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A Retrospective Observational Study of Patterns of Biologic Drug Change in Inflammatory Bowel Disease

Mahmoud Mosli

Department of Internal Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia

Keywords
Inflammatory bowel disease · Ulcerative colitis · Crohn's disease · Treatment · Patterns

Abstract
Introduction: Multiple therapies are currently available for inflammatory bowel disease (IBD); it is therefore crucial to understand patterns of drug change. This study aimed to examine the patterns of biological drug change and identify predictors of change in patients with IBD. ***Methods:*** We performed a retrospective study of patients diagnosed with IBD who were initiated on treatment with biologics between June 2017 and October 2022. The study's primary objective was to describe biologic drug change patterns. Secondary outcomes included identifying predictors of drug change. ***Results:*** 910 patients were screened; 475 patients were eligible, 319 (67%) had Crohn's disease (CD), and 253 (53.3%) were males. The most selected first and second choices of biologic were adalimumab (58.2% and 39.1%, $p < 0.001$) and infliximab (37.6% and 48.9%, $p = 0.004$) for both CD and ulcerative colitis (UC), respectively. On multiple regression analysis, a history of venous thromboembolism (VTE) (OR = 3.60, $p = 0.025$) and smoking (OR = 0.34, $p = 0.026$) were associated with drug change for all patients. When stratified by disease subtype, drug change was associated with a diagnosis made between age 17 and 40 years (OR = 0.46, $p = 0.024$) and extra-intestinal manifestations (OR = 2.07, $p = 0.015$) in CD while selecting vedolizumab as the first biologic (OR = 0.30, $p = 0.041$), male gender (OR = 2.40, $p = 0.043$), and history of VTE (OR = 7.32, $p = 0.031$) were associated with drug change in UC. ***Conclusions:*** Despite introducing several new biologics, anti-TNF therapies remain the preferred first and second choice of biologics for patients with IBD. Multiple predictors of drug change over time exist for both diseases. Selecting vedolizumab as the first biologic for UC is associated with a lower risk of drug change.

Introduction

Inflammatory bowel diseases (IBD), which include ulcerative colitis (UC) and Crohn's disease (CD), collectively describe inflammatory conditions with chronic or recurring immune-mediated inflammation of the gastrointestinal tract [1]. The clinical manifestations of both diseases include diarrhea (typically bloody in patients with UC), abdominal pain, fecal urgency, systemic features such as fever, weight loss, fatigue, and extra-intestinal manifestations (EIMs) that include stomatitis, uveitis, arthritis, and

karger@karger.com
www.karger.com/iid

Correspondence to:
Mahmoud Mosli, mmosli@kau.edu.sa

ankylosing spondylitis [2]. The diagnosis of CD or UC is usually made by clinical, endoscopic, and histologic features seen on the microscopic examination of biopsy specimens obtained during colonoscopy [2]. Several epidemiological risk factors have been linked with the development of UC and CD, such as antibiotics, oral contraceptives, and living in an urban setting [3–5]. The highest incidences of CD and UC have been reported in northern Europe, the United Kingdom (UK), and North America. According to several epidemiological studies, there is a global increase in the incidence of IBD [6–8].

Treatment of UC and CD relies on medications that control inflammation through induction and then the maintenance of disease remission [9, 10]. Treatment of UC typically follows a step-up approach [10, 11]. The mainstay of UC pharmacotherapy for induction and maintenance of remission is 5-aminosalicylic acid (5-ASAs) derivatives [10, 11], both oral and rectal. Corticosteroids are often required for UC patients who fail to respond to 5-ASAs. While corticosteroids are highly effective for the induction of remission, they are not suitable for the maintenance of remission due to their undesirable side effects, including osteoporosis, glucose intolerance, and increased risk of infection [10, 11]. Immunosuppressive agents, including thiopurines, 6-mercaptopurine (6-MP), and azathioprine (AZA), have a role in maintaining remission in moderate to severe UC, especially in those who are corticosteroid dependent [12]. Their relatively slow onset of action negates their use during disease relapse.

Conversely, cyclosporine is reserved for managing acute-severe UC during hospitalization [12]. Historically, failure of medical therapy leading to colectomy has been reported in up to 35% of patients with UC [13–15]. However, introducing biological therapies has reduced the need for surgery [16, 17] and has been linked to improved quality of life [18, 19]. The main class of biologics used to treat UC is anti-tumor necrosis factor alpha (TNFα) inhibitors. Infliximab was the first TNFα inhibitor to demonstrate significant rates of remission in UC and, due to its rapid action, is used to treat acute-severe UC [20]. Adalimumab and golimumab are subcutaneously administered TNFα inhibitors approved for UC and have shown promising safety and efficacy [21].

Depending on the patient's risk profile, patients with CD can be treated using a step-up or top-down approach [9, 22]. Although the National Cooperative CD Study demonstrated a role for sulfasalazine [21] in moderate to severe CD, the efficacy of 5-ASAs in CD has been called into question by recent data and is currently not recommended [23]. Like UC, the role of corticosteroids in treating CD is limited to the induction of remission. Immunosuppressives, including 6-MP and AZA, have a role in maintaining remission in moderate-to-severe CD [12]. Surgical removal of highly diseased, strictured, or stenotic bowel segments in CD is not curative and is seldom decided through a multidisciplinary team approach [24, 25]. Biologic therapies can be used as the first line in patients with CD who exhibit high-risk features or following the failure of conventional therapy [26]. TNFα inhibitors, such as infliximab, adalimumab, and certolizumab pegol, have been widely studied and proven helpful for the induction and maintenance of remission in CD [27].

Since the introduction of TNFα inhibitors, the treatment outcomes of patients diagnosed with UC or CD have improved dramatically [27]. Anti-TNF agents are highly effective in inducing and maintaining remission in patients with moderate-to-severe CD and UC [26]. However, a considerable portion of patients with UC and CD fail to respond to induction therapy with TNFα inhibitors (primary nonresponders) or will lose response (secondary loss of response) over time [28, 29]. Studies have indicated that further treatment with a different TNFα inhibitor can lead to a response in patients who develop secondary loss of response [30]. As for patients with primary nonresponse to TNFα inhibitors, biologics with different mechanisms of action can be used [31]. The anti-integrin vedolizumab, which is a gut-selective agent that targets the interaction between alpha-4-beta-7 and MadCam, is effective for inducing and maintaining remission in patients with CD or UC who have failed to respond to TNFα antagonists or conventional therapy [32]. Another option is ustekinumab, a p40 subunit IL12/23 antagonist and a practical choice for those who have failed to respond to TNFα inhibitors [26, 33].

