BMC Gastroenterology

RESEARCH

Open Access

Prolonged time to treatment of biologics in inflammatory bowel disease: disparities from a retrospective study in a tertiary referral centre in the UK

Charlotte Wong[1,2*], Paul Bassett[3], Nikolaos Kamperidis[1], Ravi Misra[1,2], Lisa Younge[1], Lovesh Dyall[1], Katie Yeung[1], Christy Rejee[1] and Naila Arebi[1,2]

Abstract

Background Several disparities in healthcare utilisation and delivery are reported in inflammatory bowel disease (IBD). We examined disparities for delays in biologic administration.

Methods This is a tertiary centre, retrospective, cohort study of consecutive adult IBD outpatients referred to the biologics clinic (BC) for initiation of therapy over 2 years. We collected patient-, disease- and service-related data in addition to adverse clinical outcomes (primary non-response, corticosteroid prescription, IBD hospital admission and surgery) within 6 months of the first dose of therapy. The primary outcome was time-to-therapy (TTT): time interval from referral to the first drug dose. Univariate and multivariate regression analyses examined associations between variables and TTT.

Results 240 patients started biologics: 87 (36%) ulcerative colitis (UC) and 153 (64%) Crohn's disease (CD). Median referral age was 43 years (IQR 34–56) and 128 (53%) were male. Charlson Comorbidity Index was ≤ 1 in 185 patients (77%) and 141 (59%) were biologic naïve. 91 (37.9%) were White British, 88 (36.7%) Asian (Indian or Pakistani), 61 (25.4%) were from other ethnic groups. Median TTT was 76 (IQR 56–97) days. In multivariable analysis, longer TTT was associated with CD, other ethnic groups and Adalimumab. Lack of funding at the time of BC and referral age were of borderline statistical significance. Adverse outcomes at 6 months was significantly associated with C-reactive protein level > 10 mg/L (OR 2.13; $p = 0.03$) but not with longer TTT.

Conclusions Delays in initiating biologic therapy are significantly associated with IBD type, ethnicity and therapy type. Unwarranted variation in IBD care can be mitigated by concerted initiatives to address modifiable factors for timely access to effective therapies.

Key messages

· What is already known on this topic? Disparities are reported in inflammatory bowel disease (IBD) care. Delays in therapy leads to adverse clinical outcomes. Disparities in administration of biologic therapy affects quality of care.

*Correspondence:
Charlotte Wong
charlottewong85@gmail.com
Full list of author information is available at the end of the article

· What does this study add? Sociodemographic characteristics, such as ethnicity, disease and biologic type were significantly associated with delays in initiation of therapy.

· How does this study affect research, practice or policy? Specific patient-related factors and patient profiles were identified that may benefit from focused multi-disciplinary input, and service-related factors may be modified to mitigate delays in starting biologic therapy.

Keywords Inflammatory bowel disease, Biologics, Clinical outcomes, Disparities

Background

The rising global incidence of inflammatory bowel disease (IBD), notably in newly industrialised countries, is widely reported in observational studies [1, 2]. The progressive, chronic nature of IBD, particularly Crohn's disease (CD), is associated with an increased lifetime risk of intestinal complications, extra-intestinal manifestations and disability [1] incurring significant societal and health economic burden [2].

Improved understanding of underlying immunopathophysiology over the last two decades has led to an expansion of available targeted biological and small molecule therapy [3]. Substantial evidence from prospective studies and post-hoc clinical trial data demonstrate improved clinical outcomes through earlier use of biologics [4, 5] Conversely delays in initiating biologic therapy have been associated with worse clinical outcomes, such as achieving inadequate disease control, in both paediatric [6] and adult IBD patients [7, 8].

Timely therapy is paramount for altering disease course to improve long term outcomes and may be hindered by disparate access to treatment across geographical regions, [9] variability in medical practice [10, 11] and a number of patient-related factors. The terms health inequalities or disparities are often used interchangeably for *''systematic, plausibly avoidable health differences adversely affecting socially disadvantaged groups"* [12] or *''differences in the care that people receive and the opportunities that they have to lead healthy lives"* [7]. For IBD, emerging discrete data, mostly from North America, describe disparities in medication utilisation, [8, 10, 11, 13] healthcare delivery, [14, 15] response to biologic therapy, [16] surgical outcomes, [17] and mortality [18] associated with age, sex, socio-economic status, race and ethnicity. Variation in medical practice, resources and outcomes are considered markers of poor quality healthcare and inequity [14] which should drive service improvement.

For patients with moderate to severe disease activity, initiating biologic therapy is a complex multi-step process involving specific measures, outlined by existing IBD guidelines [15, 19–24] and standards [25]. These include pre-biologic screening, vaccination, prescribing, administration and monitoring processes in addition to mandated funding approval in some countries. Delays with one or more steps can contribute to prolonged time to therapy. Time to therapy of over 40 days was reported to be associated with worse self-reported gastrointestinal symptoms, radiological and/or endoscopic appearances at one year [26]. Criteria for defining what constitutes a therapeutic delay and optimal time interval for biologic initiation in the outpatient setting are lacking, despite accumulating evidence of patients experiencing therapeutic delays in various countries [6, 26–28].

The primary aim was to measure time-to-therapy (TTT) in an observational cohort of adult IBD patients. The secondary aims were to (a) evaluate patient- and clinic-related variables that predict risk of prolonged TTT; (b) determine the association between prolonged TTT and adverse outcomes within six months of the first dose of biologic therapy, and (c) identify patient- and clinical-related factors which contribute to prolonged TTT.

Materials and methods

Study setting

Adult IBD outpatients aged ≥ 16 years who met clinical criteria for biologic therapy were referred to a dedicated biologics clinic (BC) run by a multidisciplinary team (MDT), set up to facilitate thorough counselling, safe prescribing, administrative and reimbursement tasks prior to drug administration. The adopted biologics referral pathway from the BC review are shown in Supplementary Figures S2 and S3. Pre-biologic screening requests and completion of funding application forms (where there was a clear decision about biologic agent) were mandatory for referral to BC. Pre-screening results and funding approval had to be complete before patients could receive their first dose of therapy (FD). All included patients received the standard dosing for induction and maintenance regimens for either infliximab, adalimumab, ustekinumab or vedolizumab. Study approval was obtained from the institutional review board (IRB) at London North West University Healthcare NHS Trust in the United Kingdom (evaluation reference number SE21/003) who waived the need for ethical approval and patient consent as anonymised retrospective electronic health record data was used.

Outcomes

The primary outcome was TTT, defined as the time interval between BC referral and FD. Secondary outcomes were: (a) time to BC, (b) documented adverse outcomes within the first six months of FD which included primary non-response (PNR) to therapy, oral or intravenous corticosteroid prescription, IBD-related hospitalisation, IBD-related surgery and death. PNR was defined as a lack of clinical improvement based on physician global assessment, according to clinical practice criteria for standard of care within the first six months of therapy, necessitating discontinuation of current biologic therapy and a switch in therapy.

