ORIGINAL ARTICLE

Optimising IBD patient selection for de-escalation of anti-TNF therapy to immunomodulator maintenance

Rachael Swann , Alan Boal, Seth Ian Squires, Carly Lamb, Laura Louise Clark, Selina Lamont, Graham Naismith

Department of Gastroenterology, Royal Alexandra Hospital, NHS Greater Glasgow and Clyde Division, Glasgow, UK

Correspondence to

Dr Rachael Swann, Department of Gastroenterology, Royal Alexandra Hospital, NHS Greater Glasgow and Clyde Clyde Division, Glasgow G51 4TF, UK; rswann@nhs.net

Received 27 October 2018

Revised 8 April 2019

Accepted 8 April 2019

Published Online First

3 May 2019

ABSTRACT

Objective Inflammatory bowel disease (IBD) is increasingly managed with the use of biologic therapies. National guidelines (National Institute for Health and Care Excellence (NICE)) suggest considering cessation after 1 year of therapy but lack detailed criteria for this. We aimed to describe clinical outcomes from the introduction of a biologic review panel (BRP) to implement modified criteria for cessation of antitumour necrosis factor (anti-TNF) therapy and step down to single-agent immunomodulator.

Design Retrospective review of patient outcomes following BRP implementation.

Patients All patients on biologic therapy discussed in the BRP within a 5-year period.

Setting Single IBD network covering three hospital sites.

Interventions Modified criteria for biologic cessation were based on published evidence; they excluded individuals with no suitable maintenance immunomodulator, previous surgery or evidence of active disease, additional indications for anti-TNF therapy and previous relapse on biologic cessation. All patients with IBD on a biologic were discussed at the BRP.

Main outcome measures Relapse following IBD cessation and relative cost of BRP.

Results 136 patients with IBD were reviewed, with 45 patients meeting the NICE guideline criteria for cessation. The BRP and modified criteria affected decision to withdraw therapy in 38% of these. Therapy was withdrawn in 27 patients, with a 20% 24-month relapse rate. Younger age at cessation was significantly associated with relapse ($p=0.01$).

Conclusion The BRP approach has proved a safe and effective means of decision making in stopping biologic therapy. Future work to inform exclusion criteria is required.

INTRODUCTION

Inflammatory bowel disease (IBD) is often managed with immunosuppressant

Significance of this study

What is already known on this topic

- ▶ Antitumour necrosis factor agents can safely be withdrawn in some individuals with inflammatory bowel disease (IBD), but high relapse rates of up to 50% have been reported.

What this study adds

- ▶ Detailed review of cases, ensuring deep remission and suitable immunomodulator therapy result in an acceptably low relapse rate in our experience.

How might it impact on clinical practice in the foreseeable future

- ▶ More detailed criteria for cessation of biologic therapy in IBD may enable greater number of patients to safely stop therapy once in deep remission.

therapies. While thiopurines have traditionally been the maintenance agent of choice for Crohn's disease (CD) and ulcerative colitis (UC) not controlled with 5-ASA compounds, antitumour necrosis factor (anti-TNF) agents and other biologics are increasingly being used¹ for induction therapy and maintenance therapy. Although these agents are effective, they are costly and have potentially serious side effects.²⁻⁴ In addition, antibodies to the agents may develop which reduce their efficacy.⁵ Therefore, in individuals in steroid-free remission, current UK National Institute for Health and Care Excellence (NICE) guidelines, published in 2010, suggest planned cessation of therapy after 1 year unless there is clear evidence of ongoing disease activity. The guidelines state 'Infliximab should

© Author(s) (or their employer(s)) 2020. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Swann R, Boal A, Squires SI, et al. *Frontline Gastroenterology* 2020;**11**:16–21.