The dynamics of sequencing biologics and preference for first-line biologics remain interesting. However, available data on treatment patterns and switching between different classes of biologics among patients with CD and UC in clinical practice is limited, particularly in the Kingdom of Saudi Arabia (KSA). This study aimed to provide real-world evidence regarding patterns of biological drug change in adult patients with CD or UC.

Table 1. Baseline characteristics of the study sample

	CD (*n* = 319)	UC (*n* = 156)	Total (*n* = 475)	*p* value
Gender, *n* (%)				
Female	133 (41.7)	89 (57.1)	222 (46.7)	0.002
Male	186 (58.3)	67 (42.9)	253 (53.3)	
Baseline CRP level				
Mean (SD)	4.4 (5.0)	3.1 (14.4)	4.0 (9.3)	0.174
Perianal disease, *n* (%)	93 (29.8)	0 (0.0)	93 (20.0)	
Disease course, *n* (%)				
No remission	19 (6.3)	2 (1.4)	21 (4.7)	0.071
Infrequent relapse	219 (72.5)	107 (74.8)	326 (73.3)	
Frequent relapse	64 (21.2)	34 (23.8)	98 (22.0)	
Age at diagnosis, years				
Mean (SD)	21.5 (9.8)	24.8 (13.0)	22.6 (11.0)	0.002
History of smoking, *n* (%)				
Non-smoker	234 (82.4)	108 (89.3)	342 (84.4)	0.191
Ex-smoker	15 (5.3)	5 (4.1)	20 (4.9)	
Smoker	35 (12.3)	8 (6.6)	43 (10.6)	
Previous use of corticosteroids, *n* (%)				
Never	97 (31.9)	24 (16.8)	121 (27.1)	0.009
Once	116 (38.2)	70 (49.0)	186 (41.6)	
Twice	63 (20.7)	34 (23.8)	97 (21.7)	
Three times	28 (9.2)	15 (10.5)	43 (9.6)	
EIMs, *n* (%)				
No	151 (51.2)	76 (51.7)	227 (51.4)	0.999
Yes	144 (48.8)	71 (48.3)	215 (48.6)	
Peripheral arthritis	81 (27.6)	41 (28.7)	122 (28.0)	0.912
Dermatological	38 (13.0)	20 (14.1)	58 (13.4)	0.875
Stomatitis	46 (15.7)	10 (7.0)	56 (12.9)	0.018
Isolated sacroiliitis	2 (0.7)	3 (2.1)	5 (1.2)	0.407
Ocular	16 (5.5)	10 (7.0)	26 (6.0)	0.682
Thrombosis	10 (3.4)	7 (5.0)	17 (3.9)	0.605
Primary sclerosing cholangitis	6 (2.1)	8 (5.6)	14 (3.2)	0.104

Materials and Methods

This is a retrospective study of patients diagnosed with CD and UC who have initiated biological treatment at King Abdulaziz University (KAU) hospital between June 2017 and October 2022. The institutional inflammatory bowel disease information system (IBDIS) database was used to identify eligible patients with IBD who fulfilled the study criteria. Based on typical criteria, the study population consisted of all adults (>14 years of age) with a confirmed diagnosis of CD or UC who were treated with biological therapy, including TNFα inhibitors, anti-integrins, or anti-cytokines. Patients excluded from participating in the study included patients diagnosed with indeterminate/unspecified type of IBD, patients with UC who had a total colectomy before their first anti-TNF therapy, and patients who were lost to follow-up for reasons other than death.

Data collected included disease type, gender, age, date of CD or UC diagnosis, previous treatment with corticosteroids, EIMs of IBD, the Montreal classification for UC; age at diagnosis (<16 (A1), 17–40 [A2], >40 [A3]), disease extent (ulcerative proctitis (E2), left sided or distal UC (E2) or extensive UC (E3), disease severity (UC in clinical remission (S0), mild UC (S1), moderate UC (S2), severe UC (S3)), the Montreal classification for CD; age at diagnosis (<16 [A1], 17–40 [A2], >40 [A3]), disease location (ileal [L1], colonic [L2], ilea-colonic [L3], isolated upper disease), CD behavior (non-stricturing, non-penetrating [B1], stricturing [B2], penetrating [B3]; with or without the perianal involvement [p]), disease course (Frequent relapse (≥2 relapses/year), infrequent relapse (≤1 relapse/year), or no remission (persistent symptoms without a period of remission)), baseline c-reactive protein (CRP), biological therapies used, including TNFα inhibitors (e.g., infliximab, adalimumab, golimumab, certolizumab pegol), anti-integrin (vedolizumab), or anti-cytokines (ustekinumab).

Study Outcomes

The study's primary objective is to describe patterns of biologic drug change in patients diagnosed with CD or UC. Secondary outcomes included identifying predictors of drug change and differences in the survival time for different biologics.

Table 2. Montreal classification for CD and UC patients

	Montreal classification	*n* (%)
CD	Age at diagnosis (A)	
	16 years or younger (A1)	104.0 (32.6)
	17–40 years (A2)	201.0 (63.0)
	Over 40 years (A3)	14.0 (4.4)
	Location of diagnosis (L)	
	Terminal ileum (L1)	73 (23.2)
	Colonic (L2)	46 (14.6)
	Ileocolonic (L3)	195 (62.1)
	Disease behavior (B)	
	Non-stricturing, non-penetrating (B1)	129 (40.8)
	Stricturing (B2)	91 (28.8)
	Penetrating (B3)	96 (30.4)
	Perianal disease (p)	
	No	184 (59.4)
	Yes	126 (40.6)
	Upper GI disease	
	No	237 (77.2)
	Yes	70 (22.8)
UC	Age at diagnosis (A)	
	16 years or younger (A1)	41.0 (25.9)
	17–40 years (A2)	99.0 (62.7)
	Over 40 years (A3)	18.0 (11.4)
	Extent of UC (E)	
	Ulcerative proctitis (E1)	18 (11.8)
	Left-sided UC (E2)	44 (28.8)
	Extensive UC (E3)	91 (59.5)
	Severity of UC (S)	
	UC in clinical remission (S0)	10 (6.5)
	Mild UC (S1)	16 (10.3)
	Moderate UC (S2)	73 (47.1)
	Severe UC (S3)	56 (36.1)

Definitions

Treatment patterns were defined as the sequence and risk of switching treatment after initiating biologics for UC or CD.