Eligibility criteria

Consecutive patients electronically referred to the BC for initiation of biologic therapy between 1st October 2019 and 31st October 2021 were included. Patients who had initiated biologic therapy during an inpatient hospital stay were excluded. Those initiating small molecule therapy were excluded as they were referred to a separate clinical pathway.

Data collection

The study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations [20]. The checklist is shown in Supplementary Figure S1.

Data collected retrospectively from patient electronic health records (EHR) were: patient-related (age at referral, gender, ethnicity (using standard national coding used in EHR), Index of Multiple Deprivation Decile [IMDD] score based on postcode), disease-related (Charlson Comorbidity Index [CCI], age at diagnosis, disease duration, disease location and behaviour for CD or disease extent for UC, C-reactive protein level (CRP) (mg/L) and faecal calprotectin (ug/g) obtained within 3 months prior to or within 1 month after referral, disease activity or index score, immunomodulator and biologic exposure), clinic-related (date of referral, date of BC appointment, consultation format (in person or telephone), funder, completion of pre-biologic screening and/or electronic funding request prior to BC appointment, biologic drug, date of the first dose of biologic therapy) and adverse outcomes within the first 6 months of therapy as stated above. We also documented reasons for delays in therapy.

Statistical analysis

TTT was calculated as a continuous measure. Continuous data were reported as means with standard deviations (SD) or medians with interquartile ranges (IQR). Categorical data were reported as numbers and percentages (%).

Complete-case analysis was used in univariate regression analysis which examined individual associations between each baseline variable and outcomes of interest (TTT and adverse events). Only factors showing some association ($p < 0.2$) from the univariable analysis were included in the multivariable analysis to limit the number of variables. A backwards selection procedure was performed to retain only factors showing some association with the outcome in the final model. Multivariable regression analyses was performed to identify joint associations between variables and outcomes. TTT was analysed using linear regression, with the outcome analysed on the log scale due to skewed distribution. Due to the log transformation, the results are expressed as ratios along with their 95% confidence intervals (CI) for the baseline variables and a p-value < 0.05 was considered statistically significant. Adverse outcomes were analysed using logistic regression, with the magnitude of association between factors and the outcome expressed as odds ratios (OR) and 95% CI. Statistical analysis was performed in Stata version 15.2.

Results

Patient characteristics

Of the 287 IBD patients referred to start biologic therapy, 240 were included. Reasons for exclusion are shown in Fig. 1. The demographics for 153 (63.8%) patients with CD and 87 (36.3%) with UC are shown in Table 1.

Clinical setting

Median time to BC was 35 days for all patients: 34 for CD and 36 for UC patients. Face-to-face BC consultations (188; 78.3%) were well maintained during the study period. The majority of patients were referred before completing funding applications (193; 80.4%) and pre-biologic screening (167; 69.6%), indicating that these steps were finalised after BC review. Conversely, 69 (28.8%) did not require rescreening as they attended the BC to switch to a different biological agent. Most received hospital reimbursement from a funder in London (177; 73.8%), the commonest being North West London CCG (140; 58.3%); a smaller number (63; 26.3%) lived in other areas in England. Vedolizumab (82; 34.2%) was the most common choice of biologic agent, followed by Infliximab (64; 26.7%), Adalimumab (56; 23.3%) and Ustekinumab (38; 15.8%). Median TTT was 75 days (IQR 56–96) with a range of 20 to 360 days. Figure 2 shows the distribution of TTT in the study population. One patient had a TTT of 360 days due to concurrent assessment for a renal transplant. The results are shown in Table 2.

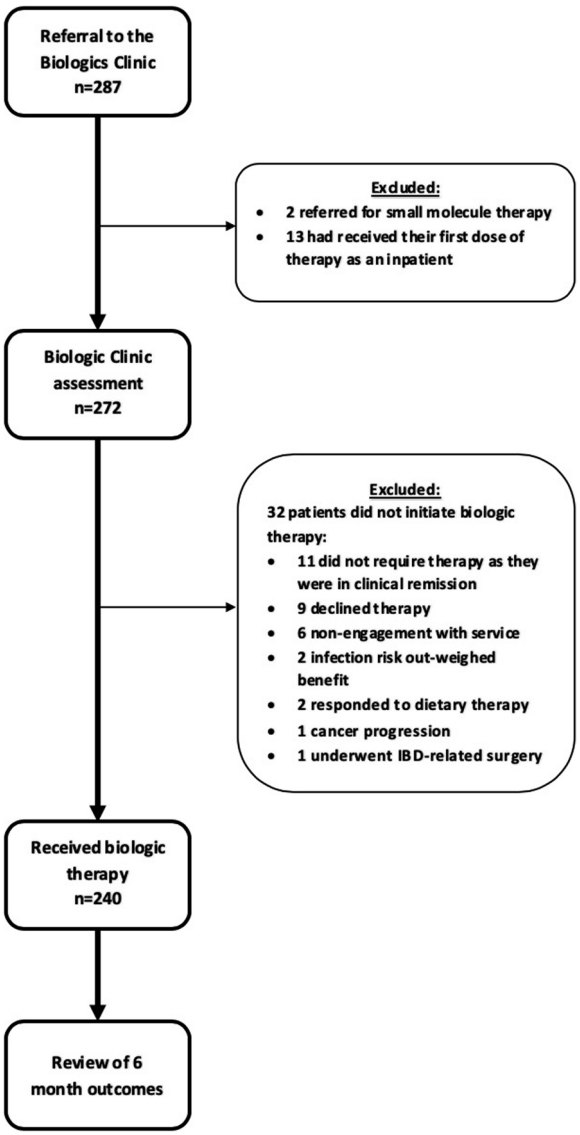

Fig. 1 Flow chart showing the patient selection process for the study and reasons for exclusion from the study

Predictors of longer time to therapy (TTT)

Ethnicity, IBD type and biologic type were associated with delayed TTT on univariable analysis. South Asians had the shortest TTT ($R=1.0$; $p=0.007$) followed by White British patients ($R=1.18$; 95% CI 1.04–1.34), whilst those from other ethnic groups had the longest ($R=1.40$; 95% CI 1.08–1.81). Average waiting times were 18% longer in the White British ($R=1.18$; 95% CI 1.04–1.34) group compared to Asian and 40% longer in other ethnic groups ($R=1.40$; 95% 1.08–1.81) compared to Asian patients ($R=1.0$; $p=0.007$). CD patients ($R=1.16$; 95% CI 1.03–1.32; $p=0.02$) waited 16% longer to start therapy than UC patients. Prescription of Adalimumab ($R=1.24$; 95% CI 1.05–1.46) was associated with a 24% longer wait to start therapy compared with Infliximab ($R=1.0$; $p=0.008$).

Univariate analysis suggested a potential association between greater deprivation (IMDD > 5th decile) and shorter TTT compared to less deprived areas (IMDD ≤ 5th decile), but this was not statistically significant ($R=1$ vs. 0.97; 95% CI 0.85–1.08; $p=0.48$).

