Original Article

Early discontinuation of biological therapy among inflammatory bowel disease patients in Bahrain: Real world experience

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Abstract

Background: Despite the effectiveness of several biological agents in the treatment of inflammatory bowel disease (IBD), some patients respond better than others. Such discrepancies are often evident early in the treatment course. The aim of this study is to identify the risks and assess the rate of early biological discontinuation (BD) among IBD patients.

Methods: In this retrospective cohort study conducted in Bahrain all IBD patients who were administered biological agents between June 2009 and June 2019 were included. Medical records were reviewed to collect study data and confirm IBD diagnoses. Early discontinuation of biological agents was defined by discontinuation of a biological agent (within 6 months from administration). Montreal classification was used to classify Crohn's disease and ulcerative colitis (UC) according to location and extension, respectively.

Results: Ineffectiveness was the most common reason for early BD. Early BD was not related to the type of IBD, biological agent used, or to most patient-related factors (such as gender and family history). Patient age at index biological initiation was the only independent significant predictor of early BD ($P = 0.045$, adjusted odds ratios (95% CI): 1.06 (1.001–1.116)] even after correction of two significant factors: comorbid diabetes and marked weight loss at diagnosis.

Conclusion: The older the IBD patient at the time of biological therapy initiation, the higher the incidence of early BD. Therefore, caution and close follow-up are required for biological therapy among elderly patients to assess effectiveness and adverse drug reactions.

Keywords: Biological therapy, Crohn's disease, inflammatory bowel diseases, ulcerative colitis

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INTRODUCTION

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis (IC), are chronic inflammatory conditions of the gastrointestinal tract (GIT) characterized by a relapsing and remitting course that may lead to progressive bowel damage.[1,2] Our previous study concluded that IBD can no longer be considered a rare disease in Bahrain, where the incidence of UC and CD is steadily increasing.[3]

Treatment of IBD has historically consisted of corticosteroids, 5-aminosalicylic acid (5-ASA), and immunomodulators, including methotrexate and thiopurines. Due to their limited therapeutic efficacy, up to 30% of UC patients and 80% of CD patients require bowel resection to treat medically refractory disease or associated complications, including strictures, fistulae, and abscesses.[4,5] The use of biological therapies, particularly anti-TNF-α agents, has resulted in achieving deep remission, a paradigm shift for IBD management.[6,7]

The biological agents approved for IBD treatment have been in use for over two decades, while others are still in the development process. These biological agents act by targeting specific steps in the local inflammation process. However, they may also cause serious adverse effects. Throughout the intestinal mucosa of IBD patients, an increase in TNF-positive cells has been reported along with high levels of TNF in patients' feces.[8] TNF presented on the cell surface can be cleaved by a metalloprotease to release soluble TNF (sTNF) into the circulation. Both forms of TNF can bind and activate TNF receptors (TNFR1 and 2), inducing cell death (apoptosis) and immune cell activation (release of cytokines, chemokines, arachidonic acid, and leukotrienes). Epithelial cells suffer the impact of this process, resulting in the characteristic mucosal ulceration, erythema, and exudates noted in IBD.[8] TNF is directly cytotoxic to virus-infected cells, making it a potent antiviral molecule despite its pro-inflammatory effects. It is also highly effective in activating cells in response to bacterial infection, particularly B-cells and macrophages.[9] Thus, the inhibition of TNF can be a double-edged sword, leading to the efficacy of anti-TNFs in IBD and their adverse effects.

Anti-TNF-α biological agents are monoclonal antibodies against both free and membrane-bound TNFα, which prevent TNFα from binding to its receptor sites, neutralizing its pro-inflammatory activity. Anti-TNF antibodies were first approved by the Food and Drug Administration (FDA) for CD in 1998. Currently, approved agents for IBD include infliximab, adalimumab, certolizumab, and golimumab. For 15 years, anti-TNFs were the only approved biological class for IBDs treatment. Recently, the FDA has approved newer agents with novel targets or mechanisms of action for the treatment of IBDs, such as Janus kinase inhibitors (tofacitinib)[10] and anti-integrins (vedolizumab and ustekinumab),[11] as well as biosimilar agents (biogenerics) such as adalimumab-adbm.[12]

With this growing arsenal of biological IBD treatments, it is important to optimize their usage and evaluate the reasons for early biological discontinuation (BD). Given the wide spectrum of IBDs, the young age of onset, and often a life-long need for treatment, there are concerns regarding severity, prognosis, effectiveness, high costs, and complications. In the last decade, biological agents have been prescribed in Bahrain to treat IBD patients. In this study, we traced back a cohort of 101 IBD patients treated with biological agents (alone or along with other drugs) to identify risk factors and assess the rate of early BD.

