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Original Article

Patients with perianal Crohn's fistulae experience delays in accessing anti-TNF therapy due to slow recognition, diagnosis and integration of specialist services: lessons learned from three referral centres

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Conflicts of interest:

Alan Lobo is an advisory board member or received lecture fees for Takeda Pharma, Abbvie, Dr Falk, Shield Pharmaceuticals and Vifor Pharma. Ailsa Hart has served as consultant, advisory board member or speaker for AbbVie, Atlantic, Bristol-Myers Squibb, Celltrion, Falk, Ferring, Janssen, MSD, Napp Pharmaceuticals, Pfizer, Pharmacosmos, Shire and Takeda. She also serves on the Global Steering Committee for Genentech. The other authors have no conflicts of interest to declare.

Author contributions:

All authors have been involved with (i) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (ii) drafting the article or revising it critically for important intellectual content, (iii) final approval of the version to be submitted.

This manuscript and its contents have not been previously published, and it is not under consideration for publication in any other journal.

Abstract

Background

Crohn's anal fistula should be managed with a multidisciplinary team. There is no clearly defined 'patient pathway' from presentation to treatment. The aim of this study was to

describe the patient route from presentation with symptomatic Crohn's anal fistula to starting anti-TNF therapy.

Method

Case note review was undertaken at three hospitals with established IBD services. Patients with Crohn's anal fistula presenting between 2010 and 2015 were identified through clinical coding and local databases. Baseline demographics were captured. Patient records were interrogated to identify route of access, and clinical contacts during the patient pathway.

Results

79 patients were included in the study, of whom 54 (68%) had an established diagnosis of Crohn's disease. Median time from presentation to anti-TNF therapy was 204 days (174 days vs 365 days for existing and new diagnosis of Crohn's disease respectively ($p=0.019$)).

The mean number of surgical outpatients attendances, operations and MRI scans per patient was 1.03, 1.71 and 1.03 respectively. Patients attended a mean of 1.49 medical clinics. Seton insertion was the most common procedure, accounting for 48.6% of all operations. Where care episodes ('clinical events per 30 days') were infrequent this correlated with prolongation of the pathway ($r = -0.87, p < 0.01$).

Discussion

This study highlights two key challenges in the treatment pathway: i) delays in diagnosis of underlying Crohn's disease in patients with anal fistula, ii) the pathway to anti-TNF therapy is long, suggesting issues with service design and delivery. These should be addressed to improve patient experience and outcome.

What does this paper add to the literature?

This study shows that patients may have delays in their treatment pathway, with most patients waiting at least 6 months for medical therapy – this is a novel finding. It also highlights the challenges in recognition of Crohn’s disease when anal fistula is the first presentation.

Background

The management of fistulating perianal Crohn’s disease is complex. Patients present in many different ways including as an emergency with perianal abscess, or with more chronic undulant symptoms or with intractable perianal sepsis¹. Recognition of Crohn’s disease in patients who present with a perianal fistula can be difficult and effective management is challenging. It is generally accepted that control of perianal sepsis and early anti-tumour necrosis factor- α (anti-TNF α) therapy is the mainstay of management². Patients report a high level of disability, leading its prominence in recent patient research prioritisation exercises^{3,4}.

A patient pathway is a process or sequence of events where a patient is taken from referral or first related clinical activity through to treatment⁵. These have been used in settings such as laparoscopic cholecystectomy⁶, complex biliary disease⁷ and oesophageal cancer⁸ and achieve more efficient use of resources with lower costs of care.

The pathway of a patient with Crohn’s anal fistula may involve primary care physicians, surgeons, gastroenterologists, radiologists and inflammatory bowel disease nurse specialists across outpatient and surgical theatre settings. Even with optimal combined therapy, healing of Crohn’s fistulae is reported to be less than 30%⁹.

Given the reported debility, it is likely that delays within this pathway will affect quality of life and influence the effectiveness of therapy.

Aim

The primary aim of the study was to explore the pathway from presentation with symptomatic Crohn's anal fistula to treatment with anti-TNF therapy in specialist hospitals with the secondary aim of identifying areas for pathway improvement.