Age at referral, ethnicity, IBD type, funding approval and biologic type were independently associated with delays in TTT on multivariable regression analysis. Age at referral and completed funding application pre-clinic were of borderline significance and were retained in the final model. Age at referral ($R=1.03$; 95% CI 0.99–1.07; $p=0.14$) was not significant in the univariable analysis, but there was some evidence of an association with TTT delays after adjusting for the effects of the other variables in this analysis. Older patients showed longer TTT, with every 10-year increase in age associated with a 4% longer wait. Patients with no funding approval ($R=1.15$; 95% CI 1.0–1.33; $p=0.06$) had an average TTT that was 115% longer than those who had approval. The results for ethnicity, IBD type, biologic type were similar to those in the univariable analysis.

Overall, univariable and multivariable regression analyses showed that other ethnic groups ($R=1.41$; 95% CI 1.10–1.80; $p=0.01$), CD ($R=1.18$; 95% CI 1.03–1.34; $p=0.02$) and Adalimumab therapy ($R=1.25$; 95% CI 1.06–1.46; $p=0.001$) were significantly associated with longer TTT. The summarised results are shown in Table 3 and the full results in Supplementary Table S1.

Adverse outcomes within 6 months of the first dose of therapy

Fifty (20.8%) IBD patients experienced one or more adverse outcomes within the first six months of starting therapy. Overall, 23 (9.6%) patients had PNR to therapy, 25 (10.4%) required corticosteroid prescription, 21 (8.8%) had at least one IBD-related hospital admission and 15 (6.3%) required IBD-related surgery of which 10 (4.7%) were elective and 5 (2.1%) were emergency procedures. Both IBD-related hospitalisation (14; 9.2%) and surgery (14; 9.2%) were more frequent in the CD group. One patient with CD was hospitalised and died of disease-related complications within 6 months of biologic initiation. The results are shown in Supplementary Table S2A. Numerically, Asian patients had higher baseline CRP (median 6.5 mg/L) in addition to higher numbers of corticosteroid prescriptions (13; 14.8%), IBD-related hospital admissions (11; 12.5%), IBD-related surgery (5; 5.7%) and total number of patients with any adverse event within 6 months of FD

Table 1 Baseline characteristics of patients initiating biologic therapy, categorised by disease type

Characteristic	All patients	Crohn's disease	Ulcerative colitis
Total number, n (%)	240	153 (63.8)	87 (36.3)
Sex			
Male	128 (53.3)	81 (52.9)	47 (54)
Female	112 (46.7)	72 (47.1)	40 (46)
Age at referral, in years			
Median (IQR)	43 (35–36)	41.1 (34.2–55.1)	44.4 (35–58.4)
≤ 60	190 (79.2)	125 (81.7)	65 (74.7)
> 60	50 (20.8)	28 (18.3)	22 (25.3)
Comorbid status [CCI]			
0	147 (61.3)	97 (63.4)	50 (57.5)
≥ 1	93 (38.8)	56 (36.6)	37 (42.5)
Ethnicity			
White British	91 (37.9)	68 (44.4)	23 (26.4)
Asian Indian or Pakistani	88 (36.7)	47 (30.7)	41 (47.1)
Other ethnic group[a]	61 (25.4)	38 (24.8)	23 (26.4)
Index of Multiple Deprivation Decile [IMDD]			
≤ 5	102 (42.5)	67 (43.8)	35 (40.2)
> 5	138 (57.5)	86 (56.2)	52 (59.8)
Mean (SD)	7.5 (2.1)	6 (2.3)	6.3 (2.4)
Age at diagnosis, years			
Median (IQR)	29 (20–41)	26 (19–39)	33 (24.5–45.5)
≤ 60	222 (92.5)	143 (93.5)	79 (90.8)
> 60	18 (7.5)	10 (6.5)	8 (9.2)
Disease duration, years			
≤ 2	44 (18.3)	28 (18.3)	16 (18.4)
Diagnosed within 6 months	*13 (5.4)*	*12 (7.8)*	*1 (1.1)*
> 2 to 10 years	90 (37.5)	53 (34.6)	37 (42.5)
> 10 years	106 (44.2)	72 (47.1)	34 (39.1)
Disease location for CD [Montreal classification]			
L1	34 (14.2)	34 (22.2)	
L2	37 (15.4)	37 (24.2)	
L3	80 (33.3)	80 (52.3)	
L4 (+)	7 (2.9)	7 (4.6)	
Disease behaviour for CD [Montreal classification]			
B1	105 (43.8)	105 (68.6)	
B2	30 (12.5)	30 (19.6)	
B3	18 (7.5)	18 (11.8)	
Perianal CD			
Yes	37 (15.4)	37 (24.2)	
Disease extent for UC [Montreal classification]			
E1	6 (2.5)		6 (1.1)
E2	37 (15.4)		37 (42.5)
E3	44 (18.3)		44 (50.6)
Previous CD surgery			
Yes	56 (23.3)	56 (36.6)	
C-reactive protein (CRP), mg/L			
Total number, n (%)	233 (97.1)	148 (96.7)	85 (97.7)
Median (IQR)	6.2 (1.8–20.2)	8.5 (2.4–29.7)	3.5 (1.0–9.9)

Table 1 (continued)

Characteristic	All patients	Crohn's disease	Ulcerative colitis
Faecal calprotectin, ug/g			
Total number, n (%)	154 (64.2)	95 (62.1)	59 (67.8)
Median (IQR)	470 (166–993)	423 (158–962)	555 (174–1070)
Concomitant oral steroids			
At the time of referral, n (%)	68 (28.3)	33 (21.6)	35 (40.2)
At the time of BC, n (%)	51 (21.3)	22 (14.4)	29 (33.3)
Immunomodulator naïve			
Yes	94 (39.2)	25 (16.3)	69 (79.3)
Biologic naïve			
Yes	141 (58.8)	87 (56.9)	54 (62.1)

(+) Consisting of Crohn's disease patients with a Montreal classification of L4 only, L1 + L4, L2 + L4 and L3 + L4

Abbreviations: *CCI* Charlson Comorbidity Index, *IMDD* Index of Multiple Deprivation Decile

[a] Subgroups include individuals who were not classed as White-British or Asian. These included the following: Black-any other background, Black-Caribbean, mixed-white and Asian, not stated, other-Arab, other-any other, other-Chinese, White-any other, White-any other background, White-Irish

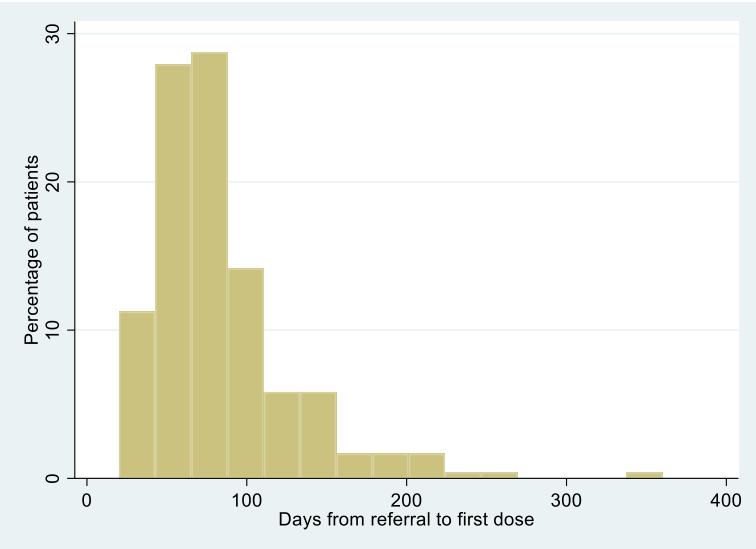

Fig. 2 Histogram of the time interval from referral to BC to the first dose of biologic therapy (TTT) in the study population

(21; 23.9%). Supplementary Table 2B shows the results for baseline CRP (mg/L) and adverse outcomes stratified by ethnic group.