be given as a planned course of treatment until treatment failure (including the need for surgery) or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed to determine whether ongoing treatment is still clinically appropriate' (NICE technology appraisal TA187).⁶ No specific definition of remission is stipulated; a Crohn's Disease Activity Index (CDAI) less than 150 is given as an example of clinical remission. However, previous follow-up studies of such individuals have shown a relapse rate of approximately 40%–50% at 24 months.^{7–9} Other analyses have highlighted factors which predict risk of relapse post anti-TNF cessation, including male sex, age at diagnosis, smoking status, the absence of surgical resection, leucocyte count $>6.0 \times 10^9/L$, haemoglobin ≤ 145 g/L, C reactive protein ≥ 5.0 mg/L and elevated faecal calprotectin. These are highlighted in the recent European Crohn's and Colitis Organisation (ECCO) guidelines.^{7 10–12} Additionally, specific features of Crohn's disease such as colonic involvement, stricturing disease¹³ and perianal fistulation¹¹ predict a lower likelihood of maintained remission. While the majority of those who relapse will respond to a further course of treatment with the same agent, a recent multicentre study reported that 12% lose their response on reintroduction of the same agent.¹³

We have previously described how the use of panel discussion in the form of an IBD multidisciplinary team meeting (MDT) can enhance biologic therapy decision making.¹⁴ Reviews of the use of MDTs in chronic disease management have suggested that further evidence of effectiveness of this approach is required.¹⁵ Here we detail the impact of an IBD biologic review panel (BRP) and evidence-based exclusion criteria for anti-TNF cessation on clinical outcomes for those stopping anti-TNF therapy.

MATERIALS AND METHODS

Since 2012, demographics and outcomes from all patients attending our IBD service treated with biologic therapy have been recorded in an IBD database to standardise clinical data collection and follow-up. The IBD

BRP was set up to review the cases of all individuals on biologic therapy on an annual basis. For this study, all individuals remaining on anti-TNF therapy for over 6 months were evaluated in the BRP regarding suitability for de-escalation of therapy. For these patients, disease activity was assessed using clinical information (resolution of diarrhoea, abdominal pain and fatigue), radiological (where appropriate), biochemical (C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), albumin, calprotectin) and endoscopic tests. All those thought to be in remission were included for consideration of cessation of biologic therapy.

The NICE guidelines do not give specific criteria for remission but suggest this consists of 'clinical symptoms suggesting absence of active disease and biological markers suggestive of remission with endoscopy if necessary', suggesting a CDAI less than 150 for an example of clinical remission. It should be noted that the NICE guidance does not specify thresholds for biological markers of inflammation and does not mandate confirmation of endoscopic remission in the absence of other markers of activity. As recent evidence has suggested that those with histological remission have lower relapse rates, the BRP defined remission as the following:

- ▶ No active clinical symptoms (ie, stool frequency <4 per day, no blood *per rectum*, no abdominal pain, no other

Table 2 Patients felt to be in clinical remission excluded from anti-TNF withdrawal

Main reason for exclusion	Patients (n)	Further information
Penetrating or high-risk disease (including >1 previous surgeries)	4	Small bowel or perianal disease, upper gastrointestinal disease.
Previous relapse on biologic cessation	1	
No other maintenance option	4	Intolerant of or non-compliant with thiopurines $\pm$ other oral immunosuppressants.
Dual pathology requiring biologic	2	Episcleritis. ¹ Rheumatoid arthritis. ¹
Found not to be in remission at BRP	6	Recent colonoscopy not performed, subsequently showed active disease. ³ Review of pathology showed evidence of active disease. ¹ Review of imaging showed evidence of active small bowel disease. ¹ Review of clinical notes revealed evidence of recently active perianal disease. ¹
Moved out of region	1	

The main reason for not stopping biologic therapy is given in the table above. Where more than one criterion applied, patients have been listed under the one that was the most influential in the decision-making process.

anti-TNF, antitumour necrosis factor; BRP, biologic review panel.

Table 1 Characteristics of the total cohort of patients on biologic therapy and discussed at the BRP during the study period

Characteristics	N=136		
Sex	Male, 64 (47%)	Female, 72 (53%)	
Biologic agent	Adalimumab, 70 (51%)	Infliximab, 49 (36%)	Both, 17 (13%)
Age at first biologic prescription	Median, 37 years (range 14–71)		
UC/Crohn's disease/Indeterminate	CD, 89 (65%)	UC, 42 (31%)	IBDI, 5 (4%)

BRP, biologic review panel; CD, Crohn's disease; IBDI, Indeterminate colitis; UC, ulcerative colitis.

symptoms likely to reflect active disease, eg, perianal symptoms).