Method

Three teaching hospitals with large Inflammatory Bowel Disease (IBD) services participated in this study. Hospital administrative databases were searched using ICD-9 clinical codes K50.x (Crohn's disease) AND K60.x OR K61 (anal fistula), for events between 2010 and 2015. Identified cases were cross-checked against local biologic therapy databases to confirm which patients had received anti-TNF treatment. Patient records were retrieved for identified cases.

Adults with newly symptomatic Crohn's anal fistula not on anti-TNF therapy at the start of the study period, and who had received anti-TNF therapy by the end of the study period, were included. Those with non-fistulating perianal manifestations of disease, those who declined anti-TNF therapy, those already established on anti-TNF therapy, and those who transferred care from one hospital to another during the study, were excluded.

Demographic and clinical data extracted from clinical records included: time since diagnosis of Crohn's disease, and prior anti-TNF α , thiopurine or methotrexate use. Crohn's disease phenotype was classified according to Montreal criteria¹⁰.

Pathway data extracted included: date of first presentation with symptomatic fistula within the study period, date of first anti-TNF α dose, date and location of all IBD-related documented clinical interactions (outpatient/inpatient), date of MRI scans, and the date and nature of any surgical procedures.

Overall pathway length was calculated as time from first presentation to time of first dose of anti-TNF in days. Clinical events identified included attendance at surgical and medical outpatient clinics, MRI scans, admissions, and surgical procedures. Time to transition from each care event (i.e. medical outpatients, surgical outpatients, medical admissions, radiology (MRI), elective theatre) was for each event in days. Mean number of events per pathway was calculated, as was the rate of care events and unplanned readmission per 30 days of pathway (care events/(pathway length/30)). These values were plotted following log transformation to normalise the distribution.

Comparison of medians between groups was performed using Mann-Whitney U-test. Other statistical tests used are indicated in parenthesis. A p value of <0.05 was set as the threshold for statistical significance *a priori*. This study was registered as a service evaluation with audit departments at respective hospitals.

Results

Clinical coding identified a total of 311 cases across all sites. Following removal of duplicates and excluded cases, a total of 79 (25.4%) of patients were eligible for the study. These were split 24/23/32 across the three sites.

Clinical characteristics

54 patients (68%) had a pre-existing diagnosis of Crohn's disease (CD). The date of diagnosis was confirmed from clinical records. In these patients, the mean time from diagnosis of CD to presentation in this study was 9.5 years (S.D.+/-7.2). Patient phenotype is presented in table 1. Of the 54 patients with a prior diagnosis of CD, 14 (25.9%) had previously received anti-TNF α therapy, 27 (50.0%) had previously received thiopurine agents, and 1 (1.8%) methotrexate.

Interval between presentation and anti-TNF treatment

The median time from presentation of a symptomatic Crohn's fistula to receiving the first dose of anti-TNF therapy was 204 days (IQR 113-453 days) (Figure 1) across the whole cohort. The median interval for patients with existing CD was 174 days compared to 365 days for those with a new diagnosis of CD ($p=0.019$). There was no significant difference in the length of the pathway in those patients with a pre-existing diagnosis of CD according to whether they had previously received anti-TNF α agents or were naïve to them (median 136 vs 199 days respectively, $p=0.29$).

Number of care events per 30 days underwent log transformation. Longer pathways showed a negative correlation with the number of clinical events per 30 days of the pathway (Spearman $r = -0.87$, (-0.91 to -0.79) $p<0.01$) and with unplanned readmissions Spearman $r = -0.95$ (-0.97 to -0.91) $p<0.01$.

Route of access and outpatient use

Overall, 29 of 79 (36.7%) patients initially presented via an acute surgical route, 5 of 79 (6.3%) presented via a medical admissions unit, 21 of 79 (26.6%) and 22 of 79 (27.8%) via surgical outpatients and medical outpatients respectively, and 2 of 79 (2.5%) presented through contact with an IBD specialist nurse. For those 25 patients with no prior diagnosis of CD, 9 (36.0%) presented via surgical outpatients and 9 (36.0%) as an acute surgical admission. 7 (28.0%) patients presented through medical outpatients. The distribution of point of access by diagnosis is detailed in Table 1. The mean number of surgical outpatient events per patient was 1.10 across the pathway, and occurred at a mean rate of 0.17 (S.D. +/-0.19) per 30 days of pathway. The mean number of medical outpatient events per patient was 1.49, and occurred at a mean rate of 0.28 per 30 days of the pathway (S.D. +/-0.40).