Univariate analyses showed that a baseline CRP level > 10 mg/L was significantly associated with an adverse outcome within 6 months of starting a biologic (OR = 2.13; 95% CI 1.06–4.27; $p = 0.03$) whereas longer TTT was not (OR = 1.03; 95% CI 0.82–1.30; $p = 0.78$). Furthermore, although there was some indication that higher IMDD may be associated with a higher likelihood of adverse events, this finding did not reach statistical significance ((IMDD ≤ 5th decile: OR = 1.0) versus (IMDD > 5th decile: OR = 0.52); 95% CI 0.26–1.04; $p = 0.06$).

In multivariable analysis, which examined the joint association between variables and adverse events within 6 months, only CRP remained significantly associated with this outcome. After adjusting for this factor, no other variables were found to be significant. Since CRP was the only variable in the final model, the results were equivalent to those in the univariable analysis. (Supplementary Table S3).

Table 2 Clinic related data for included IBD referrals, categorised by disease type

Clinic data	All patients	Crohn's disease	Ulcerative colitis
Total number, n (%)	240	153 (63.8)	87 (36.2)
Type of appointment			
Face to face	188 (78.3)	115 (75.2)	73 (83.9)
Telephone	52 (21.7)	38 (24.8)	14 (16.1)
Indication for referral			
Biologic naïve	146 (60.8)	90 (58.8)	54 (62)
Restart biologic after a drug holiday	25 (10.4)	23 (15)	2 (2.3)
Switch in biologic therapy	69 (28.8)	40 (26.1)	29 (33.3)
Primary non-response	9 (2.8)	3 (2)	6 (6.9)
Secondary loss of response	47 (19.6)	30 (19.6)	17 (19.5)
Adverse drug reaction to biologic drug	13 (5.4)	7 (4.6)	6 (6.9)
Geographic location of funder			
London	177 (73.8)	110 (71.9)	67 (77)
North Central London	22 (9.2)	11 (7.2)	11 (12.6)
North East London	3 (1.3)	3 (2)	0
North West London	140 (58.3)	87 (56.9)	53 (60.9)
South East London	6 (2.5)	4 (2.6)	2 (2.3)
South West London	6 (2.5)	5 (3.3)	1 (1.1)
East of England	35 (14.6)	22 (14.4)	13 (14.9)
North East and Yorkshire	0	0	0
North West	0	0	0
Midlands	3 (1.3)	2 (1.3)	1 (1.1)
South West	2 (0.8)	2 (1.3)	0
South East	23 (9.6)	17 (11.1)	6 (6.9)
Clinical activities prior to Biologics Clinic			
Completed infection screen			
Yes	73 (30.4)	49 (32)	24 (27.6)
No	167 (69.6)	104 (68)	63 (72.4)
Not required due to switch in therapy	56 (23.3)	32 (20.9)	24 (27.6)
Completed funding application			
Yes	47 (19.6)	30 (19.6)	17 (19.5)
No	193 (80.4)	123 (80.4)	70 (80.5)
Agreed biologic drug			
Vedolizumab	82 (34.2)	34 (22.2)	48 (55.2)
Adalimumab	56 (23.3)	38 (24.8)	18 (20.7)
Infliximab	64 (26,7)	52 (34)	12 (13.8)
Ustekinumab	38 (15.8)	31 (20.3)	7 (8)
Time to therapy, in days			
Median (IQR)	75.5 (56–96)	78 (58–103)	70 (50–88.5)
Range	20–360	20–360	21–215

Patient- and clinical-related factors contributing to delays

We conducted a qualitative analysis to describe factors contributing to TTT delays (Supplementary Table S4) and identified several key categories: case review, funding application and review, pharmacy administrative, patient-related, and multifactorial factors where there was more than one primary reason. Following initial BC, the majority of case reviews (183; 76.3%) occurred after 7 days, with the most common time frame between 7 and 14 days (139; 57.9%) and a smaller subset of cases (19; 7.9%) extending beyond 28 days. Patient-related factors emerged as a significant contributor, accounting for 41 cases (17.1%). Combined factors, where multiple issues overlapped, were

Table 3 Variables significantly associated with time to therapy (TTT) in univariate and multivariate analyses

Baseline data	Univariate analysis		Multivariate analysis	
	Relative ratio (95% CI)	*p*-value	Relative ratio (95% CI)	*p*-value
Age at referral[a]	1.03 (0.99–1.07)	**0.14**		
Ethnicity				
Asian or Pakistani	1	**0.007**	1	**0.01**
White British	1.18 (1.04–1.34)		1.13 (1.00–1.28)	
Other ethnic group	1.40 (1.08–1.81)		1.41 (1.10–1.80)	
IBD type				
UC (+)	1	**0.02**	1	**0.02**
CD	1.16 (1.03–1.32)		1.18 (1.03–1.34)	
Completed funding application				
Yes	1	**0.07**	1	0.06
No	1.15 (0.99–1.34)		1.15 (1.00–1.33)	
Biologic drug				
Infliximab	1	**0.008**	1	**0.001**
Adalimumab	1.24 (105–1.46)		1.25 (1.06–1.46)	
Vedolizumab	1.02 (0.87–1.18)		1.00 (0.86–1.19)	
Ustekinumab	0.91 (0.75–1.10)		0.86 (0.71–1.04)	

(+) Including IBD-unclassified patients

Abbreviations: *CI* confidence interval, *CD* Crohn's disease, *UC* ulcerative colitis

[a] Odds ratio given for a 10-year increase in age at referral or diagnosis

responsible for 28 cases (11.7%), while abnormal laboratory results were a factor in 16 cases (6.7%). Within patient-related factors, the most frequent reasons included patient indecision about initiating therapy (12; 5%), medical illness (12; 5%), and patient non-engagement with pre-biologic screening (10; 4.2%).

Among patients > 60 years at referral (50; 20.8%), patient-related factors were the most frequent cause of delays (7; 14%) with indecision (4; 8%) being the leading cause followed by non-engagement with pre-screening (3; 6%). Certain factors were notably more common in CD than UC such as patient-related factors (CD: 26 (17%); UC: 7 (8%)), combined reasons (CD: 18 (11.8%); UC: 4 (4.6%)) and medical illness (CD: 9 (5.9%); UC: 2 (2.3%)). Medical illness included: 3 infections, 2 perianal sepsis requiring surgery, 1 small bowel obstruction, 1 symptomatic anaemia, 1 renal transplant work-up and 1 required oncology clearance before starting therapy. For patients initiating Adalimumab therapy (56; 23.3%), pharmacy and/or homecare company delays (12; 5%) followed by patient-related factors (7; 2.9%) were the most frequent primary causes of delays.

