retreated with anti-TNF therapy. The other patient (pt 7) was treated with azathioprine for endoscopic, but not clinical, recurrence 13 months postwithdrawal and remains well. A further two patients (pts 8 and 9) who were stepped down to maintenance with an immunomodulator relapsed after withdrawal of anti-TNF therapy. One of these patients (pt 8) had several negative prognostic indicators at time of withdrawal; however, the patient was keen to stop anti-TNF therapy. The other patient (pt 9) was low risk for relapse; all patients in whom IFX was reinstituted responded to therapy. A planned trial of withdrawal was cancelled in the remaining two patients (pts 10 and 11) on clinical grounds (previous disease behaviour and worsening symptoms prior to a trial of withdrawal, respectively).

Retrospective application of low-risk risk stratification for withdrawal from STORI

Adequate information was available to assess 23 patients using the low-risk risk stratification score (table 1 and figure 3). In the absence of FC readings we identified a further group of 29 patients either with a score of ≤ 1 or ≥ 3 , rendering the FC reading irrelevant to the score and included these patients so that a total 52 patients were deemed assessable against low-risk criteria.

Overall, 37% (19/52) patients eligible for assessment were identified as low risk of relapse. Of these, only 26% (5/19) had been deemed clinically appropriate by the multidisciplinary team for a trial of withdrawal when taking into account endoscopic, radiological and clinical assessment. Of these, two relapsed, one being a patient who chose not to take an immunosuppressive agent (table 3: pts 6 and 9).

Of the 74% (14/19) of patients who met low-risk criteria for withdrawal but were deemed unsuitable, seven had endoscopically active disease, two had

active disease on MRE, one had improved yet ongoing perianal disease on pelvic MRI, and two had raised FC ($\sim 180 \mu\text{g/g}$), one of whom was subsequently found to have activity on MRE, while the second patient's personal circumstances were felt incompatible with a trial of withdrawal. Two patients had raised CRP, one continued IFX due to ongoing symptoms and disease activity on MRE and the second required IFX due to intolerance of immunomodulators and hence a lack of other treatment options.

DISCUSSION

Treatment of moderate to severe CD has been revolutionised by anti-TNF therapy. In the UK, NICE mandates yearly reassessment with a view to demonstrating ongoing requirement for treatment. While the data regarding the success of withdrawal of anti-TNF therapy in patients in remission are sparse, identifying who should withdraw from treatment and when to do so remains a major question in IBD. In addition, while data in general support the relative safety of anti-TNF therapy, however, it remains an expensive treatment accounting for approximately two-thirds of all health-care costs for people with CD in one recent study.⁴ Unfortunately, endoscopic, radiological and biochemical remission, in combination with lack of symptoms, is only achieved in a small proportion of patients and the limited data available suggest that this is the group of patients who are most likely to maintain remission after withdrawal of therapy.

We report that relatively few patients in our cohort (15% (11/73)) achieved our locally defined criteria after at least 12 months treatment. However, in the cohort in whom it was possible to apply the criteria, more patients (37% (19/52)) fulfilled favourable parameters for withdrawal identified in the STORI trial. However, it must be noted that in this study, being a 'real world' cohort, there were many differences to the patients included in the STORI trial. For example, unlike in STORI, some of our patients were on adalimumab, not all were taking concomitant azathioprine, many had clinical characteristics that would have precluded their inclusion in STORI and, finally, only a small number had FC measured. This highlights the difficulties of using criteria derived from a well-defined cohort of patients in a clinical trial in clinical practice. Indeed, when considering withdrawal of anti-TNF therapy, other factors also need to be taken into account, including length of sustained remission, patient wishes, adequate ongoing immunosuppression and pretreatment morbidity. Despite the reassuring data regarding successful retreatment in patients withdrawn from anti-TNF therapy, risk of relapse is often a contraindication to trial of withdrawal particularly for personal reasons such as work, education or a desire to become pregnant.¹¹ It is perhaps, therefore,