PATIENTS AND METHODS

Study Setting and Design

This retrospective cohort study was conducted in Salmaniya Medical Complex (Kingdom of Bahrain). After the study research proposal was approved by the Secondary Health Care Research Sub Committee (SHCRC) of the Kingdom of Bahrain Ministry of Health, the institutional research review board granted us access to medical records under the condition of data anonymity.

Our cohort included all patients with confirmed IBD who were started on biological therapy (infliximab, adalimumab, or vedolizumab) between June 2009 and June 2019. Each patient's medical records were reviewed to confirm diagnosis of IBD based on the available clinical, endoscopic, histologic, and radiographic information. Data regarding biological agent usage, IBD type, behavior, age, signs and symptoms at diagnosis, sex, job status, nationality, comorbidities, vaccination history, screening for tuberculosis (TB) and cytomegalovirus (CMV), IBD disease extension, extraintestinal manifestations, surgical interventions, and detailed drug history were extracted from chart review. Early discontinuation of a biological agent was defined as discontinuation of the biological agent within 6 months from administration.

Montreal classification[13] was used to classify CD according to the location, and UC according to the extension [Tables 1 and 2].

Table 1: Montreal classification for Crohn's disease Location[14]

L1: Ileal
L2: Colonic
L3: Ileocolonic
L4: Isolated upper disease*

*L4 is a modifier that can be added to L1-L3 when concomitant upper gastrointestinal disease is present

Table 2: Montreal classification of the extent of ulcerative colitis (UC)[14]

Extent	Anatomy
E1: Ulcerative proctitis	Involvement limited to the rectum (i.e., proximal extent of inflammation is distal to the rectosigmoid junction)
E2: Left-sided UC (distal UC)	Involvement limited to a proportion of the colorectum distal to the splenic flexure
E3: Extensive UC (pancolitis)	Involvement extends proximally to the splenic flexure

Statistical Analysis

Data manipulation and analysis were conducted using SPSS software, version 20.0 (IBM SPSS, Chicago, IL, USA). Across all quantitative variables in all (sub) groups, Shapiro test for normality was used to test for significant deviation from normal distribution. Continuous parameters were reported as medians and interquartile ranges (IQRs). Mann–Whitney U test was used to compare continuous parameters. Nominal discrete parameters were reported as count and percent (%) and compared using either Fisher exact (2 × 2), free Freeman–Halton extension of the Fisher exact (2 × 3 or 3 × 3), or Pearson Chi-square tests of independence (r x c i.e for tables with other numbers of Rows X columns). Univariate and multiple logistic regression analyses were performed to assess predictive associations between demographic variables and early BD. Odds ratios (unadjusted and adjusted) were calculated. Multicollinearity diagnostics were computed, and assumptions were met for all regression analyses.

RESULTS

Across participating hospitals, we identified 311 IBD patients. After excluding duplicates and ineligible entries, 305 patients were included, 101 (33.1%) of which were treated with a total of 118 courses of biological therapy. Of these patients, 40 (39.6%) were diagnosed with UC, 59 (58.4%) with CD, and 2 (2%) with indeterminate colitis. All 101 patients were treated with a biological agent for the first time (biological-naïve); 17 (16.8%) of these patients also required a second course of biological agents (biological-experienced). The overall rate of early BD (discontinued in ≤6 months from biological initiation) was 15/118 (13.7%).

According to BD, biological-naïve IBDs patients were subdivided into three groups: "early BD," "persistent," and "fresh undetermined." The early BD group included 14 patients (13.9%) who discontinued their index biological agent within ≤6 months of initiation (provided that by the time of our study, those patients were clinically followed up for persistence of symptoms for more than 6 months from biological initiation). The persistent group included 79 patients (78.2%) who continued their index biological agent for >6 months from initiation. The fresh undetermined group included 8 patients (7.9%), representing those who were still on their index biological agent for <6 months (as of June 2019), who were thus excluded. Analysis was then conducted on a total of 93 patients subdivided into the early BD group and persistent group [Tables 3–6].

The same subdivisions were also applied to our 17 biological-experienced patients. The early BD group included only one patient (6%), the persistent group included 12 patients (70.6%), and the remaining 4 patients belonged to the fresh undetermined group and thus were excluded. Therefore, only 13 patients represented the biological-experienced cohort divided into early BD (1; 7.7%) and persistent (12; 92.3%).