Discussion

Timely therapy is a fundamental aspect of treatment of moderate to severe disease in IBD, yet there are no key performance indicators nor standards by which to judge the therapeutic timing. This observational cohort study, from a busy tertiary IBD referral centre, identified a substantial variation for TTT (20–360 days) in patients with moderate to severe disease activity initiating biologic therapy.

Our median TTT interval of 75 days (IQR 56–96) was due to several factors and delays were associated with other ethnic groups, CD diagnosis and Adalimumab therapy. There was a trend that older age at referral (>60 years) was associated with longer TTT but this did not reach statistical significance. It is well recognised that older people are less likely to receive biologic drugs possibly due to concerns about infections and addressing co-morbidities. When we explored underlying reasons in this age group, indecision about accepting therapy and poor adherence to pre-screening protocols were noted. Larger, focused qualitative studies to explore underlying reasons for delays in this sub-group would help guide the development of interventions aimed at addressing patient-related delays.

Longer TTT was associated with other ethnic groups which may allude to underlying barriers to care and unmet needs within the healthcare system. A systematic review by Ahmed et al. reported that ethnic minority groups with chronic bowel diseases experienced health inequalities relating to cultural, religious and social contexts in addition to challenges with language barriers and reduced health literacy [29]. Likewise, disparities in the acceptance and uptake of biologic therapy between White British patients and those from other ethnic groups have been observed in rheumatoid arthritis [30]. Our findings were unexpected in that South Asians received treatment quicker. Our local population is predominantly of South Asian origin and it has been reported that this subgroup may present with more severe disease. Such a presentation may have expedited therapy to avoid hospital admission or may have been offered during a hospital stay. Our results showed that a greater proportion of Asian patients experienced primary non-response (10; 11.4%) and required corticosteroid prescriptions (13; 14.8%), IBD-related hospital admission (11; 12.5%) and IBD-related surgery (5; 5.7%) within the first 6 months of therapy.

Univariate analysis indicated a possible link between higher deprivation (IMDD > 5th decile) and shorter TTT, compared to less deprived areas (IMDD ≤ 5th decile), however this did not reach statistical significance ($R = 1$ vs. 0.97; 95% CI 0.85–1.08; $p = 0.48$). No significant association was found between IMDD and the occurrence of adverse events (OR 1.0 versus 0.52; 95% CI 0.26–1.04; $p = 0.06$).

CD patients encountered longer TTT (median 78; IQR 58–103) which may reflect the relative disease complexity and associated complications, such as sepsis requiring therapy before starting biologic therapy, compared with UC (median 70; IQR 50–90) [31]. The total number of individual adverse events at 6 months was higher in the CD group (51; 33.3%) and more patients had medical illness including requirement for surgical intervention (14; 9.2%). Numerically, a higher proportion of UC patients (14; 16.1%) had documented PNR, which may suggest that assessing response in CD is more challenging.

In univariate and multivariate analyses, longer TTT was not significantly associated with worse outcomes at 6 months, however those with a baseline CRP > 10 mg/L had double the odds (OR 2.13; 95% CI 1.06–4.27; $p = 0.03$) of experiencing an adverse event at this timepoint (PNR, hospital admission and need for corticosteroids, IBD-related surgery or death) compared to those with a normal CRP (< 10 mg/L). This suggests the need to facilitate earlier medical therapy and closer monitoring in those with biochemical evidence of active disease. The lack of significant association between TTT and adverse outcomes at 6 months could have been related to expedition of higher-risk cases although attributing this as a definitive cause would require further exploration of clinician decision-making and triaging processes.

Starting a subcutaneously administered biologic (Adalimumab) was associated with delays due to the logistics of homecare set-up. In contrast Ustekinumab was associated with the shortest TTT possibly because the first dose is administered intravenously as a bolus compared to Infliximab or Vedolizumab where three timed sequential induction doses are required prior to ongoing maintenance therapy through an intravenous or subcutaneous route.

Overall, the most common reasons contributing to delays in our study population were cases extending beyond > 14 days after BC and patient-related factors, the latter highlights the need to develop strategies aimed at improving patient engagement.

We acknowledge a few limitations. The retrospective observational design inherently incurs potential bias from unobserved confounders and missing data. Efforts were made to minimise bias by employing multivariable logistic regression during the statistical analysis to adjust for known confounding variables. The study was hampered by the COVID-19 pandemic which may have resulted in greater delays in access to therapy, however delays in therapy were recognised prior to this event ($n = 24$; TTT range 13–87 days) and after ($n = 216$; TTT range 1–169 days) within the study population. Detailed comparative statistical analysis is limited by the differences in sample size.

The small sample sizes of some individual ethnic groups precluded detailed analyses and a few individuals had unrecorded ethnic status ($n = 7$) where there was a missed opportunity to identify specific trends within these smaller subgroups which may have masked ethnic disparities. Furthermore, the relatively short 6 month follow-up period and potential clinical selection bias when assessing outcomes during this time may have under-estimated the number of adverse outcomes associated with treatment delays. Future studies with a larger sample size, extended follow up and additional clinical response measures including patient-reported outcomes are required to determine whether longer TTT is associated with disease progression or complications. Although the process of prescribing biologic therapy is unique to our centre, the tasks required before administration of the first dose are generalisable to all centres (Supplementary Figure S2 and S3).

We recognise that retrospective documentation may not capture all contributing factors leading to therapeutic delays, and that attributing a single cause in some cases may oversimplify the process. However,

we aimed to highlight instances where multiple factors were involved, acknowledging the complexity of these delays as a baseline measure by which to gauge initiative to improve care.

A key strength is that, this is the largest published cohort study that reports delays in biologic initiation, examines predictors associated with therapeutic delays, and highlights disparities in patient care. We also included additional socio-economic data collected during routine care, such as ethnicity and relative deprivation status (IMDD), which may be lacking in similar studies, and accounted for baseline disease activity (CRP and faecal calprotectin) which were included within our predictive modelling. While the study was conducted at a tertiary centre for colorectal disease, it also provides IBD care for its local population, who are included in the study population. However, multicentre centre studies could identify geographical variations in this area of patient care, while qualitative research could offer further insights in to patient-specific reasons contributing to these disparities.

There are a few studies with which we can compare our findings. McCulloch *et al.* reported delays of > 40 days associated with worsening symptoms in a UK IBD cohort [26]. In contrast we found no significant association between delays and adverse outcomes. A second UK cohort study by Liu et al. showed delays of > 21 days for many IBD patients: subcutaneous therapy was associated with longer delays due to drug delivery [27]. The findings concur with our results where longer TTT was associated with subcutaneous drug administration of the first dose.