Table 3 Characteristics of patients suitable for withdrawal (all patients were treated with infliximab)

Patient no	Outcome after reassessment	Outcome at 1 year	Age	Time on treatment (months)	Crohn's location and behaviour	Immunomodulator	Treatment postwithdrawal	Endoscopy finding	Pelvic MRE	Pelvic MRI	Sex	Previous surgery	Hb (g/dL)	WCC (×10 ⁹)	CRP (mg/L)	FC (μ/L)	STORI criteria score
1	Withdrawn	No relapse	26	33	L2+B1	Nil	AZA	MH	NA	NA	F	N	14.9	8	<5	Not done	NA
2	Withdrawn	No relapse*	30	21	L2+B1	AZA	AZA	MH	NA	NA	F	N	13	5.6	<5	47	2
3	Withdrawn	No relapse	23	61	L3+B2p	AZA	AZA	MH	NA	R	M	Y	15.6	7.3	<5	13	2
4	Withdrawn	No relapse	29	35	L2+B1	AZA	AZA	MH	NA	NA	M	Y	13.3	4.6	<5	Not done	NA
5	Withdrawn	No relapse	34	29	L3+B2p	MP	MP	MH	A1	NA	F	Y	13.6	2.5	<5	13	1
6	Withdrawn†	Relapse at 11 months successfully re-treated	41	46	L2+B1	Nil	Nil	MH	NA	NA	F	N	12.6	5.8	<5	92	2
7	Withdrawn†	Mild local endoscopic recurrence at 13 months—started on azathioprine	41	74	L2+B1p	AZA	Nil	NA	NA	EUA—R	F	Y	12.4	6.8	<5	Not done	NA
8	Withdrawn	Relapse at 6 months—successfully retreated with anti-TNF therapy	28	29	L3+B2p	MP	MP	I	A2	R	M	Y	14.1	6.1	16	329	5
9	Withdrawn	Relapse at 4 months—successfully retreated with anti-TNF therapy	21	96	L3+B2	MTX	NA	NA	A1	NA	F	N	12.9	5.7	<5	42	2
10	Continued pt preference due to previous morbidity		30	29	L1+B3	MTX	NA	NA	A1	NA	M	Y	14.6	6.6	<5	Not done	NA
11	Continued due to increasing symptoms		55	19	L1+B1p	6 MP	NA	MH	NA	R	M	N	13.9	5.9	<5	78	3

*No relapse at 6 months—withdrawal delayed due to personal circumstances.

†Patient chose to stop all treatment.

A1, inactive; A2, mild activity; AZA, azathioprine; B1, non-stricturing/penetrating; B2, stricturing; B3, penetrating; EUA, examination under anaesthesia; F, female; FC, faecal calprotectin; Hb, haemoglobin; I, inflammation; L1, terminal ileum; L2, colon; L3, ileocolon; M, male; MH, mucosal healing; MP, mercaptopurine; MRE, magnetic resonance enterography; MTX, methotrexate; p, perianal disease; R, resolved; TNF, tumour necrosis factor; WCC, white cell count.

Figure 3 Patients assessed by retrospective application of low-risk STORI criteria. *n=23 Had all four STORI laboratory parameters assessed. n=29 Had no faecal calprotectin (FC) available; however, score was either ≤ 1 or ≥ 3 and so included in this analysis.

unsurprising that some patients have concerns regarding withdrawal of anti-TNF therapy.^{16 17}

NICE guidance has brought the debate of how and when to withdraw anti-TNF therapy to the fore.⁹ The recent EPACT-II update advises that withdrawal of therapy may be attempted after 2 years for those in clinical and endoscopic remission, and 4 years after clinical remission alone.¹⁰ However, these recommendations are largely based on expert consensus opinion highlighting the lack of evidence available. The STORI trial was the first major study to address the issue of anti-TNF withdrawal. It prospectively investigated withdrawal of IFX in patients achieving steroid-free remission and demonstrated that 50% of patients relapsed within 1 year despite ongoing immunomodulation. However, investigators were able to define a group at low risk of relapse making up 29% of patients in the study, of whom only 15% relapsed at 1 year.¹¹ The STORI trial identifies an FC $<300 \mu\text{g/g}$ as being associated with a favourable prognosis. However, there remains an understandable clinical wariness over FC outwith the normal range and further studies are required to validate this.