Statistical Analysis

Quantitative data were presented as mean and standard deviation (SD), while categorical data were presented as frequencies and percentages. The χ^2 test was used to test the association of choice of first, second, and third biologics with CD and UC. The χ^2 test and *t* test were used to compare the baseline characteristics of the study sample for both diseases. Univariable and multivariable odds ratios (ORs) were used to determine the predictors of drug change. Kaplan-Meier curves and log-rank tests were used to compare the time to change the choice of biologics stratified by disease type. A Sankey diagram was used to present the flow of change of the choice of biologics. A p value of <0.05 was considered significant. The R and the finalfit R packages were used for analysis.

Results

Baseline Characteristics

Nine hundred ten patients registered in the IBDIS database were screened; 475 (52.2%) patients fulfilled the study criteria. Most excluded patients were not treated with advanced therapies. 67% had CD, and 53.3% were males. The mean age at diagnosis was 22.6 (11.0) years (21.5 [9.8] in CD versus 24.8 [13.0] in UC, p = 0.002), and 48.6% had EIMs of IBD; the most common was peripheral arthritis (28%) (Table 1). The most common disease course was infrequent relapse, which 73.3% of patients reported. For CD, 63% of patients were diagnosed between ages 17 and 40 years,

Table 3. Primary study outcome

	CD, *n* (%)	UC, *n* (%)	Total, *n* (%)	*p* value
First choice of biologic				
Infliximab	117 (36.8)	56 (35.9)	173 (36.5)	<0.001
Adalimumab	185 (58.2)	61 (39.1)	246 (51.9)	
Vedolizumab	12 (3.8)	39 (25.0)	51 (10.8)	
Ustekinumab	4 (1.3)	0 (0.0)	4 (0.8)	
Second choice of biologic				
Infliximab	38 (37.6)	23 (48.9)	61 (41.2)	0.004
Adalimumab	24 (23.8)	8 (17.0)	32 (21.6)	
Vedolizumab	14 (13.9)	14 (29.8)	28 (18.9)	
Ustekinumab	25 (24.8)	2 (4.3)	27 (18.2)	
Third choice of biologic				
Vedolizumab	9 (34.6)	10 (83.3)	19 (50.0)	0.015
Ustekinumab	17 (65.4)	2 (16.7)	19 (50.0)	

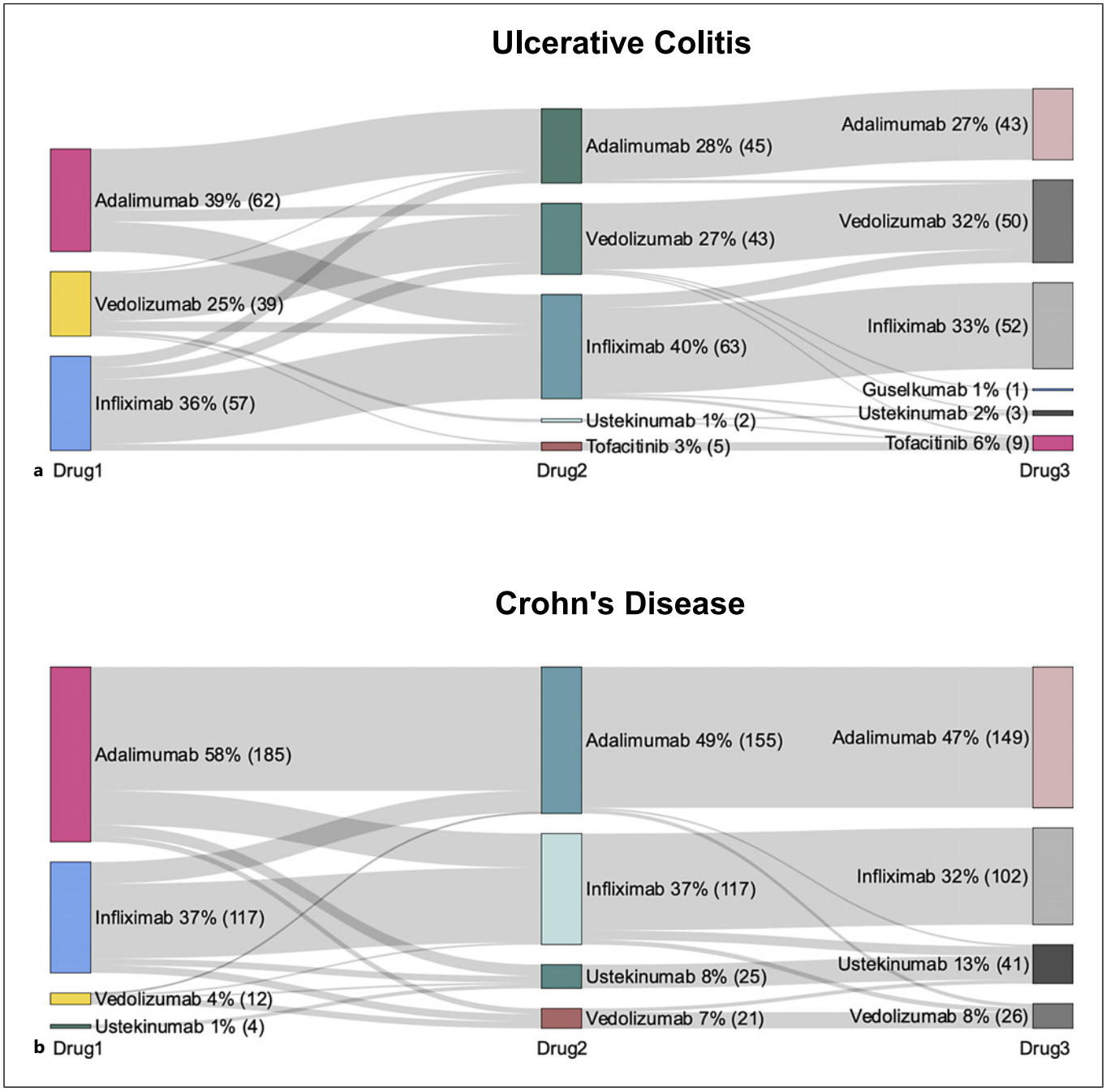


Fig. 1. A Sankey diagram displaying the change in the choice of biologics for UC (**a**) and CD (**b**) over time.