Disparities in biologic initiation are reported in paediatric and post-surgical patients in North America. Constant et al., reported a median biologic initiation time of 21 days in a paediatric IBD cohort with insurer authorisation being associated with prolonged TTT and increased IBD-related healthcare utilisation [6]. Similarly, delays with initiating post-operative prophylactic biological therapy were reported by Mekelberg et al. in a CD cohort following bowel resection [32]. In other inflammatory conditions such as asthma [33–35] and rheumatoid arthritis [36] delays due to challenges with funder authorisation, regional differences in prescription criteria and variation in clinician practice are reported.

Balarajah e*t al.*, conducted a prospective cohort study through interrogation of the IBD BioResource platform and found that provision of medical and surgical therapy in the UK was consistent regardless of ethnicity and no disparities were identified [37]. Therefore, disparities in IBD biologic initiation may be influenced by patient-driven factors in different settings which are not captured within EHR and there is an unmet need to identify key barriers to therapy.

The importance of earlier biologic therapy in CD has been reinforced by recently published studies. The PROFILE study demonstrated a window of opportunity for early top-down therapy in newly diagnosed CD patients which achieved significantly better clinical outcomes compared to a step-up approach which is considered to delay the introduction of effective disease-modifying therapy, resulting in the development of complications and structural bowel damage [38]. Lujan et al., observed a reduction in corticosteroid dependency and surgery in patients who initiated biologic therapy within the first year of CD diagnosis [39].

There have been a few studies from the United Stats which identified variability in the use of immunosuppressive therapies between specialist IBD centres and between Gastroenterologists in the United States [10, 11, 13]. Differences in local guidelines, clinical practice or experience may lead to variations in the use of these agents and contribute to prolonged TTT. The absence of UK and European-specific evidence leaves uncertainty about the impact of therapy-related delays on long term clinical outcomes, exposing a gap in international guidance and quality standards on an acceptable time interval to initiate biologic therapy in an outpatient setting.

Conclusions

Unwarranted treatment delays and disparities in care prevail. The lack of a defined and acceptable timeline, highlights a pressing need to establish quality-of-care standards for timely biologic initiation. As IBD prevalence increases and biologic therapies costs decline with increasing biosimilar availability, easier access to drugs will arguably offset the burden on patients and health services with improved health outcomes. Quality of care initiatives that address timely access to specialist drugs merit attention.

Abbreviations

BC	Biologics clinic
CCG	Clinical Commissioning Group
CCI	Charlson Comorbidity Index
CD	Crohn's disease
CI	Confidence intervals
CRP	C-reactive protein
EHR	Electronic health records
FD	First dose of therapy
IBD	Inflammatory bowel disease
IBDU	Inflammatory bowel disease unclassified
IMDD	Index of Multiple Deprivation decile
IQR	Interquartile range
MDT	Multidisciplinary team
OR	Odds ratio
PNR	Primary non-response
SD	Standard deviation
TTT	Time to therapy

UC Ulcerative colitis
UK United Kingdom

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03909-9.

Supplementary Material 1.

Acknowledgements
There are no acknowledgements.

Authors' contributions
N.A. co-designed the study, oversaw the protocol development, analysed data, interpreted results, collated the first draft of the manuscript, critically appraised the manuscript and revised the manuscript. C.W. co-designed the study, generated the final protocol from the drafts and reiterations, formulated the data extraction sheet, extracted data, analysed data, interpreted results, wrote the manuscript and revised it. P.B. provided the statistical analysis, interpreted the results and critically appraised the manuscript and revised it. N.K. interpreted results, critically appraised the manuscript and revised the manuscript. R.M. interpreted results, critically appraised the manuscript and revised the manuscript. L.Y. contributed to data presentation and critically appraised the manuscript. L.D. contributed to data presentation and critically appraised the manuscript. K.Y. contributed to data presentation and critically appraised the manuscript. C.R. contributed to data presentation and critically appraised the manuscript. All authors read the manuscript and gave final approval of the version that was submitted.

Funding
The project was funded through Pfizer Global Medical Grants (grant number 63641015). As the grant recipient, London North West University Healthcare NHS Trust is the sponsor.

Data availability
The data underlying this article are available in the article and its online supplementary material. The datasets used and/or analysed during the study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study does not report on experiments on humans and/or the use of human tissue samples. It was conducted in accordance with the Declaration of Helsinki, Health Research Authority (HRA) in the United Kingdom and Good Clinical Practice (GCP) guidelines. Institutional review board (IRB) approval was obtained from London North West University Healthcare NHS Trust in the United Kingdom (evaluation reference number SE21/003) who waived the need for ethical approval and patient consent as anonymised retrospective EHR was used.

Consent for publication
We did not use any personally identifiable patient data and therefore patient consent was not required for publication.

Competing interests
C.W. has received sponsor fees with Dr Falk Pharma. P.B. has no conflicts of interest. N.K. has received speaker fees from Abbvie, Janssen and Takeda in addition to sponsor fees from Tillots, Takeda and Janssen. R.M has received speaker fees from Abbvie. L.Y. has received lecture, advisory board and personal fees from Abbvie, Janssen and Takeda. L.D. has received speaker fees from Dr Falk Pharma and Abbvie. K.Y. has received sponsor and speaker fees from Abbvie. C.R. has no conflicts of interest. N.A. has received grant support from Janssen in addition to lecture, advisory and personal fees from Takeda, Janssen, Galapagos and Pfizer.

Author details
[1]Department of Inflammatory Bowel Disease, St Mark's National Bowel Hospital, London, UK. [2]Department of Metabolism, Digestion and Reproduction, Imperial College London, London, UK. [3]Statsconsultancy Ltd, Amersham, UK.