Frequency of MRI scanning

An MRI was performed in 59 (74.6%) of patients during the pathway. Of those undergoing MRI, 42 (71.1%) underwent one scan, 15 (25.4%) patients underwent two MRI scans. The mean number of MRI was 1.03 per patient, and occurred at a mean rate of 0.43 per 30 days of the pathway (S.D. +/-1.01).

Frequency of surgical interventions

Of the 79 patients, 72 (91.0%) underwent a total of 140 surgical procedures, including examination under anaesthetic, seton insertion, drainage of sepsis only, or other fistula procedures (Table 2). Of these, 36 (50.0%) had a single procedure, 17 (23.6%) had two procedures, 6 (8.3%) had three procedures, 13 (18.0%) had four procedures. The mean

number of operations was 1.9 per patient, and occurred at a mean rate of 0.54 per 30 days of the pathway (S.D. +/-1.09).

Time to transition

Time to and from each point of care (medical or surgical outpatients, medical or surgical admission, nurse specialist appointments, MRI scans and elective theatres) was calculated.

Transition from medical outpatients or admission to surgical outpatients tended to be shorter than transition from surgical admission or outpatients to medical outpatients (32.0 vs 56.5 days; $p = 0.08$) (Table 3). The median time to commencement of anti-TNF from last clinic appointment was 77 days (IQR 27.5-225.5 days).

Establishing Current Pathways

Based upon this data, there are 3 potential clinical pathways from presentation of perianal Crohn's disease to anti-TNF therapy. The pathways are essentially determined by mode of presentation.

Surgical outpatient presentation

Patients presenting to surgical outpatients tend to undergo elective surgery (median wait 22 days), followed by attendance at medical outpatients (median wait 48.5 days). Most then undergo an MRI (median wait of 34 days) then return to medical outpatients (median wait 29 days). After this, patients will be started on anti-TNF therapy (median wait 77 days).

Emergency surgery presentation

Patients entering the pathway via acute surgical admission will undergo MRI (median wait 29.5 days), before attending for surgical follow up (median wait 42 days) and undergoing elective surgery (median wait 22 days), and then attending medical outpatients (median wait 48.5 days) and accessing anti-TNF therapy (median wait 77 days).

Medical outpatient presentation

Finally, patients may present to medical outpatients and be referred for an MRI (median wait 34 days), before referral for a surgical opinion (median wait 42 days) and undergoing elective surgery (median wait 22 days). They may then proceed to anti-TNF therapy (median wait 77 days) (see figure 1).

It is important to note that these reflect frequently represented pathways for the whole cohort, and sequences may vary. As suggested by above findings, some patients will have multiple clinic appointments and multiple MRI scans. Patients presenting to the surgeons as an emergency typically underwent outpatient MRI scan, although a small number underwent emergency examination under anaesthesia, with same day discharge and outpatient imaging.

Discussion

This is the first study to assess the patient pathway in patients with perianal Crohn's disease. It has shown that the median pathway length is substantial, even in centres with an established IBD service. There is median delay of 204 days (174 days for patients with known CD, and 365 days for new presentations).

This work identifies two areas, which if improved, could shorten the patient pathway.

Firstly, the need to diagnose Crohn's disease in a newly diagnosed fistula and secondly, the need for very close collaboration between medical and surgical teams.

Perianal fistula may be the first presentation of Crohn's disease in 15% of patients¹¹. Some presentations of perianal disease may be immediately apparent as Crohn's disease. There may be clinical features typical of Crohn's disease such as florid oedematous skin tags, multiple fistulae and proctitis. In others without these features, patients may be treated initially as having cryptoglandular disease. There is currently no other diagnostic tool allowing early identification of disease Crohn's disease. It is therefore important to ensure that symptoms of intestinal disease and a family history of inflammatory bowel disease are sought and further investigated.

Acute perianal abscesses, presenting as an emergency, may be treated by a less experienced junior surgeon, possibly with limited senior input and sometimes minimal follow up again which may contribute to delays in the pathway.