Impact of previous exposures to biological on persistence

The overall rate of early BD (biological-naïve and biological-experienced) was 15/106 (14.15%) courses. Early BD among the biological-naïve cohort (14/93; 15.1%) was much higher than in the biological-experienced cohort (1/13; 7.7%); however, this difference was not statistically significant ($P^{FE} = 0.688$) as shown in Figure S1.

Reasons for early BD

Ineffectiveness (primary nonresponse) was the most common reason for early BD found in 12/15 (80%) cases. Similar results were noted among biological-naïve in 11/14 (78.6%) patients and among biological-experienced in 1/1 (100%). Comparing primary nonresponse rates in both cohorts revealed no statistically significant difference ($P^{FE} = 1$). Among biological-naïve patients, the second most common reason for early BD was adverse reactions, seen in 3/14 (21.4%) patients; out of them, two had CMV infection and one had allergic reactions [Figure S2].

Type of biological therapy

All 93 patients had exclusively been treated with anti-TNFs, either infliximab (51; 54.8%) or adalimumab (42; 45.2%), as their first biological therapy. Only one of the 13 patients in the biological-experienced cohort (8%) had vedolizumab as his second biological agent. Thus,

Table 3: A and B - Comparison of patients' demographic characteristics, comorbidity, and recent laboratory results in early BD versus persistent group among biological-naïve patients

	Patients who continued 1st biological therapy for >6 months (*n*=79 pts.)	Patients who discontinued 1st biological therapy≤6 months (*n*=14 pts.)	*P*
A- Nominal variables presented as [positive counts/total entries, (%)]			
Gender			
Male	50/79 (63.3%)	7/14 (50%)	P^{FE}=0.383
Female	29/79 (36.7%)	7/14 (50%)	
Current tobacco smoking	10/76 (13.2%)	3/13 (23.1%)	P^{FE}=0.395
Bahraini Nationality	73/79, (92.4%)	13/14, (92.9%)	P^{FE}=1
Employment	31/70, (44.3%)	2/11, (18.2%)	P^{FE}=0.185
Vaccination	34/56, (60.7%)	4/7, (57.1%)	P^{FE}=1
Alcohol intake	1/76, (1.3%)	1/13, (7.7%)	P^{FE}=0.272
Family history of IBD	6/75, (8%)	0/13, (0%)	P^{FE}=0.586
Diabetes mellitus	2/77, (2.6%)	4/13, (30.8%)	P^{FE}=0.004
Hypertension	2/77, (2.6%)	2/13, (15.4%)	P^{FE}=0.098
Marked weight loss at IBD Dx	27/79, (34.2%)	9/14, (64.3%)	P^{FE}=0.041
B-Quantitative variables presented as [median (IQR), *n*=Total entries]			
Age (yrs.) at IBD Dx	23 (13), *n*=79	29 (21), *n*=13	*Z*=−2.11, *P*=0.033
Age (yrs.) at biological initiation	27 (15), *n*=79	41.5 (35), *n*=14	*Z*=−2.39, *P*=0.014
Last Laboratory Results			
ESR 1st h	27 (24.5), *n*=69	40 (40), *n*=11	*Z*=−1.73, *P*=0.090
CRP	19 (54.25), *n*=68	29.45 (70.96), *n*=10	*Z*=−0.75, *P*=0.462
Hb g/dl	11 (2.4), *n*=79	10.05 (3.575), *n*=14	*Z*=−0.99, *P*=0.333
MCV	73 (13), *n*=79	69 (17.85), *n*=13	*Z*=−0.25, *P*=0.814
Platelets (x103)	346 (204), *n*=79	315 (293.5), *n*=13	*Z*=−0.31, *P*=0.758
ALT U/L	27 (19.75), *n*=76	27 (33.5), *n*=13	*Z*=−0.26, *P*=0.804
Bili μmol/L	6.5 (5), *n*=76	6 (16.5), *n*=13	*Z*=−0.67, *P*=0.522
Cr μmol/L	62 (20.75), *n*=76	64 (38.25), *n*=14	*Z*=−0.16, *P*=0.875

Z; Mann-Whitney standardized statistics, IQR=Interquartile range (Q3-Q1); PFE=Fisher Exact test *P*

12 (94%) patients in the biological-experienced cohort also had anti-TNFs as their second biological therapy, infliximab in 7/13 (53.8%) patients, and adalimumab in 5/16 (38.5%) patients. No statistically significant difference was found between the three types of biological agents among both cohorts ($P = 0.153$). No statistically significant difference ($P = 0.564$) was found when comparing rates of early BD among 51 biological-naïve patients treated with infliximab (9/51; 17.6%) versus 42 biological-naïve patients treated with adalimumab (5/42; 11.9%). The same applies to the biologicals-experienced cohort for infliximab discontinuation (1/7 (14.3%) versus adalimumab discontinuation (0/5; 0%) ($P = 1$).