Received: 27 January 2025 Accepted: 17 April 2025
Published online: 09 May 2025

References

1. Lichtenstein GR, Shahabi A, Seabury SA, Lakdawalla DN, Espinosa OD, Green S, Brauer M, Baldassano RN. Increased Lifetime Risk of Intestinal Complications and Extraintestinal Manifestations in Crohn's Disease and Ulcerative Colitis. Gastroenterol Hepatol (N Y). 2022;18(1):32–43.
2. Park KT, Ehrlich OG, Allen JI, Meadows P, Szigethy EM, Henrichsen K, Kim SC, Lawton RC, Murphy SM, Regueiro M, Rubin DT, Engel-Nitz NM, Heller CA. The Cost of Inflammatory Bowel Disease: An Initiative From the Crohn's & Colitis Foundation. Inflamm Bowel Dis. 2020;26(1):1–10.
3. Juillerat P, Grueber MM, Ruetsch R, Santi G, Vuillemoz M, Michetti P. Positioning biologics in the treatment of IBD: A practical guide - Which mechanism of action for whom? Curr Res Pharmacol Drug Discov. 2022;3:100104.
4. Berg DR, Colombel JF, Ungaro R. The Role of Early Biologic Therapy in Inflammatory Bowel Disease. Inflamm Bowel Dis. 2019;25(12):1896–905.
5. Mantzaris GJ, Zeglinas C, Theodoropoulou A, Koutroubakis I, Orfanoudaki E, Katsanos K, Christodoulou D, Michalopoulos G, Tzouvala M, Moschovis D, Michopoulos S, Zampeli E, Soufleris K, Ilias A, Chatzievangelinou C, Kyriakakis A, Antachopoulou K, Karmiris K. The Effect of Early vs Delayed Initiation of Adalimumab on Remission Rates in Patients With Crohn's Disease With Poor Prognostic Factors: The MODIFY Study. Crohns Colitis 360. 2021;3(4):otab064.
6. Constant BD, de Zoeten EF, Stahl MG, Vajravelu RK, Lewis JD, Fennimore B, Gerich ME, Scott FI. Delays Related to Prior Authorization in Inflammatory Bowel Disease. Pediatrics. 2022;149(3):e2021052501.
7. What are health inequalities? : The King's Fund; 2022 [Available from: https://www.kingsfund.org.uk/publications/what-are-health-inequalities.
8. Farrukh A, Mayberry J. Apparent Disparities in Hospital Admission and Biologic Use in the Management of Inflammatory Bowel Disease between 2014–2018 in Some Black and Ethnic Minority (BEM) Populations in England. Gastrointestinal Disord. 2020;22:144–51.
9. Raine T, Gkini MA, Irving PM, Kaul A, Korendowych E, Laws P, Foulkes AC. Maintaining Clinical Freedom Whilst Achieving Value in Biologics Prescribing: An Integrated Cross-Specialty Consensus of UK Dermatologists. Rheumatol Gastroenterol BioDrugs. 2021;35(2):187–99.
10. Ananthakrishnan AN, Kwon J, Raffals L, Sands B, Stenson WF, McGovern D, Kwon JH, Rheaume RL, Sandler RS. Variation in treatment of patients with inflammatory bowel diseases at major referral centers in the United States. Clin Gastroenterol Hepatol. 2015;13(6):1197–200.
11. Singh S, Chowdhry M, Umar S, Bilal M, Clarke K. Variations in the medical treatment of inflammatory bowel disease among gastroenterologists. Gastroenterol Rep (Oxf). 2018;6(1):61–4.
12. Braveman PA, Kumanyika S, Fielding J, Laveist T, Borrell LN, Manderscheid R, Troutman A. Health disparities and health equity: the issue is justice. Am J Public Health. 2011;101(Suppl 1):S149–55.
13. Kappelman MD, Bousvaros A, Hyams J, Markowitz J, Pfefferkorn M, Kugathasan S, Rosh J, Otley A, Mack D, Griffiths A, Evans J, Grand R, Langton C, Kleinman K, Finkelstein JA. Intercenter variation in initial management of children with Crohn's disease. Inflamm Bowel Dis. 2007;13(7):890–5.
14. Berry SK, Siegel CA, Melmed GY. Quality Improvement Initiatives in Inflammatory Bowel Disease. Curr Gastroenterol Rep. 2017;19(8):41.
15. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, Hayee B, Lomer MCE, Parkes GC, Selinger C, Barrett KJ, Davies RJ, Bennett C, Gittens S, Dunlop MG, Faiz O, Fraser A, Garrick V, Johnston PD, Parkes M, Sanderson J, Terry H, group IBDgec, Gaya DR, Iqbal TH, Taylor SA, Smith M, Brookes M, Hansen R, Hawthorne AB. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68(Suppl 3):s1–106.