Patients with suspected Crohn's disease do not have the enhanced pathways available to patients with suspected cancer, and yet a rapidly progressive disease process may mean that, by the time of clinical review, return to an earlier point in the pathway may be needed - for example, further urgent surgery to drain recurrent infection or repeat MRI scan to assess new fistulae. Even with an uncomplicated disease pathway, delayed medical, radiological and surgical review or intervention will have an adverse impact on quality of life, potentially on long-term outcomes and the likelihood of successful treatment.

Options to reduce the delays at each of these steps should be considered. This could include agreed fast track referral pathways between medical and surgical arms of the IBD service, including directly into surgical admissions units and then back to receive anti-TNF α infusions. Combined in-patient rounds and out-patient clinics are likely to help precision of diagnosis and appropriate decision-making. There may be delays relating to screening for underlying occult or latent infection, the need to repeat indeterminate TB screening tests and capacity issues in biologic clinics.

The importance of shortening the pathway to anti-TNF α treatment assumes that earlier anti-TNF α treatment improves both clinical outcomes and quality of life. Although this is established in luminal Crohn's disease^{12,13}, no trial has tested this hypothesis in perianal Crohn's disease. The duration of fistula presence is a poor prognostic factor, indirectly suggesting the benefit of a time-based approach^{8,14,15}. However, given the impact of fistula symptoms on quality of life and frequent disease deterioration whilst waiting for the next step, a streamlined pathway would seem important.

There are limitations to this work, particularly its retrospective nature. We have only captured the timing of events, not the intention that led to the event, nor have we captured factors related to patient choice. We have also defined the pathway as terminating only when anti-TNF therapy has been commenced. Nevertheless we feel that focusing on this element of the treatment pathway is relevant as a surrogate both for the experience of these patients in terms of symptomatic disability^{3,4} and because of the perception that delays in treatment may be associated with a poorer outcome – a finding replicated in other aspects of Crohn's disease^{16,17}.

There is considerable variation in the pathway to anti-TNF therapy for patients with fistulating perianal Crohn's disease. In most cases the delay to treatment is substantial. It is very likely that such delays affect both quality of life and overall outcome. These findings could be used to test strategies to reduce delay, or to understand barriers to implementation of effective treatments from randomized trials into clinical practice.

Conclusion

There is delay in many of the elements of the pathway in patients with Crohn's anal fistula. In particular, commencement of anti-TNF therapy is often delayed with new diagnoses of Crohn's disease waiting 365 days and patients with established CD waiting 174 days. Diagnosis is a challenge in patients with first presentation of Crohn's disease. Resolving these delays is important to reduce the debility associated with perianal Crohn's disease.

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	New CD (n=25)	Known CD (n=54)	Overall (n=79)
Medical Outpatients	7 (28%)	15 (27.8%)	22 (27.8%)
Acute medical admission	0	5 (9.3%)	5 (6.3%)
Surgical Outpatients	9 (36.0%)	12 (22.9%)	21 (26.6%)
Acute surgical admission	9 (36.0%)	20 (37.0%)	29 (36.7%)
IBD Specialist Nurse	0	2 (3.7%)	2 (2.5%)

Table 1: Number of patients (%) accessing pathway at different points according to pre-existing diagnosis of Crohn's disease.

Procedure performed	Number (percentage of all procedures)
Examination under anaesthetic	14 (10.0%)
Drainage of abscess	39 (27.8%)
Insertion of seton	67 (47.8%)
Lay open of fistula	10 (7.1%)
Anal fistula plug	1 (0.7%)
Video assisted anal fistula treatment (VAAFT)	1 (0.7%)
Seton removal	5 (3.5%)
Stoma formation	2 (1.4%)
Proctectomy	1 (0.7%)

Table 2: Procedures performed during patient treatment.

To From	MRI	SOPD	MOPD	MAU	SAU	CNS	Elective Theatre
MRI	-	42	29	-	19	-	-
SOPD	24	51.5	56	-	59	-	22
MOPD	34	35	89.5	16	70	43	35
MAU	24	11	26	-	18	-	-
SAU	29.5	45	75	60	61	-	0
CNS	16	40	39	18	-	-	-
Elective Theatre	-	59	48.5	55.5	38	25	73.5

Table 3: Median time (days) to move from one part of the pathway to the next. Point of origin is in the left column, and destination is in the horizontal column. ‘-’ indicates no data available. MRI = Magnetic Resonance Imaging, SOPD = Surgical Outpatient Department, MOPD = Medical Outpatient Department, MAU = Medical Admissions Unit, SAU = Surgical Admissions Unit, CNS = Clinical Nurse Specialist.