We also compared the early BD index biological-naïve group who continued the first biological agent for >6 months (n = 79) versus the index biological persistent group who discontinued it in ≤6 months (n = 14) [Tables 3–5].

Differences in patient characteristics

We found that the age of the patient at IBD diagnosis was significantly higher in the early index BD group compared to the index biological persistent group ($Z = -2.11$, $P = 0.033$) [Figure S3]. Similar findings were observed for the patients' age at index biological initiation, $Z = -2.39$, $P = 0.015$ [Figure S4].

On comparing the comorbidities between the groups, diabetes mellitus was found to be significantly higher in the early index BD group (4/13; 30.8%) compared to the index biological persistent group (2/77; 2.6%); $P^{FE} = 0.004$. The rate of marked weight loss at IBD diagnosis was also significantly higher in the early index BD group (9/14; 64.3%) compared to the index biological persistent group (27/79; 34.2%); $P^{FE} = 0.041$. No significant differences were found among other demographic characteristics or laboratory results [Table 3].

Differences in IBD disease characteristics

No statistically significant difference was found concerning the distribution of the three types of IBD (CD, UC, or ID) across early BD versus persistent groups (Freeman–Halton $P^{FE} = 0.382$). Applying the Montreal classification[13] for CD location, no significant difference was found in the rates of the four classes of CD locations. Applying the Montreal classification of extent of UC also revealed no significant difference in the rates of the three classes of UC extension as shown in Table 4. No significant difference was found concerning the median disease duration at index biological initiation between the two groups ($Z = -1.037$, $P = 0.301$). On comparing the symptoms and signs of IBDs at diagnosis, no statistically significant difference was found except for the significantly higher rate of marked

Table 4: A&B - Comparison of IBD disease characteristics in the early BD versus the persistent group among biological-naïve patients

	Patients who Continued 1st biological therapy for >6 months	Patients who discontinued 1st biological therapy ≤6 months	*P*
A-Nominal variables presented as [positive counts/total entries, (%)]			
Type of IBD			
Crohn's disease	48/79 (60.8%)	8/14 (57.1%)	P^{FE}*=0.442
Ulcerative Colitis	30/79 (38%)	5/14 (35.7%)	
Indetermined IBD	1/79 (1.3%)	1/14 (7.1%)	
Crohn's disease according to Montreal classification of CD location			
L1 Ileal	15/48 (31.3%)	3/8 (37.5%)	P^{FE}=0.703
L3 Ileocolonic	6/48 (12.5%)	1/8 (12.5%)	P^{FE}=1
L2 Colonic	17/48 (35.4%)	3/8 (37.5%)	P^{FE}=1
L4 Isolated upper disease	10/48 (20.8%)	1/8 (12.5%)	P^{FE}=1
Ulcerative Colitis according to Montreal classification of UC			
Extension			
E1 Ulcerative proctitis	7/30 (23.3%)	1/5 (20%)	P^{FE}=1
E2 Left sided (distal) UC	10/30 (33.3%)	3/5 (60%)	P^{FE}=0.337
E3 Extensive UC (pancolitis)	10/30 (33.3%)	1/5 (20%)	P^{FE}=1
Unknown	3/30 (10%)	0/5 (0%)	
Positive histopathological findings			
Granulation	14/74, (18.9%)	5/14, (35.7%)	P^{FE}=0.172
Dysplasia	3/74, (4.1%)	1/14, (7.1%)	P^{FE}=0.507
Symptoms and Signs of IBDs at Diagnosis			
Bleeding per-rectum	38/79, (48.1%)	9/14, (64.3%)	P^{FE}=0.386
Mucus	14/79, (17.7%)	5/14, (35.7%)	P^{FE}=0.152
Anorexia	25/79, (31.6%)	10/14, (71.4%)	P^{FE}=0.007
Marked weight loss	27/79, (34.2%)	9/14, (64.3%)	P^{FE}=0.041
Fever	16/79, (20.3%)	3/14, (21.4%)	P^{FE}=1
Perianal symptoms	7/79, (8.9%)	0/14, (0%)	P^{FE}=0.589
Perianal abscess	8/79, (10.1%)	0/14, (0%)	P^{FE}=0.602
Fistula	13/79, (16.5%)	2/14, (14.3%)	P^{FE}=1
Fissure	4/79, (5.1%)	0/14, (0%)	P^{FE}=1
GIT stenosis	4/79, (5.1%)	1/14, (7.1%)	P^{FE}=0.566
Tags	3/79, (3.8%)	0/13, (0%)	P^{FE}=1
B-Quantitative variables presented as [median (IQR), *n*=Total entries]			
Disease duration at biologic initiation	3 (6), *n*=79	5.5 (13) *n*=14	*Z*=−1.037, *P*=0.316