The NICE guidance is not accompanied by criteria for the assessment of remission. The minimal requirement is to demonstrate need for ongoing anti-TNF therapy; however, standardisation of the reassessment process would be useful. Reassessment must be flexible, tailored to the individual, acceptable to patients and cost-effective. Although yearly colonoscopy and MRE give comprehensive information on disease status, these are expensive and time-consuming, and colonoscopy is invasive. Furthermore, inter-reporter

variation in endoscopic and MRE surveillance can cloud reassessment, and standardisation of reporting methods using scoring systems would increase utility for reassessment. FC can demonstrate, yet does not accurately quantify, disease activity, and in isolation in some patients might be sufficient to demonstrate ongoing need for anti-TNF therapy. However, the optimum mode and interval for reassessment and restaging of CD is yet to be defined and requires further prospective study.

Defining the criteria for withdrawal of anti-TNF therapy, therefore, remains problematic. Even the best data available, the STORI data, come from a relatively small, uncontrolled trial which is yet to be externally validated. Therefore, the criteria we adopted in our patients may have been too harsh and excluded some patients who may have had a reasonable chance of successfully withdrawing therapy. However, it is important to note that the cohort described is a tertiary referral cohort and therefore may represent a group of patients with more refractory disease who were less likely to tolerate withdrawal of anti-TNF therapy. Finally, use of anti-TNF therapy has recently increased in patients with a short disease duration who tend to have a better response to therapy and are therefore more likely to achieve criteria for remission than those with longer standing disease. Such patients represent a small proportion of this cohort and it is unknown if they are more likely to be able to withdraw from therapy than those with a longer disease duration.

This study has several limitations. Case-note review is dependent on the quality and maintenance of case-notes and interpretation of endoscopy reports from a

range of operators. However, all patients treated with anti-TNF in our unit are reviewed in a multi-disciplinary meeting on an 8-weekly basis allowing an element of standardisation. In addition, the vast majority of the endoscopic evaluation of patients with CD is performed by three consultants who specialise in IBD. To minimise inter-reporter variation of MRE, we used a scoring system which was applied by a single radiologist.

Anti-TNF therapy is not a panacea, and a significant proportion of patients have ongoing disease activity; that the majority of patients in our cohort fell into this category, despite steroid-free clinical remission, shows that reassessment is not just important for withdrawal of therapy, but also identifies active disease, which in some cases may require treatment escalation.^{1 2}

What is already known on this topic

- ▶ There is no formal guidance on how and when to withdraw patients from anti-TNF therapy in Crohn's disease
- ▶ The STORI trial provides some, yet to be validated low-risk criteria for withdrawal, in a selected sub-population of those on anti-TNF therapy

What this study adds

- ▶ This study provides a real world analysis of reassessment and withdrawal of patients on anti-TNF therapy for Crohn's disease.
- ▶ This study demonstrates that the STORI criteria may be limited in their application when considering a heterogeneous tertiary centre cohort

How might it impact on clinical practice in the foreseeable future

The results suggest that withdrawal may be appropriate in a small minority of patients. It also suggests that, in the absence of better evidence, a thorough reassessment of patients prior to withdrawal is still necessary.

Contributors PMI, JS and RJD conceived the study. RJD, KT, JD and MS collected data. RJD analysed the data and RJD and PMI drafted the manuscript. NG reviewed the imaging and scored the MRE. All authors approved the submitted manuscript.

Competing interests PI has received honoraria for speaking and acting in an advisory capacity to Abbott and MSD. JS has received honoraria for speaking for MSD and Abbvie. JD has received honoraria for speaking for Abbvie.

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