Figure 1: Case identification chart and reasons for exclusion

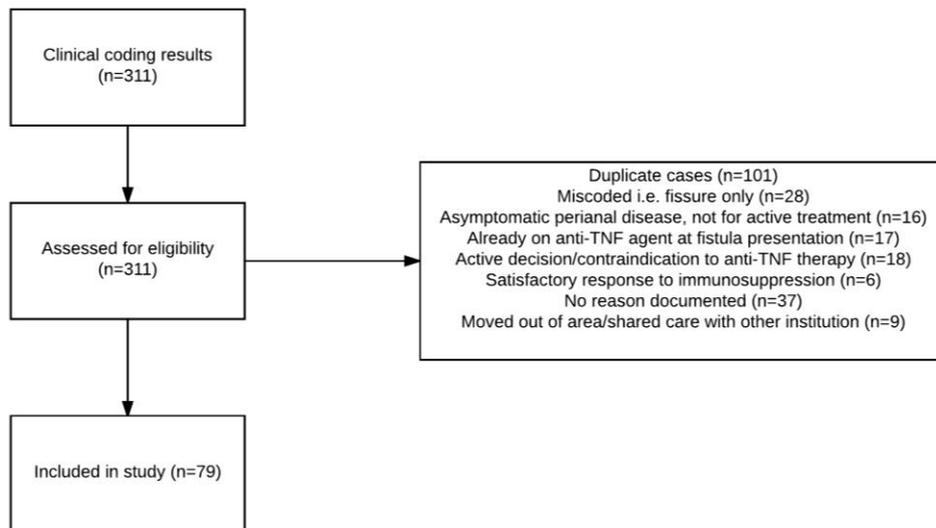


Figure 2: Cumulative percentage of patients receiving initial anti-TNF α therapy in days following start of treatment pathway, split by new and existing diagnoses of Crohn's disease

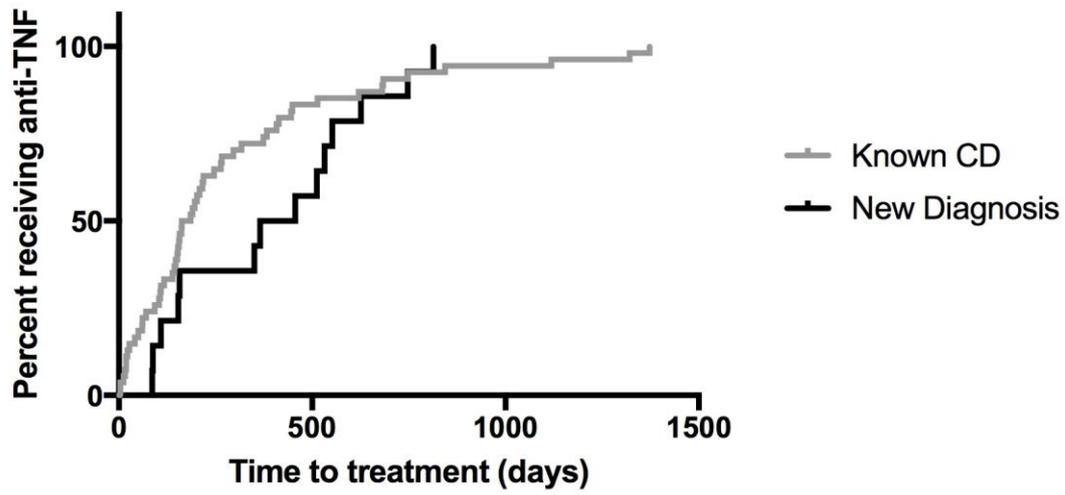


Figure 3: Log transformation of rates per 30 days of pathway for any clinical event, and unplanned readmission compared to length of pathway (days). Both show significant negative correlation of rates with pathway length. (Clinical event Spearman $r = -0.87$, (-0.91 to -0.79) $p < 0.01$; Unplanned readmission Spearman $r = -0.95$ (-0.97 to -0.91) $p < 0.01$).