Z=Mann-Whitney standardized statistics, IQR=Interquartile range (Q3-Q1); P^{FE}=Fisher Exact test P. PFE*=Freeman-Halton extension of Fisher Exact test for 3 × 2 applications

weight loss and anorexia in the early index BD group (as shown in Table 4).

IBD course complication, interventions, and extraintestinal manifestations

No statistically significant differences were found regarding the rate of occurrence of complications, except for jaundice which was significantly higher in the early index BD group compared to the index biological persistent group (P^{FE} = 0.003), and the higher rate of positive recent screening for CMV in early index BD group than the index biological persistent group (P^{FE} = 0.021) [Table 5].

Predictors of early BD

Regression analysis was performed to identify potential independent predictors of index BD at 6 months. Three patient-related predictors were first explored in a univariate manner, including age at biological initiation, comorbidity with diabetes mellitus, and presence of marked weight loss at IBD diagnosis. All three were shown to be significant predictors of index BD at 6 months [Table 6 A]. However, on multivariate logistic regression model (R^2 = 28.1%), only the age at biological initiation remained a significant independent predictor of early BD (P = 0.045, adjusted Odds ratio: 1.06; 95% CI: 1.001–1.116) denoting that the odds of early BD increase by a factor of 1.06 for every one-year increase in patient age at index biological initiation [Table 6B]. Both comorbidity with diabetes mellitus and presence of marked weight loss at IBD diagnosis turn insignificant in the model (i.e. after adjusting for age of IBD patient at index biological initiation [P = 0.194, adjusted Odds ratio: 4.58; 95% CI: 0.46–45.6) and P = 0.113, adjusted Odds ratio: 3.06; 95% CI: 0.77–12.19]), respectively.

Finally, the median age at index biological initiation among our diabetic IBD patients was found to be significantly higher compared to nondiabetic IBD patients (Z = −2.05, P = 0.04) as shown in Figure S5.

Table 5: A&B - Comparison of IBD disease course complication, interventions and extraintestinal manifestations in the early BD group versus the persistent group among biological-naïve patients

	Patients who Continued 1st biological for >6 months	Patients who discontinued 1st biological ≤6 months	*P*
A-Nominal variables presented as [positive counts/total entries, (%)]			
Complications of IBDs throughout the course of the disease			
Anemia	44/78, (56.4%)	11/14, (78.6%)	P^{FE}=0.147
Intestinal obstruction	13/79, (16.5%)	3/14, (21.4%)	P^{FE}=0.703
Jaundice	0/79, (0%)	3/14, (21.4%)	P^{FE}=0.003
Sepsis	2/79, (2.5%)	2/14, (14.3%)	P^{FE}=0.106
Perforation	2/79, (2.5%)	0/14, (0%)	P^{FE}=1
Stricture	10/79, (12.7%)	3/14, (21.4%)	P^{FE}=0.407
Fulminant colitis	1/50, (2%)	1/12, (8.3%)	P^{FE}=0.352
Abscess	10/79, (12.7%)	1/14, (7.1%)	P^{FE}=1
Osteoporosis	3/50, (6%)	0/12, (0%)	P^{FE}=1
Fistula	19/79, (24.1%)	3/14, (21.4%)	P^{FE}=1
Pregnancy related complication	8/79, (10.1%)	1/14, (7.1%)	P^{FE}=1
Malignant dysphagia	3/79, (3.8%)	1/14, (7.1%)	P^{FE}=0.485
Recent CMV positive screening	0/79, (0%)	2/14, (14.3%)	P^{FE}=0.021
Recent TB positive screening	1/50, (2%)	2/12, (16.7%)	P^{FE}=0.093
IBD-related surgical intervention			
Large bowel resection colectomy	19/79, (24.1%)	3/14, (21.4%)	P^{FE}=1
Small Bowel resection	7/79, (8.9%)	1/14, (7.1%)	P^{FE}=1
Stricturo-plasty	5/79, (6.3%)	2/14, (14.3%)	P^{FE}=0.283
Fistulotomy	5/79, (6.3%)	1/14, (7.1%)	P^{FE}=1
Fistulectomy	4/79, (5.1%)	0/14, (0%)	P^{FE}=1
Diversion	14/79, (17.7%)	3/14, (21.4%)	P^{FE}=0.716
Abscess drain	11/79, (13.9%)	1/14, (7.1%)	P^{FE}=0.685
Extraintestinal manifestations			
Ankylosing spondylitis	1/79, (1.3%)	0/14, (0%)	P^{FE}=1
Arthritis	9/79, (11.4%)	0/14, (0%)	P^{FE}=0.346
Uveitis	1/79, (1.3%)	0/14, (0%)	P^{FE}=1
Gallstones	0/79, (0%)	1/14, (7.1%)	P^{FE}=0.151
B-Quantitative variables presented as [median (IQR), *n*=Total entries]			
Number of IBD-related Admissions	4 (4), n=69	4 (8) n=11	Z=−1.3, P=0.204