195 (62.1%) had ileocolonic (L3) disease distribution, 93 (29.8%) had a history of perianal disease, and 129 (40.8%) had non-stricturing, non-penetrating (B1) disease behavior. For UC patients, 63% of patients were diagnosed between ages 17 and 40 years, 91 (59.5%) had extensive UC (E3) disease distribution, and 73 (47.1%) had moderately severe UC (S2) (Table 2).

Study Outcomes

The most selected first and second choices of a biologic were adalimumab (58.2% and 39.1%, $p < 0.001$) and infliximab (37.6% and 48.9%, $p = 0.004$) for both CD and UC, respectively. Ustekinumab was the primary third choice for CD (65.4%), while vedolizumab was the leading third choice for UC (83.3%) (Table 3; Fig. 1). The

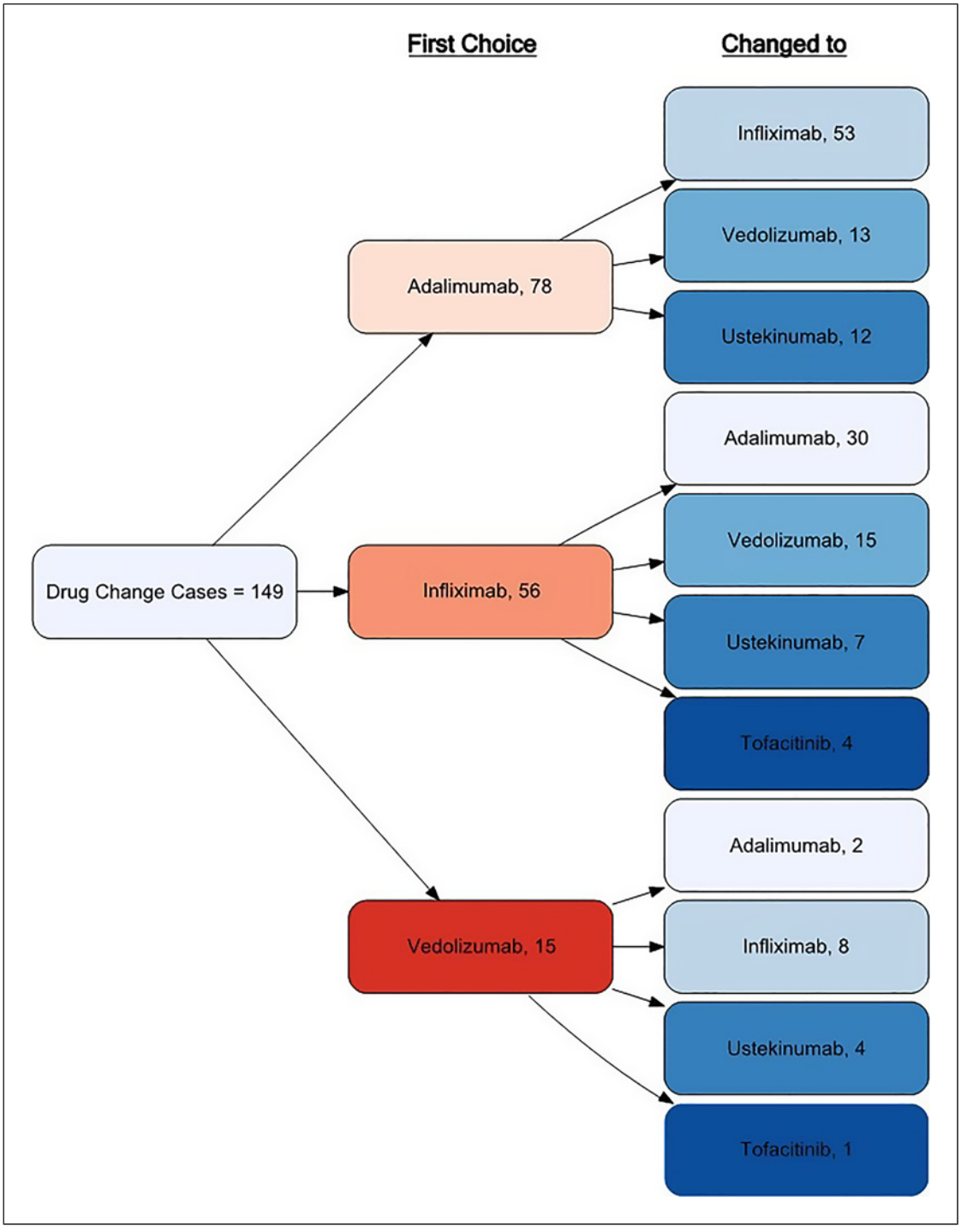


Fig. 2. A flow diagram illustrating changes in advanced therapies.

proportions of patients who switched from adalimumab as first- and second-line therapy were 52.3% and 20.9%. Similarly, 37.6% and 39.9% were changed from first- and second-line infliximab therapy, and 10.1% and 18.3% were changed from first- and second-line vedolizumab therapy, respectively (Fig. 2).