- ▶ Quiescent disease macroscopically at endoscopy (ie, no evidence of inflammation, eg, Mayo score 0 for UC or Simple Endoscopic Score for Crohn's Disease (SES-CD) <3 for CD) with quiescent or mildly active histological disease.
- ▶ Radiologically no evidence of active inflammation for patients with Crohn's with small bowel disease.
- ▶ Biochemical evidence of resolution included a normal ESR and/or CRP, and where available a faecal calprotectin <250 µg/g. In some individuals where other causes of raised inflammatory markers were present, for example, active arthropathy, these were not used in determining whether the patient was suitable for drug withdrawal.

Use of the database and review panel helped identify any individuals who had not undergone complete evaluation at this time point, and further investigations were ordered as appropriate prior to reviewing the case.

All of those judged to be in deep remission according to the criteria above were discussed in the review panel to determine their suitability for anti-TNF cessation. The additional exclusion criteria for stopping anti-TNF agents applied are as follows:

- ▶ No suitable immunomodulator: all patients were planned to step down to single-agent immunomodulator; therefore, those without an option for maintenance immunosuppression were excluded.

- ▶ Postsurgical recurrence of IBD despite immunomodulator.
- ▶ Difficult to control the disease, for example, requiring switch of anti-TNF therapy or frequent courses of steroids on single-agent immunomodulator.
- ▶ Penetrating disease or perianal disease requiring anti-TNF therapy to achieve resolution.
- ▶ Additional indication for anti-TNF.
- ▶ Previous relapse on anti-TNF cessation.

The BRP consisted of a minimum of one gastroenterology consultant and two IBD nurse specialists, with input from a consultant radiologist, pathologist and surgeon available if required through a separate IBD MDT. In addition to the exclusion criteria listed, the MDT took a holistic approach to the patient, the course of their disease and other comorbidities which may have implications for therapy cessation, for example, rheumatological disorders.

Following cessation of therapy, patients were followed up for a minimum of 12 months. During this period, individuals had regular clinical assessments, as well as access to an IBD nurse telephone and email helpline. Relapse was defined as an increase in symptoms with appearances of active disease on biochemical, endoscopic and/or radiological testing requiring steroid therapy, surgery or recommencement of a biological agent. Those with clinical and biochemical/endoscopic confirmation of relapse were offered further treatment with the same anti-TNF agent in the first instance unless clinically contraindicated.

Figure 1 Flow chart of patients considered in the multidisciplinary team meeting (MDT) for cessation of therapy.

RESULTS

Between January 2012 and 2017, a total of 136 individuals underwent BRP review. Eighty-eight individuals received treatment with adalimumab and 51 with infliximab, with 17 receiving both therapies during this time period (see [table 1](#) for demographics). Of these 45 (33%) met the NICE criteria for deep clinical remission. From these individuals, six (4%) were excluded as further investigations requested by the BRP or review of imaging revealed evidence of active disease. One additional patient moved out of the region during the BRP process. A further 11 (8%) did not meet the extended criteria for anti-TNF withdrawal. The number of patients excluded for each criterion is given in [table 2](#). During this time period, 21 additional patients had biologic therapy withdrawn due to side effects, non-compliance or surgical resection of active disease.

Following the BRP process, 27 individuals (20%) were approved for planned cessation of anti-TNF

therapy. This decision was communicated to the patient's usual gastroenterologist, who then discussed drug cessation with the patient. No patients objected to drug withdrawal. A flow chart detailing the stages of consideration for cessation of anti-TNF therapy and exclusions is shown in [figure 1](#). Following biologic cessation, these individuals were followed up for a median of 29 months (range 12–60 months). During this period a total of six individuals experienced relapse (22%). Demographics and clinical features comparing those relapsing with those who did not relapse are shown in [table 3](#). The median time to relapse was 15 months (4–36 months; see [figure 2](#)), with a 1-year relapse rate of 11% and a 2-year relapse rate of 20% (4 of 20 patients followed up for at least 24 months). No clinical tests were significantly associated with relapse. Fewer than half of individuals provided samples for faecal calprotectin prior to cessation. In those where precessation calprotectin was available, there was no association with relapse; however, the lack of data makes it difficult to draw any firm conclusions from this. Relapse rates were equal in those taking infliximab at the time of anti-TNF cessation (4/18, 22%) and adalimumab (2/9, 22%). Younger age at cessation was significantly associated with a higher risk of relapse ($p=0.01$).