16. Greywoode R, Petralia F, Ullman TA, Frederic Colombel J, Ungaro RC. Racial Difference in Efficacy of Golimumab in Ulcerative Colitis. Inflamm Bowel Dis. 2023;29(6):843–9.
17. Booth A, Ford W, Brennan E, Magwood G, Forster E, Curran T. Towards Equitable Surgical Management of Inflammatory Bowel Disease: A Systematic Review of Disparities in Surgery for Inflammatory Bowel Disease. Inflamm Bowel Dis. 2022;28(9):1405–19.
18. Galoosian A, Rezapour M, Liu B, Bhuket T, Wong RJ. Race/Ethnicity-specific Disparities in In-Hospital Mortality and Hospital Charges Among Inflammatory Bowel Disease-related Hospitalizations in the United States. J Clin Gastroenterol. 2020;54(7):e63–72.
19. Torres J, Bonovas S, Doherty G, Kucharzik T, Gisbert JP, Raine T, Adamina M, Armuzzi A, Bachmann O, Bager P, Biancone L, Bokemeyer B, Bossuyt P, Burisch J, Collins P, El-Hussuna A, Ellul P, Frei-Lanter C, Furfaro F, Gingert C, Gionchetti P, Gomollon F, Gonzalez-Lorenzo M, Gordon H, Hlavaty T, Juillerat P, Katsanos K, Kopylov U, Krustins E, Lytras T, Maaser C, Magro F, Marshall JK, Myrelid P, Pellino G, Rosa I, Sabino J, Savarino E, Spinelli A, Stassen L, Uzzan M, Vavricka S, Verstockt B, Warusavitarne J, Zmora O, Fiorino G. ECCO Guidelines on Therapeutics in Crohn's Disease: Medical Treatment. J Crohns Colitis. 2020;14(1):4–22.
20. Raine T, Bonovas S, Burisch J, Kucharzik T, Adamina M, Annese V, Bachmann O, Bettenworth D, Chaparro M, Czuber-Dochan W, Eder P, Ellul P, Fidalgo C, Fiorino G, Gionchetti P, Gisbert JP, Gordon H, Hedin C, Holubar S, Iacucci M, Karmiris K, Katsanos K, Kopylov U, Lakatos PL, Lytras T, Lyutakov I, Noor N, Pellino G, Piovani D, Savarino E, Selvaggi F, Verstockt B, Spinelli A, Panis Y, Doherty G. ECCO Guidelines on Therapeutics in Ulcerative Colitis: Medical Treatment. J Crohns Colitis. 2022;16(1):2–17.
21. Ko CW, Singh S, Feuerstein JD, Falck-Ytter C, Falck-Ytter Y, Cross RK, American Gastroenterological Association Institute Clinical Guidelines C. AGA Clinical Practice Guidelines on the Management of Mild-to-Moderate Ulcerative Colitis. Gastroenterol. 2019;156(3):748–64.
22. Feuerstein JD, Ho EY, Shmidt E, Singh H, Falck-Ytter Y, Sultan S, Terdiman JP, American Gastroenterological Association Institute Clinical Guidelines C. AGA Clinical Practice Guidelines on the Medical Management of Moderate to Severe Luminal and Perianal Fistulizing Crohn's Disease. Gastroenterology. 2021;160(7):2496–508.
23. Bressler B, Marshall JK, Bernstein CN, Bitton A, Jones J, Leontiadis GI, Panaccione R, Steinhart AH, Tse F, Feagan B, Toronto Ulcerative Colitis Consensus G. Clinical practice guidelines for the medical management of nonhospitalized ulcerative colitis: the Toronto consensus. Gastroenterology. 2015;148(5):1035-58 e3.
24. Panaccione R, Steinhart AH, Bressler B, Khanna R, Marshall JK, Targownik L, Afif W, Bitton A, Borgaonkar M, Chauhan U, Halloran B, Jones J, Kennedy E, Leontiadis GI, Loftus EV Jr, Meddings J, Moayyedi P, Murthy S, Plamondon S, Rosenfeld G, Schwartz D, Seow CH, Williams C, Bernstein CN. Canadian Association of Gastroenterology Clinical Practice Guideline for the Management of Luminal Crohn's Disease. J Can Assoc Gastroenterol. 2019;2(3):e1–34.
25. Kapasi R, Glatter J, Lamb CA, Acheson AG, Andrews C, Arnott ID, Barrett KJ, Bell G, Bhatnagar G, Bloom S, Brookes MJ, Brown SR, Burch N, Burman A, Crook K, Cummings JF, Davies J, Demick A, Epstein J, Faiz O, Feakins R, Fletcher M, Garrick V, Jaffray B, Johnson M, Keetarut K, Limdi J, Meade U, Muhammed R, Murdock A, Posford N, Rowse G, Shaw I, St Clair Jones A, Taylor S, Weaver S, Younge L, Hawthorne AB. Consensus standards of healthcare for adults and children with inflammatory bowel disease in the UK. Frontline Gastroenterol. 2020;11(3):178–87.
26. McCulloch A, Abbas M, Bannaga A, McDowell P, Bate T, Kandathil M, Shah J, Sharif Q, Love M, Sharma N, Cooney R. P174 System delays have real consequences: Impact of timing of biologic commencement on inflammatory bowel disease patient response. J Crohn's Colitis. 2019;13(Supplement_1):S176-S.
27. Liu E, Jatale R, DeSilva D, Hussain S, Danso Y, Sabine J, Taylor J, Sattar H, Smith P, Subramanian S, Limdi J. PMO-39 Factors influencing delays in biologic initiation in inflammatory bowel disease. Gut. 2021;70(Suppl 4):A96–7.
28. Choi DK, Cohen NA, Choden T, Cohen RD, Rubin DT. Delays in Therapy Associated With Current Prior Authorization Process for the Treatment of Inflammatory Bowel Disease. Inflamm Bowel Dis. 2023;29(10):1658–61.
29. Ahmed S, Newton PD, Ojo O, Dibley L. Experiences of ethnic minority patients who are living with a primary chronic bowel condition: a systematic scoping review with narrative synthesis. BMC Gastroenterol. 2021;21(1):322.
30. Selvaskandan H, Moorthy A. An Ethnic Variation in the Acceptance of Biological Disease-Modifying Therapies: A University Hospital Experience. Cureus. 2021;13(5):e15270.
31. Le Berre C, Danese S, Peyrin-Biroulet L. Timely Use of Biologics in Early Crohn's Disease: The Return of "Hit Hard and Early"? Dig Dis Sci. 2019;64(11):3035–7.
32. Cohen-Mekelburg S, Gold S, Schneider Y, Dennis M, Oromendia C, Yeo H, Michelassi F, Scherl E, Steinlauf A. Delays in Initiating Post-operative Prophylactic Biologic Therapy Are Common Among Crohn's Disease Patients. Dig Dis Sci. 2019;64(1):196–203.
33. Dudiak GJ, Popyack J, Grimm C, Tyson S, Solic J, Ishmael FT. Prior authorization delays biologic initiation and is associated with a risk of asthma exacerbations. Allergy Asthma Proc. 2021;42(1):65–71.
34. Sehanobish E, Ye K, Imam K, Sariahmed K, Kurian J, Patel J, Belletti D, Chung Y, Jariwala S, White A, Jerschow E. Elaborate biologic approval process delays care of patients with moderate-to-severe asthma. J Allergy Clin Immunol Glob. 2023;2(2):100076.
35. Porsbjerg CM, Menzies-Gow AN, Tran TN, Murray RB, Unni B, Audrey Ang SL, Alacqua M, Al-Ahmad M, Al-Lehebi R, Altraja A, Belevskiy AS, Bjornsdottir US, Bourdin A, Busby J, Canonica GW, Christoff GC, Cosio BG, Costello RW, FitzGerald JM, Fonseca JA, Hansen S, Heaney LG, Heffler E, Hew M, Iwanaga T, Jackson DJ, Kocks JWH, Kallieri M, Bruce Ko HK, Koh MS, Larenas-Linnemann D, Lehtimaki LA, Loukides S, Lugogo N, Maspero J, Papaioannou AI, Perez-de-Llano L, Pitrez PM, Popov TA, Rasmussen LM, Rhee CK, Sadatsafavi M, Schmid J, Siddiqui S, Taille C, Taube C, Torres-Duque CA, Ulrik C, Upham JW, Wang E, Wechsler ME, Bulathsinhala L, Carter V, Chaudhry I, Eleangovan N, Hosseini N, Rowlands MA, Price DB, van Boven JFM. Global Variability in Administrative Approval Prescription Criteria for Biologic Therapy in Severe Asthma. J Allergy Clin Immunol Pract. 2022;10(5):1202-16 e23.
36. Tatangelo M, Tomlinson G, Paterson JM, Ahluwalia V, Kopp A, Gomes T, Bansback N, Bombardier C. Association of Patient, Prescriber, and Region With the Initiation of First Prescription of Biologic Disease-Modifying Antirheumatic Drug Among Older Patients With Rheumatoid Arthritis and Identical Health Insurance Coverage. JAMA Netw Open. 2019;2(12):e1917053.
37. Balarajah S, Martinez-Gili L, Alexander JL, Mullish BH, Perry RW, Li JV, Marchesi JR, Parkes M, Orchard TR, Hicks LC, Williams HRT. Diverse Phenotypes, Consistent Treatment: A Study of 30 997 South Asian and White Inflammatory Bowel Disease Patients Using the UK Inflammatory Bowel Disease BioResource. J Crohns Colitis. 2025;19(1):jjae186.
38. Noor NM, Lee JC, Bond S, Dowling F, Brezina B, Patel KV, Ahmad T, Banim PJ, Berrill JW, Cooney R, De La Revilla Negro J, de Silva S, Din S, Durai D, Gordon JN, Irving PM, Johnson M, Kent AJ, Kok KB, Moran GW, Mowat C, Patel P, Probert CS, Raine T, Saich R, Seward A, Sharpstone D, Smith MA, Subramanian S, Upponi SS, Wiles A, Williams HRT, van den Brink GR, Vermeire S, Jairath V, D'Haens GR, McKinney EF, Lyons PA, Lindsay JO, Kennedy NA, Smith KGC, Parkes M, Group PS. A biomarker-stratified comparison of top-down versus accelerated step-up treatment strategies for patients with newly diagnosed Crohn's disease (PROFILE): a multicentre, open-label randomised controlled trial. Lancet Gastroenterol Hepatol. 2024;9(5):415–27.
39. Lujan R, Buchuk R, Focht G, Yogev D, Greenfeld S, Ben-Tov A, Weisband YL, Lederman N, Matz E, Ben Horin S, Dotan I, Nevo D, Turner D. Early Initiation of Biologics and Disease Outcomes in Adults and Children With Inflammatory Bowel Diseases: Results From the Epidemiology Group of the Nationwide Israeli Inflammatory Bowel Disease Research Nucleus Cohort. Gastroenterol. 2024;166(5):815-25 e22.

Publisher's Note