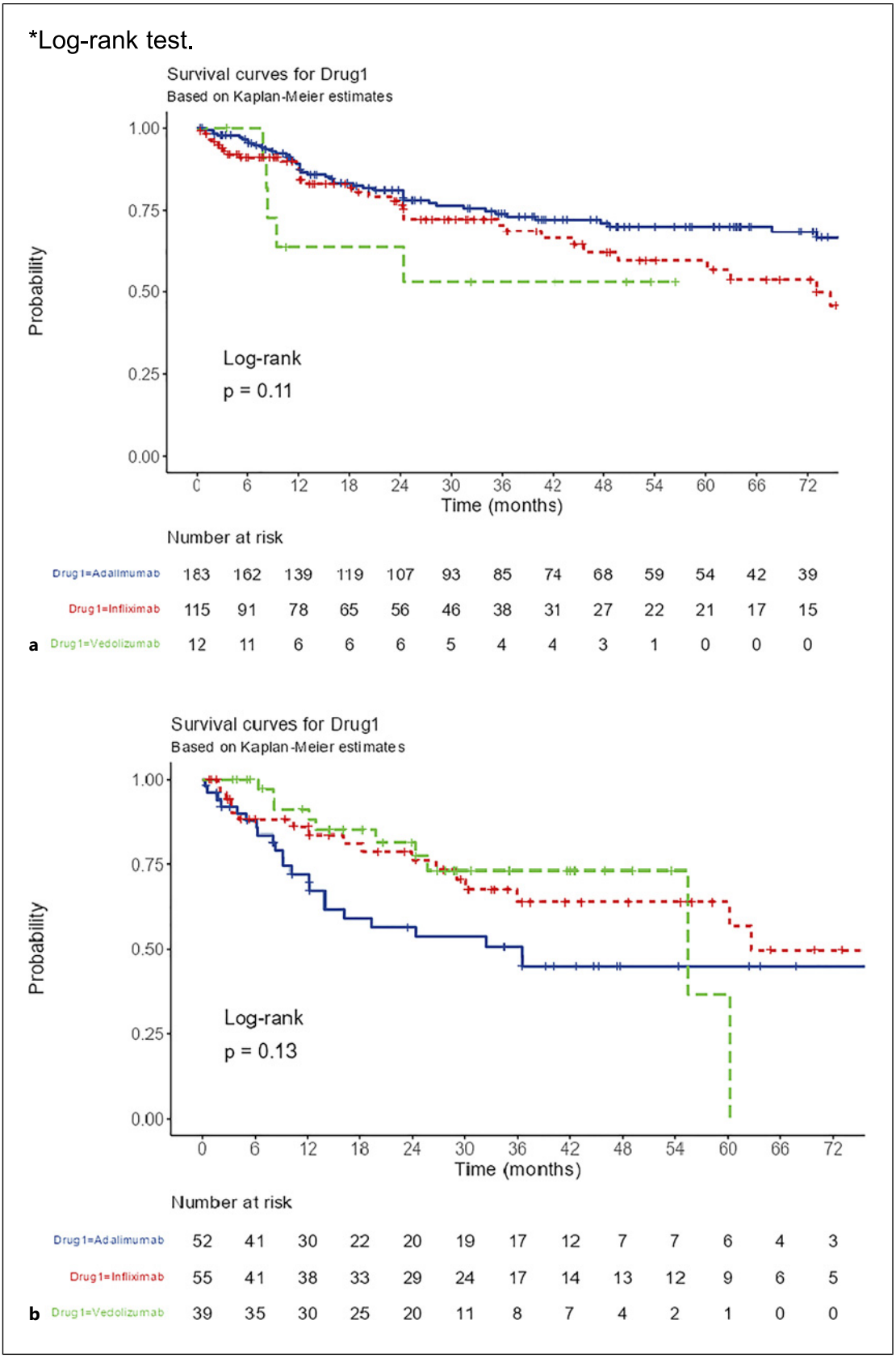


Fig. 3. Kaplan-Meier curves comparing the time to change the choice of biologics for CD (**a**) and UC (**b**).

Table 4. Predictors of drug change for IBD patients

Drug change status	No	Yes	OR (univariable)	OR (multivariable)
First choice of biologic				
Adalimumab	169 (68.4)	78 (31.6)	–	–
Infliximab	117 (67.6)	56 (32.4)	1.04 (0.68–1.57, $p = 0.864$)	0.76 (0.46–1.26, $p = 0.289$)
Vedolizumab	36 (70.6)	15 (29.4)	0.90 (0.46–1.72, $p = 0.761$)	0.59 (0.24–1.37, $p = 0.231$)
Gender				
Female	151 (68.0)	71 (32.0)	–	–
Male	170 (67.5)	82 (32.5)	1.03 (0.70–1.51, $p = 0.897$)	1.49 (0.91–2.44, $p = 0.113$)
Diagnosis				
CD	217 (68.2)	101 (31.8)	–	–
UC	105 (66.9)	52 (33.1)	1.06 (0.71–1.60, $p = 0.765$)	1.37 (0.77–2.45, $p = 0.280$)
CRP level				
Mean (SD)	4.2 (10.8)	3.4 (4.4)	0.99 (0.95–1.01, $p = 0.443$)	0.96 (0.90–1.00, $p = 0.124$)
Perianal disease				
Never	248 (66.7)	124 (33.3)	–	–
Ever	64 (68.8)	29 (31.2)	0.91 (0.55–1.47, $p = 0.693$)	0.73 (0.38–1.35, $p = 0.320$)
Disease course				
No Remission	10 (47.6)	11 (52.4)	–	–
Infrequent relapse	220 (67.7)	105 (32.3)	0.43 (0.18–1.06, $p = 0.065$)	0.42 (0.15–1.19, $p = 0.100$)
Frequent relapse	63 (64.3)	35 (35.7)	0.51 (0.19–1.31, $p = 0.159$)	0.54 (0.18–1.64, $p = 0.273$)
Thrombosis				
Never	283 (68.5)	130 (31.5)	–	–
Ever	7 (41.2)	10 (58.8)	3.11 (1.17–8.74, $p = 0.024$)	**3.60 (1.20-11.71, $p = 0.025$)**
EIMs				
No	158 (69.9)	68 (30.1)	–	–
Yes	141 (65.6)	74 (34.4)	1.22 (0.82–1.82, $p = 0.331$)	1.31 (0.81–2.12, $p = 0.271$)
History of smoking				
Non-smoker	221 (64.8)	120 (35.2)	–	–
Ex-smoker	11 (55.0)	9 (45.0)	1.51 (0.59–3.74, $p = 0.376$)	1.57 (0.56–4.34, $p = 0.381$)
Smoker	33 (78.6)	9 (21.4)	0.50 (0.22–1.04, $p = 0.080$)	**0.34 (0.12-0.82, $p = 0.026$)**

Drug Survival

There were no statistically significant differences observed in the survival times between different types of biologics for CD (Log-Rank = 0.11) or UC (Log-Rank = 0.13) (Fig. 3).

Predictors of Drug Change

On multiple regression analysis, a history of venous thromboembolism (VTE) (OR = 3.60, 95% CI = 1.20–11.71, $p = 0.025$) and active smoking (OR = 0.34, 95% CI = 0.12–0.82, $p = 0.026$) were associated with drug change for all IBD patients (Table 4). When stratified by disease subtype, drug change was associated with diagnosis between age 17 and 40 years (OR = 0.46, 95% CI = 0.23–0.90, $p = 0.024$) and EIMs of IBD (OR = 2.07, 95% CI = 1.16–3.76, $p = 0.015$) in CD (Table 5) while selecting vedolizumab as first biologic (OR = 0.30, 95% CI = 0.09–0.92, $p = 0.041$), male gender (OR = 2.40, 95% CI = 1.04–5.73, $p = 0.043$), and history of VTE (OR = 7.32, 95% CI = 0.23–49.97, $p = 0.031$) were associated with drug change in UC but not in CD patients (Table 6) (Fig. 4).