All relapsing patients suffered from Crohn's disease, with none of the seven patients with UC experiencing relapse. This gives an unprecedented relapse rate of 0% in UC sufferers and a relapse rate of 30% in those with CD.

All six relapsing individuals were given anti-TNF agent as soon possible after symptoms were reported. The median time from diagnosis of relapse to first dose infusion was 105 days (range 28–300, the highest value being due to delay related to pregnancy). One relapsing individual required hospital admission, with the remainder managed solely in the outpatient setting. Four individuals were re-treated with the same agent. One patient switched agent as drug levels had been undetectable in the presence of antibodies prior to cessation, and the second switched agent due to preferred mode of administration. All individuals achieved remission, with only one requiring a course of steroids in the follow-up period (due to postpartum flare) and none required a further change of biologic agent.

DISCUSSION

Our data demonstrate the importance of careful patient selection when considering cessation of anti-TNF therapy. The 22% relapse rate seen in this series is one of the lowest reported. Use of the modified criteria and BRP discussion affected management in 17 of 45 (38%) of those meeting the NICE criteria for biologic withdrawal in this cohort. Where the decision was taken not to de-escalate patient therapy, this was most often because they were not in deep remission

Table 3 Comparison of clinical factors in relapsers and non-relapsers

Factor	Relapse (n=6)	Non-relapse (n=21)	P value
Treatment with adalimumab (%)	2 (33)	7 (33)	1.00
Treatment with infliximab (%)	4 (67)	14 (67)	1.00
Median duration of disease prior to biologic therapy (years) (range)	5.5 (2–13)	5.5 (0–30)	0.89
Median duration of biologic therapy prior to cessation (years) (range)	2.75 (2–4.5)	2 (0.5–8.5)	0.65
Crohn's disease (%)	6 (100)	14 (67)	0.14
Ulcerative colitis (%)	0 (0)	7 (33)	0.14
Smoker (%)	0 (0)	4 (19)	1.00
Ex-smoker (%)	2 (33)	3 (14)	1.00
Age at cessation (years) (range)	25.5 (17–42)	48 (21–65)	0.01
Male sex (%)	2 (33)	6 (29)	1.00
Combination therapy with immunomodulator (%)	6 (100)	21 (100)	1.00
Median C-reactive protein prior to cessation (range)	3 (1–5)	4 (1–17)	0.27
Median white cell count prior to cessation (range)	6.3 (5.2–6.5)	6.1 (3.7–14.0)	0.55
Median haemoglobin at cessation (range)	139.5 (113–145)	141.5 (112–173)	0.95
Median calprotectin at cessation*	79.5 (34–221)	53 (<30–220)	0.56

P values were calculated using Student's t-test for continuous data, Wilcoxon rank-sum test for ordinal data and Fisher's exact test for categorical data. Significant p value is indicated in bold type.

*Calprotectin values <6 months prior to antitumour necrosis factor cessation were only available in 4 of 6 relapsers and 7 of 21 non-relapsers.

or because they had no suitable immunomodulator for maintenance therapy. It is possible that some individuals excluded would have been able to stop therapy without experiencing a disease flare. Further observational studies are required to determine the optimum criteria for drug cessation which allow the maximum possible number of individuals to stop treatment without relapse.