Log transformations of event rates per 30 days of pathway

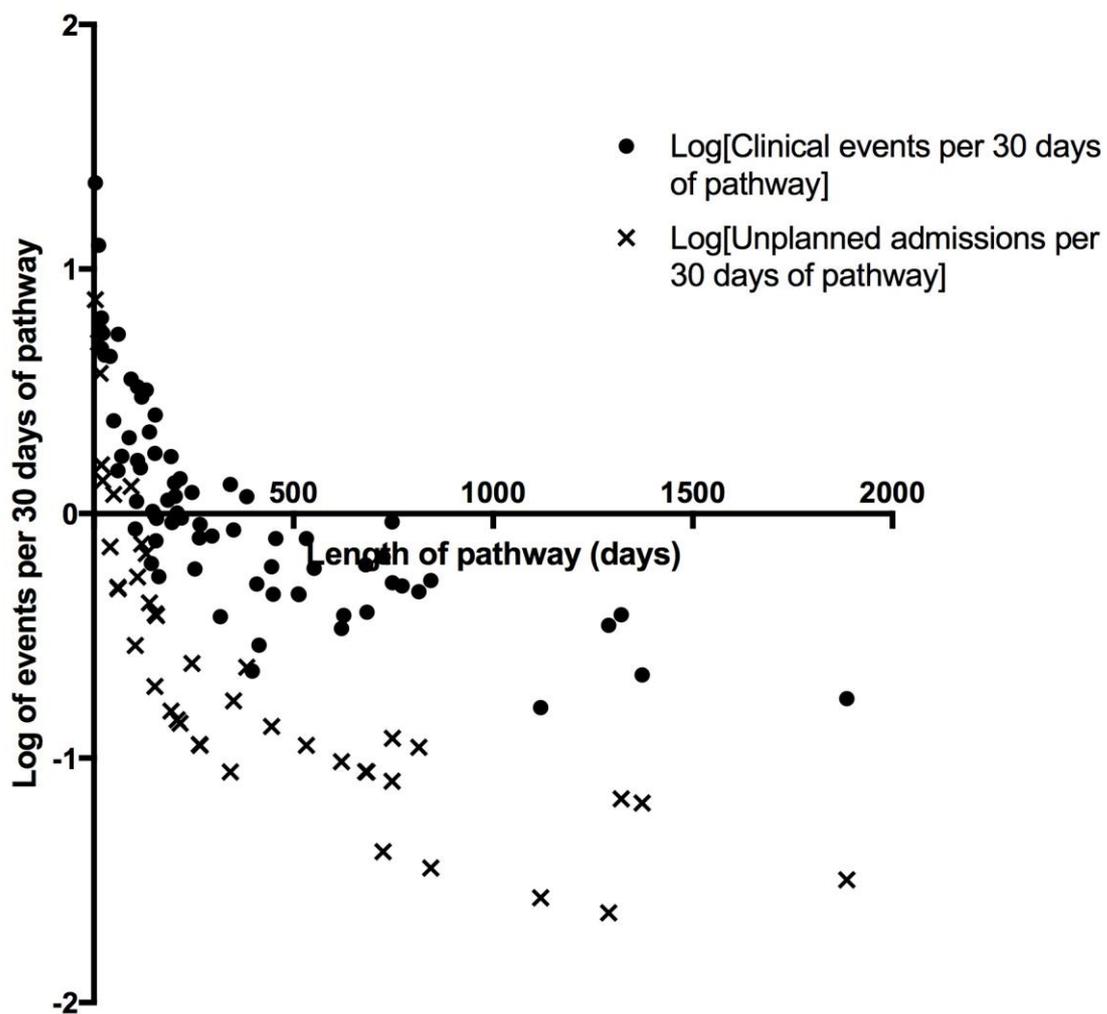


Figure 4: Typical pathways of patients from presentation with Crohn’s anal fistula to commencement of anti-TNF therapy: a) for patients presenting to surgical outpatients, b) for patients presented acutely to the surgical team and c) for patients presenting initially to the medical outpatient team. Curved arrows are labelled with median waiting times (in days) between sequential steps in the pathways described. NB not to scale.