DISCUSSION

In our retrospective cohort study on 101 IBDs patients, the rate of early discontinuation of a biological agent was 12.7%, where biological therapy was stopped within the first 6 months of use. This rate was 13.9% in biological-naïve and 6% in biological-experienced patients, although this was not statistically different. These rates are much lower than rates of biological-treated psoriasis patients, where 46% discontinued treatment within 12 months,[15] and rates for rheumatoid arthritis patients where 21% discontinued therapy within 6 months.[16]

We found no significant impact of previous exposures to biologicals on persistence. Lower but still insignificant (P^{FE} = 0.688) rates of early BD were found among biological-experienced patients compared to biological-naïve patients. Our results oppose the findings reported by Harrold *et al.*[17] who studied the impact of prior biological use on persistence of treatment with psoriatic arthritis patients. They reported greater treatment persistence in biological-naïve patients than in biological-experienced patients; however, unlike our study, they did not address early discontinuity as a separate criterion.

Among all our patients treated with biologicals, ineffectiveness (primary nonresponse) was found to be the most common reason for early BD (80%). Similar results were noted among biological-naïve (78.6%) and biological-experienced (100%) patients. Among biological-naïve patients, the second most common reason for early BD was adverse reaction (21.4%). These results are comparable to the results of a meta-analysis of studies that include rheumatologic patients on biologicals.[16]

Similar to studies on psoriasis and rheumatoid arthritis,[15,16] we found that the choice of treatment (infliximab or adalimumab) did not impact rates of early BD. The number of patients using alternative biologicals was too small for adequate comparison. Currently, there are three FDA-approved anti-TNFα therapies in the United States: infliximab, adalimumab, and golimumab. The safety profile and efficacy of these therapies are similar; thus, the choice depends on patient preference.[18,19]

Table 6: A and B - Results of univariate versus multivariate logistic regression analysis of potential patient-related predictors of early discontinuation of index biological

Logistic regression analysis of predictors of early discontinuation of index biological								
	A-Univariate				B-Multivariate model (R^2=28.1%)			
	β	S.E.	Sig.	OR (95% C.I.)	B	S.E.	Sig.	Adj. OR (95% C.I.)
Age (yrs.) at biological initiation	0.072	0.023	0.002	1.07 (1.03-1.12)	0.055	0.028	0.045	1.06 (1.001-1.116)
DM	2.813	0.935	0.003	16.7 (2.7-104.2)	1.522	1.173	0.194	4.58 (0.46-45.6)
Marked weight loss at Dx	1.243	0.606	0.040	3.47 (1.06-11.37)	1.119	0.705	0.113	3.06 (0.77-12.19)

OR=crude odds ratio; Adj. OR=adjusted odds ratio; β=beta-coefficient (regression estimate), S.E.=standard error of estimate

Unlike results of Chen *et al.*, who reported a significant negative impact of female gender on non-persistence of biologic medication across IBDs patients,[15] and unlike previous studies with similar findings on other autoimmune diseases like rheumatoid arthritis,[16] our study found no difference in early BD rates between male and female IBDs patients. We found that the age of the patient at IBD diagnosis, as well as the patients' age at index biological initiation, were both significantly higher in the early BD group compared to the persistent group. Ineffectiveness was the most common reason for early BD among IBD patients in our study, which concurs with the results reported by Lobaton *et al.*[20] on the efficacy and safety of anti-TNF therapy in elderly patients with IBD. Their study was limited by the retrospective study design, as was ours, and the response was based on clinical assessment only, rather than endoscopic evaluation.