Discussion

Over the past 3 decades, the treatment of IBD has dramatically transformed into a more objective, strategic approach based on evolving concepts such as risk stratification, tailored treatment selection, and treatment escalation according to a treat-to-target approach [34]. Accordingly, many patients with IBD can be treated successfully with conventional therapies [11, 12]. Nevertheless, the role biologics play in treating IBD remains paramount. Almost 50% of patients with IBD require escalation to advanced

Table 5. Predictors of drug change for CD patients

Drug change status	No	Yes	OR (univariable)	OR (multivariable)
First choice of biologic				
Adalimumab	132 (71.0)	54 (29.0)	–	–
Infliximab	79 (67.5)	38 (32.5)	1.18 (0.71–1.94, $p = 0.525$)	0.87 (0.47–1.60, $p = 0.663$)
Vedolizumab	7 (58.3)	5 (41.7)	1.75 (0.50–5.71, $p = 0.359$)	2.43 (0.57–9.42, $p = 0.204$)
Gender				
Female	91 (67.9)	43 (32.1)	–	–
Male	127 (68.6)	58 (31.4)	0.97 (0.60–1.56, $p = 0.889$)	1.37 (0.76–2.49, $p = 0.300$)
CRP level				
Mean (SD)	4.3 (5.1)	4.4 (4.8)	1.00 (0.95–1.05, $p = 0.871$)	0.98 (0.92–1.04, $p = 0.531$)
Perianal disease				
Never	147 (67.1)	72 (32.9)	–	–
Ever	64 (68.8)	29 (31.2)	0.93 (0.54–1.55, $p = 0.770$)	0.81 (0.34–1.95, $p = 0.642$)
Disease course				
No remission	8 (42.1)	11 (57.9)	–	–
Infrequent relapse	155 (70.8)	64 (29.2)	0.30 (0.11–0.78, $p = 0.014$)	0.34 (0.11–1.03, $p = 0.056$)
Frequent relapse	40 (62.5)	24 (37.5)	0.44 (0.15–1.23, $p = 0.119$)	0.47 (0.14–1.57, $p = 0.221$)
Age at diagnosis				
16 years or younger (A1)	59 (59.0)	41 (41.0)	–	–
17–40 years (A2)	144 (71.6)	57 (28.4)	0.57 (0.34–0.94, $p = 0.028$)	**0.46 (0.23-0.90, $p = 0.024$)**
Over 40 years (A3)	14 (82.4)	3 (17.6)	0.31 (0.07–1.02, $p = 0.078$)	0.22 (0.03–0.99, $p = 0.075$)
Location of diagnosis				
Terminal ileum (L1)	52 (71.2)	21 (28.8)	–	–
Colonic (L2)	33 (71.7)	13 (28.3)	0.98 (0.42–2.19, $p = 0.953$)	0.65 (0.23–1.74, $p = 0.403$)
Ileocolonic (L3)	127 (65.5)	67 (34.5)	1.31 (0.73–2.38, $p = 0.372$)	1.14 (0.58–2.30, $p = 0.717$)
Presence of upper GI disease				
No	162 (68.6)	74 (31.4)	–	–
Yes	44 (62.9)	26 (37.1)	1.29 (0.73–2.25, $p = 0.365$)	1.05 (0.51–2.13, $p = 0.900$)
Disease behavior				
Non-stricturing, non-penetrating (B1)	84 (65.1)	45 (34.9)	–	–
Stricturing (B2)	60 (66.7)	30 (33.3)	0.93 (0.53–1.64, $p = 0.812$)	0.87 (0.43–1.74, $p = 0.687$)
Penetrating (B3)	70 (72.9)	26 (27.1)	0.69 (0.39–1.23, $p = 0.214$)	0.63 (0.26–1.48, $p = 0.290$)
Thrombosis				
Never	195 (69.4)	86 (30.6)	–	–
Ever	4 (40.0)	6 (60.0)	3.40 (0.95–13.59, $p = 0.063$)	3.79 (0.94–17.05, $p = 0.065$)
EIMs				
No	112 (74.2)	39 (25.8)	–	–
Yes	89 (61.8)	55 (38.2)	1.77 (1.08–2.93, $p = 0.023$)	**2.07 (1.16-3.76, $p = 0.015$)**

therapies such as biologics following the failure of conventional therapies [11, 12]. Since the introduction of TNFα inhibitors, the risk of hospitalization and colectomy has rapidly declined [16, 35]. However, over 50% of patients fail to respond (primary nonresponse) or lose their initial response (secondary loss of response) to therapy within the first year [11, 28, 29, 33]. Such patients experience symptoms and require treatment modification through dose escalation, switching to another TNFα inhibitor, switching to another class of biologics, or undergoing surgery [36, 37]. Several new biologics have been introduced and proven effective and safe for CD and UC [21]. Moreover, additional biologics are in the late stages of drug development and will be made available soon [38].

For this reason, it is prudent to understand the dynamics of switching between classes of biologics, starting with those who have been started on TNFα inhibitors since they are the first class of biologics to be available. In our study, we examined 475 patients with IBD treated with biologics in a Saudi tertiary care hospital, which