No statistical differences were observed in baseline laboratory parameters of those who relapsed compared with those who did not. There was also no association between the type of anti-TNF agent (prior to cessation) and relapse. While this may reflect the small numbers in this group, it suggests better biomarkers are required to predict the risk of recurrence of active disease. Older age at cessation and a diagnosis of ulcerative colitis were associated with a lower risk of relapse. This reflects existing data, with two previous studies showing a similar association with older age at diagnosis⁷ and at time of cessation.¹³ While the cohort was too small to analyse relapse by Crohn's phenotype, as those with penetrating disease were excluded, the majority had an inflammatory phenotype.

In addition to optimising patient care by reducing unnecessary exposure to drug, regular panel review of biologic therapy can be cost-saving.¹⁶ In our experience, the costs of running the BRP are minimal, taking up four sessions (24 hours) for each specialist nurse, with two further sessions of preparation. In addition, three consultants each give six sessions per year (24

hours each), that is, a total cost of £19 600 over 5 years. While the costs of anti-TNF agents have reduced with the introduction of biosimilars, at the time of the study this was more than offset by cost savings from deprescription of anti-TNF therapy over the 5-year period.

As therapeutic drug monitoring became available to us mid-way through the study (from 2015), we have not analysed its role in this study. However, after 2015 it has formed part of the BRP discussion for most patients, allowing optimisation of therapy for those not in remission with inadequate drug levels and also identification of those in remission with no active drug in the system. This enabled a timely switch to other medical or surgical therapies, avoiding costs and potential morbidity from continued administration of ineffective medication.

Additional potential benefits from a review panel-style approach to patient care are in streamlining investigation and maximising efficiency of clinic appointments. These are difficult to quantify, and it is arguable that some patients would receive equivalent care without the BRP; however, at least 6 of 45 (13%) felt to be in clinical remission by their usual clinician were subsequently found to have active disease and excluded from biologic withdrawal on further investigation by the BRP. Additionally, all patients recommended for withdrawal subsequently had biologics withdrawn, suggesting that patients and clinicians had confidence in the panel decision. This may also reflect

Months	0	10	20	30
Survival (%)	100	93	82	81
Number at risk	27	25	18	10

Figure 2 Kaplan-Meier curve for survival without relapse or surgery. The solid line shows percentage survival without relapse requiring steroids, surgery or retreatment with biologic therapy. The dotted line shows the 95% CIs of the curve. Patients were censored at last recorded follow-up (minimum 12 months).

the impact of our robust local IBD nurse service with clear channels for direct patient communication and the ability to rapidly assess patients in the nurse-led clinic. This enabled efficient disease evaluation and outpatient retreatment when relapse has occurred, thus limiting potential harms of anti-TNF cessation. In future, with reducing costs of anti-TNF agents and concerns regarding the risks of long-term thiopurine usage,¹⁰ a similar approach could be used to identify individuals who would be suitable for maintenance anti-TNF or other biologic monotherapy without an additional immunomodulator.

There are some limitations to the data presented in this study, in particular the incomplete calprotectin data in patients at the beginning of the study period, with more comprehensive use of calprotectin testing prior to cessation more recently. This reflects the increasing use of this assay in our trust over this period. In addition, while all patients were clinically assessed prior to cessation, CDAI scores were not routinely calculated. Nevertheless, this reflects the reality of patient assessment in the clinic, and our findings demonstrate the real-world effectiveness of a focused review panel approach to important clinical decisions in the management of patients with IBD on biologic therapy.

In conclusion, our data demonstrate one of the lowest reported relapse rates in a series of elective anti-TNF cessation in IBD. We have shown how the use of a review panel, excluding those at high risk of relapse, can optimise selection of suitable patients. Proactive de-escalation of biologic agents to maintenance immunomodulator therapy in carefully selected individuals has the potential for significant cost savings. Further work to refine inclusion and exclusion criteria should make such an approach even more effective.

Acknowledgements The authors would like to thank Dr Mathis Heydtmann, Dr Rizwana Hamid and Ms Fiona McLuskey for their contribution to developing and for participating in the BRP.

Contributors RS is the guarantor of the study. All authors (GN, SIS, RS, CL, AB, SL and LLC) participated in data collection and drafting the manuscript. The original idea for the study was devised by GN, AB and SIS, and further developed by RS. GN, SL, LLC, SIS and AB conducted the BRP intervention.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval As the review panel was introduced as part of a service development initiative and formed the standard of care for all patients, external ethical approval was not sought.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Raw anonymised data are available upon reasonable request from the corresponding author.