Desai *et al.*[21] also concluded that the IBD population aged over 60 (at the time of anti-TNF therapy initiation) was at a higher risk for discontinuation of therapy. In our study, we found that age at index biological initiation, comorbidity with diabetes mellitus, and marked weight loss were significantly higher in the early index BD group than in the index biological persistent group. However, significance was lost in a multivariate logistic regression model and only patients' age remained the significant potential independent predictor of early index BD. Results confirmed that it was the effect of the age at index biological initiation rather than DM comorbidity. We traced back this effect of DM comorbidity and found that median age at index biological initiation among our diabetic IBD patients was significantly higher compared to our nondiabetic IBD patients ($Z = -2.05$, $P = 0.04$). This finding concurs with Katz *et al.*,[22] who reported that over half of elderly IBDs patients had a significant comorbidity such as cardiovascular disease or history of cancer.

High-quality evidence-based data to evaluate the safety and efficacy of anti-TNFα biologicals in older adults is limited, possibly due to older adults being routinely excluded from clinical trials.[23] Thus, the indication to use biological medications in older populations remains the same as that of younger patients.[24] Treatment decisions for older adults are complicated not only by the lack of trials but also because older adults have a higher incidence of comorbid diseases, drug-drug interactions potentially induced by polypharmacy (including supplements and over-the-counter medications), aging immune systems, and extended social or financial issues.

Finally, both, rates of jaundice and positive screening for CMV were significantly higher in the early index BD group, indicating a possible direct adverse effect reported with anti-TNF-α therapy,[14,25] and thus, a direct cause for drug discontinuation rather than just a predictor of early BD. Such serious adverse effects are possibly due to the reactivation of latent CMV or hepatic virus. Such findings not only emphasize the importance of the serological screening for viral infections and vaccination prior to anti-TNF but also the importance of closely monitoring patients on anti-TNF for early signs of infection. In these patients, anti-TNF therapy should be withdrawn when serious infections occur until the infection has been identified and properly treated. Close monitoring is incredibly important in the first 6 months of anti-TNF therapy and in high-risk patients such as elderly patients.

This study was limited by its retrospective study design and the fact that the response to biological drugs was based solely on clinical assessment rather than endoscopic evaluation. Finally, our patients were almost exclusively treated with only one family of biological agents, anti-TNF-α.

In view of the retrospective nature of our study, inherent difficulties should be considered in future studies, amongst which is the unavailability of consistent data concerning the level of biologicals, or albumin level and BMI at the time of discontinuation, to assess the bioavailability and drug kinetics of biological in each patient as important predictors of early biological discontinuity. Thorough investigation is needed to investigate the cause of weight loss and jaundice and its relation to disease severity and biological side effects, respectively, especially with so many possible comorbidities and possible causes.

In conclusion, this retrospective study from Bahrain shows that treatment ineffectiveness (primary nonresponse) represents the most common reason for early discontinuation of biological agents. We found that the age of the patient at index biological initiation was the only independent significant predictor of early BD. Other apparently significant factors, such as diabetes mellitus comorbidity and marked weight loss at diagnosis, were revealed to be insignificant after adjusting for age at index biological initiation. Both jaundice and CMV infection were significantly higher in the early index BD group, indicating a possible direct adverse effect, well-reported with anti-TNFα therapy.

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Conflicts of interest

There are no conflicts of interest.

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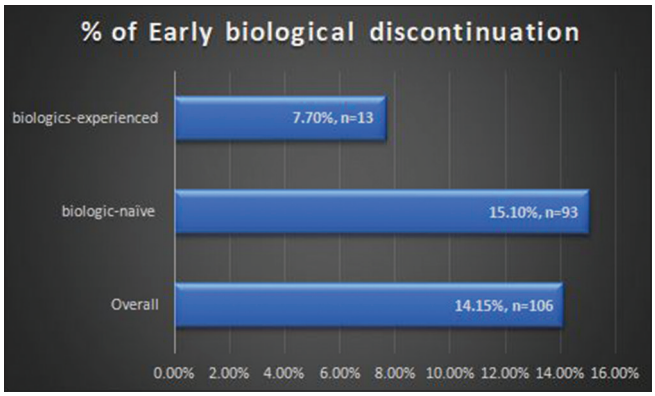

Figure S1: Bar chart representing the rates of early BD among biological-native cohort, biological-experienced, and overall patients