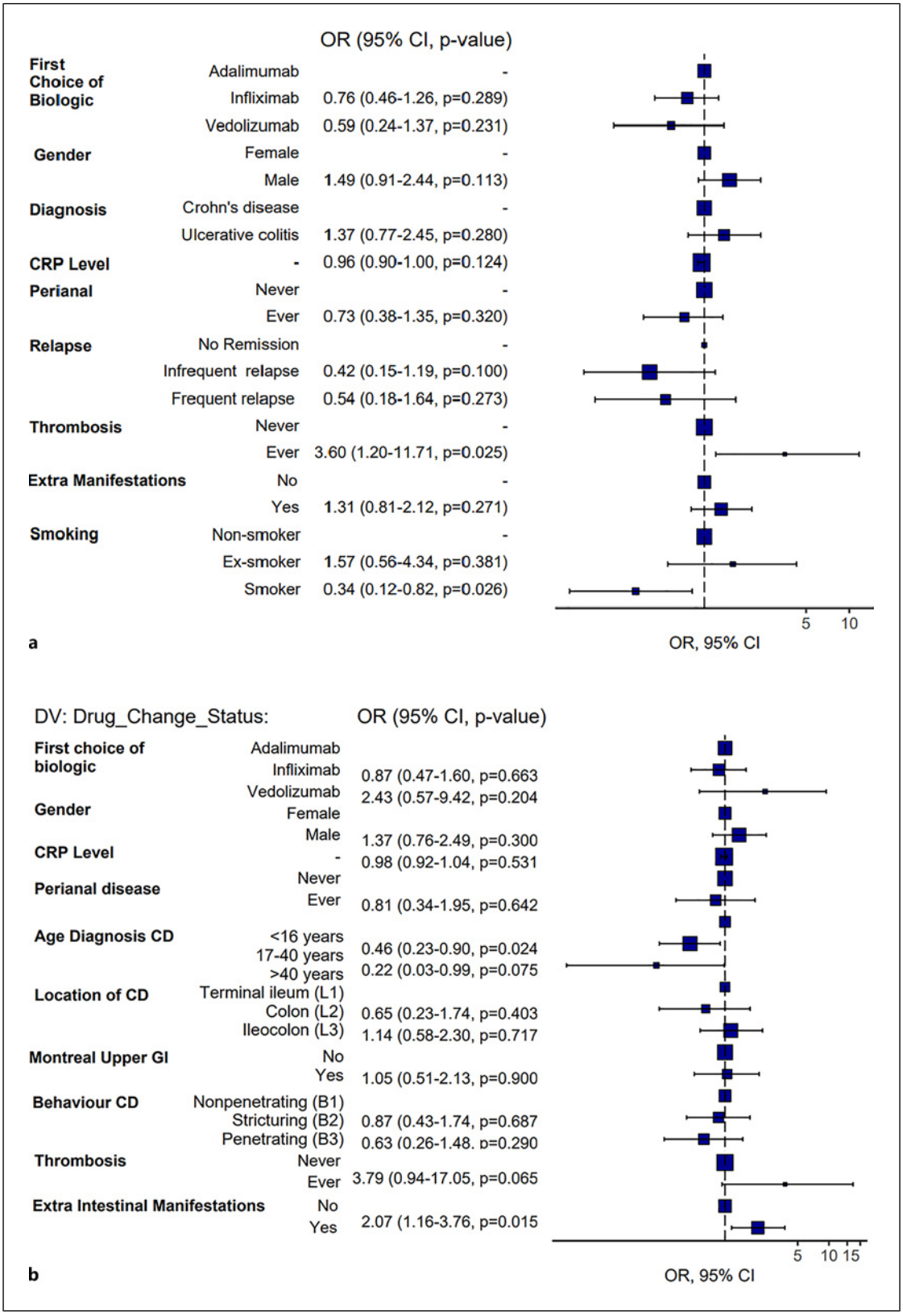
Table 6. Predictors of drug change for UC patients

Drug change status	No	Yes	OR (univariable)	OR (multivariable)
First choice of biologic				
Adalimumab	37 (60.7)	24 (39.3)	–	–
Infliximab	38 (67.9)	18 (32.1)	0.73 (0.34–1.56, $p = 0.418$)	0.70 (0.28–1.75, $p = 0.452$)
Vedolizumab	29 (74.4)	10 (25.6)	0.53 (0.21–1.26, $p = 0.161$)	**0.30 (0.09-0.92, $p = 0.041$)**
Gender				
Female	60 (68.2)	28 (31.8)	–	–
Male	43 (64.2)	24 (35.8)	1.20 (0.61–2.34, $p = 0.601$)	**2.40 (1.04-5.73, $p = 0.043$)**
CRP level				
Mean (SD)	3.9 (17.5)	1.6 (2.6)	0.95 (0.84–1.01, $p = 0.343$)	0.85 (0.68–0.99, $p = 0.083$)
Extent of UC				
Ulcerative proctitis (E1)	11 (61.1)	7 (38.9)	–	–
Left-sided UC (E2)	29 (65.9)	15 (34.1)	0.81 (0.26–2.61, $p = 0.720$)	0.46 (0.11–1.87, $p = 0.275$)
Extensive UC (E3)	61 (67.8)	29 (32.2)	0.75 (0.27–2.21, $p = 0.585$)	0.57 (0.16–2.11, $p = 0.386$)
Severity of UC				
UC in clinical remission (S0)	6 (60.0)	4 (40.0)	–	–
Mild UC (S1)	8 (50.0)	8 (50.0)	1.50 (0.31–7.91, $p = 0.619$)	1.02 (0.15–7.03, $p = 0.981$)
Moderate UC (S2)	51 (70.8)	21 (29.2)	0.62 (0.16–2.62, $p = 0.489$)	0.44 (0.09–2.24, $p = 0.315$)
Severe UC (S3)	38 (67.9)	18 (32.1)	0.71 (0.18–3.07, $p = 0.628$)	0.60 (0.12–3.03, $p = 0.522$)
Thrombosis				
Never	88 (66.7)	44 (33.3)	–	–
Ever	3 (42.9)	4 (57.1)	2.67 (0.56–14.03, $p = 0.212$)	**7.32 (1.23-49.97, $p = 0.031$)**
EIMs				
No	46 (61.3)	29 (38.7)	–	–
Yes	52 (73.2)	19 (26.8)	0.58 (0.28–1.16, $p = 0.127$)	0.51 (0.21–1.20, $p = 0.129$)

accounted for 52.2% of patients in the registry. The most selected first and second choices of a biologic were adalimumab (58.2% and 39.1%, $p < 0.001$) and infliximab (37.6% and 48.9%, $p = 0.004$) for both CD and UC, respectively. This highlights the critical role of TNFα inhibitors in the treatment of IBD. Additionally, we note that the proportion of patients who switched from first- and second-line adalimumab, infliximab, and vedolizumab was 52.3% and 20.9%, 37.6% and 39.9%, and 10.1% and 18.3%, respectively, which is in line with previously reported literature that reports a lower risk of drug persistence with TNFα inhibitors when compared to other classes of biologics [15].