ORCID iD

Rachael Swann <http://orcid.org/0000-0002-3945-2253>

REFERENCES

- 1 Blotière P-O, Rudant J, Barré A, *et al.* Conditions of prescription of anti-TNF agents in newly treated patients with inflammatory bowel disease in France (2011-2013). *Dig Liver Dis* 2016;48:620-5.
- 2 Park KT, Crandall WV, Fridge J, *et al.* Implementable strategies and exploratory considerations to reduce costs associated with anti-TNF therapy in inflammatory bowel disease. *Inflamm Bowel Dis* 2014;20:946-51.
- 3 Nyboe Andersen N, Pasternak B, Friis-Møller N, *et al.* Association between tumour necrosis factor- α inhibitors and risk of serious infections in people with inflammatory bowel disease: nationwide Danish cohort study. *BMJ* 2015;350:h2809.
- 4 Karmiris K, Bossuyt P, Sorrentino D, *et al.* Cerebrovascular events in inflammatory bowel disease patients treated with anti-tumour necrosis factor alpha agents. *J Crohns Colitis* 2015;9:382-9.
- 5 Cohen BL, Sachar DB. Update on anti-tumor necrosis factor agents and other new drugs for inflammatory bowel disease. *BMJ* 2017;357.
- 6 National Institute for Health and Care Excellence. Technology appraisal 187: infliximab (review) and adalimumab for the treatment of Crohn's disease (including a review of technology appraisal guidance 40), 2011. Available: www.nice.org.uk/guidance/TA187
- 7 Kennedy NA, Warner B, Johnston EL, *et al.* Relapse after withdrawal from anti-TNF therapy for inflammatory bowel disease: an observational study, plus systematic review and meta-analysis. *Aliment Pharmacol Ther* 2016;43:910-23.
- 8 Brooks AJ, Sebastian S, Cross SS, *et al.* Outcome of elective withdrawal of anti-tumour necrosis factor- α therapy in patients with Crohn's disease in established remission. *J Crohns Colitis* 2017;11:1456-62.
- 9 Sorrentino D, Nash P, Viladomiu M, *et al.* Stopping anti-TNF agents in patients with Crohn's disease in remission: is it a feasible long-term strategy? *Inflamm Bowel Dis* 2014;20:757-66.
- 10 Doherty G, Katsanos KH, Burisch J, *et al.* European Crohn's and Colitis Organisation Topical Review on Treatment Withdrawal [Exit Strategies] in Inflammatory Bowel Disease. *J Crohns Colitis* 2018;12:17-31.
- 11 Gisbert JP, Marín AC, Chaparro M. Systematic review: factors associated with relapse of inflammatory bowel disease after discontinuation of anti-TNF therapy. *Aliment Pharmacol Ther* 2015;42:391-405.
- 12 Baert F, Glorieux E, Reenaers C, *et al.* Adalimumab dose escalation and dose de-escalation success rate and predictors in a large national cohort of Crohn's patients. *J Crohns Colitis* 2013;7:154-60.
- 13 Casanova MJ, Chaparro M, García-Sánchez V, *et al.* Evolution after anti-TNF discontinuation in patients with inflammatory bowel disease: a multicenter long-term follow-up study. *Am J Gastroenterol* 2017;112:120-31.
- 14 Squires S, Naismith G, Boal A. Combining NICE guidelines with exclusion criteria to identify patients with Crohn's disease for treatment withdrawal: 12-month prospective cohort study. *Gastrointestinal Nursing* 2016;14:20-8.
- 15 Raine R, Xanthopoulou P, Wallace I, *et al.* Determinants of treatment plan implementation in multidisciplinary team meetings for patients with chronic diseases: A mixed-methods study. *BMJ Qual Saf* 2014;23:867-76.
- 16 Ghosh N, Premchand P. A UK cost of care model for inflammatory bowel disease. *Frontline Gastroenterol* 2015;6:169-74.