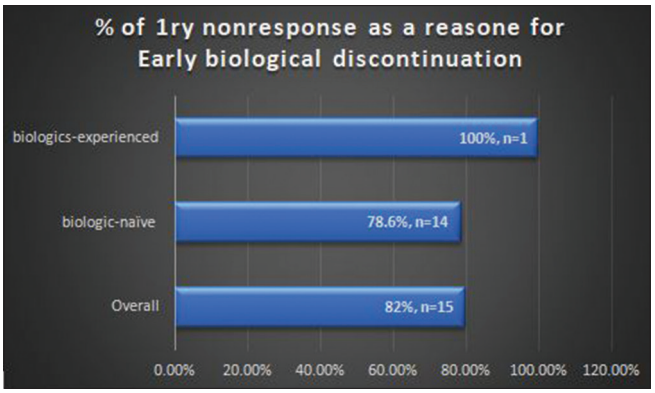

Figure S2: Bar chart representing the rates of ineffectiveness (primary nonresponse) as the reason for early BD among biological-naive cohort, biological-experienced, and overall patients

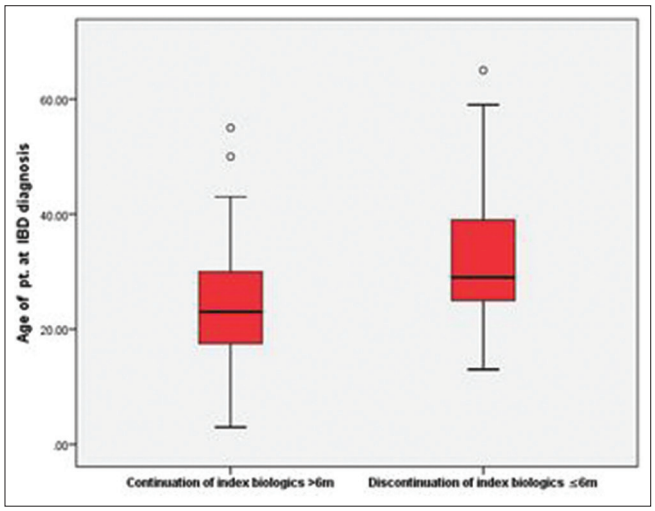

Figure S3: Box plot representing age IBD diagnosis across studied groups

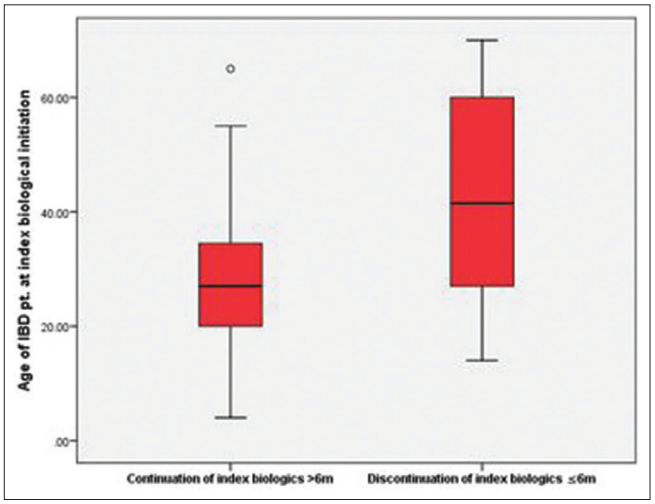

Figure S4: Box plot representing age at index biological initiation across studied groups

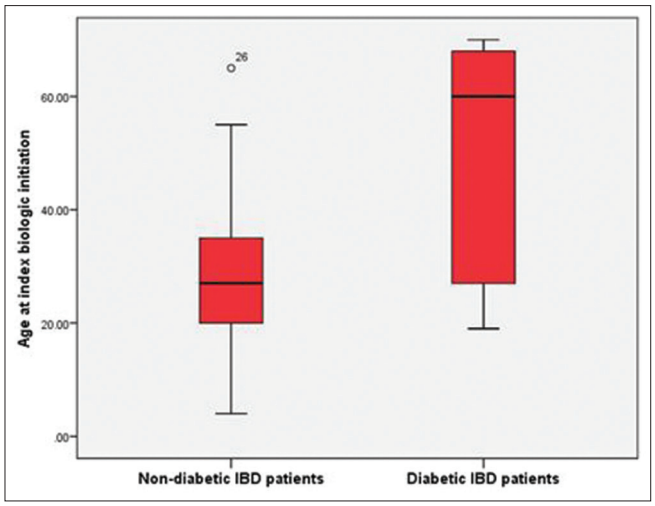

Figure S5: Box plot comparing the age at index biological initiation among both diabetic versus nondiabetic IBD patients