Two main classes of biologics, other than TNFα inhibitors, are available for patients with CD and UC. Vedolizumab, currently the only licensed medication in the anti-integrin class of biologics, is effective for inducing and maintaining remission for both CD and UC and can be used as first- or second-line therapy [26, 27, 32]. Similarly, among the other available classes of biologics, anti-cytokines, ustekinumab is approved to treat CD and UC. Recently, other medications in this class have been released [39], risankizumab [40], and mirikizumab [41] have already been approved for CD and UC, respectively. In IBD, biologics are typically approved for one disease and then receive approval for the other shortly after. According to our study results, ustekinumab was CDs primary third choice of biologics (65.4%), while vedolizumab was the third choice for UC (83.3%). This observation can be explained by the fact that ustekinumab was first approved for CD, and vedolizumab was first approved for UC.

Drug persistence or drug survival can vary between biologics and typically depends on several factors, one of which is the immunogenic profile of the drug. TNFα inhibitors are notoriously known for their tendency to trigger the development of neutralizing anti-drug antibodies (ADAs). This leads to secondary loss of response and, hence, short drug survival [33, 36]. The annual risk of developing ADAs to TNFα inhibitors can reach 50%, associated with drug interruption and suboptimal serum drug levels [33, 36]. Combining TNFα inhibitors with immunosuppressants and therapeutic drug monitoring (TDM) has been utilized to mitigate the development of ADAs and prolong the drug survival of TNFα inhibitors [25–27] [42].



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(Figure continued on next page.)

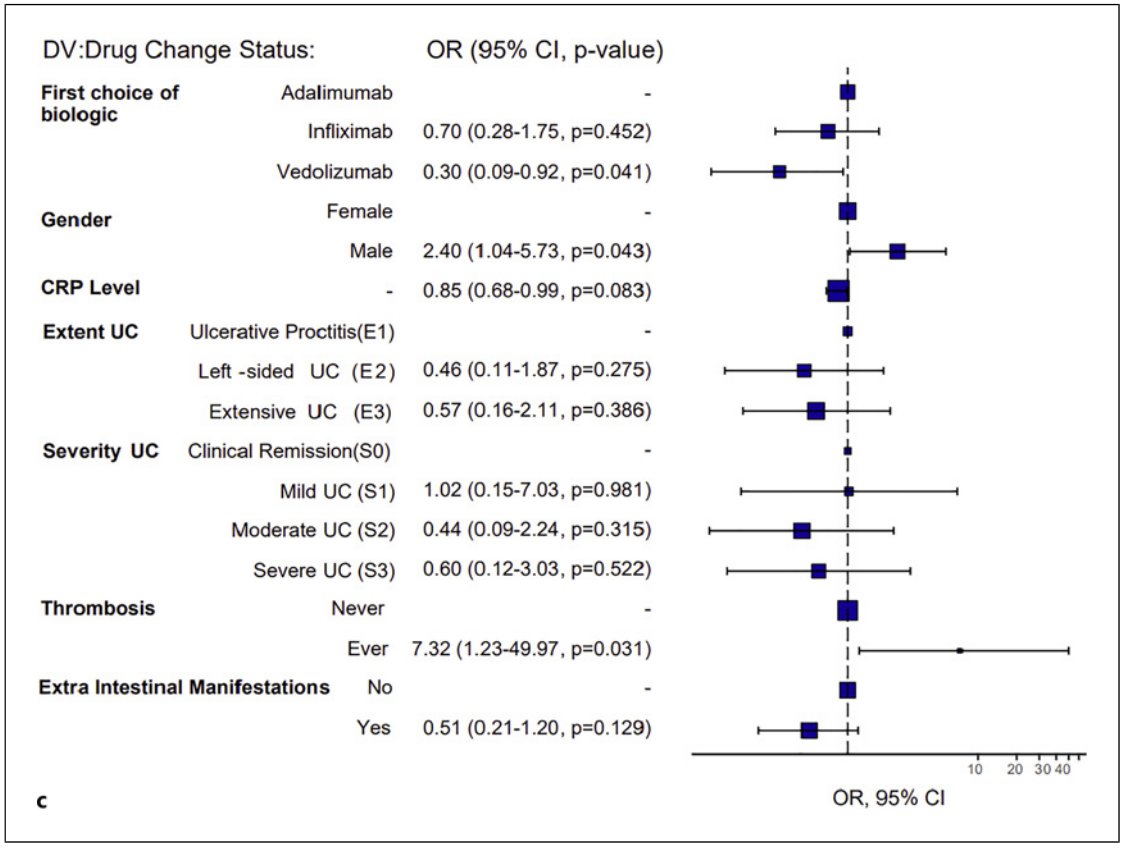

Fig. 4. Odds-ratio plot for IBD (**a**), CD (**b**), UC (**c**).

On the other hand, vedolizumab and ustekinumab carry the advantage of low immunogenicity and are not associated with the development of ADAs.

Nevertheless, secondary loss of response to these agents occurs through other mechanisms such as mechanical shift [33, 36]. In our attempt to study drug survival in our cohort of patients, we first estimated the proportions of patients who switched from one biologic to another biologic and found that they correspond to previously published data, which point towards higher rates of drug discontinuation with TNFα inhibitors compared to other classes of biologics [11, 29, 43]. Furthermore, we used a Kaplan-Meier curve to compare survival between different classes of biologics. There was no difference in survival time between different types of biologics for CD or UC, a finding in line with currently available literature as well [11, 29, 43].

The shift between biologics over time is mainly due to treatment failure or intolerance [30]. One way to identify predictors of treatment failure is to identify predictors of switching between biologics. For this purpose, we performed single- and multiple-logistic regression analyses. On multiple regression analysis, history of VTE (OR = 3.60, 95% CI = 1.20–11.71, $p = 0.025$) and active smoking (OR = 0.34, 95% CI = 0.12–0.82, $p = 0.026$) were associated with drug change for all IBD patients. When stratified by disease subtype, drug change was associated with diagnosis between age 17 and 40 years (OR = 0.46, 95% CI = 0.23–0.90, $p = 0.024$) and EIMs of IBD (OR = 2.07, 95% CI = 1.16–3.76, $p = 0.015$) in CD while selecting vedolizumab as first biologic (OR = 0.30, 95% CI = 0.09–0.92, $p = 0.041$), male gender (OR = 2.40, 95% CI = 1.04–5.73, $p = 0.043$), and history of VTE (OR = 7.32, 95% CI = 0.23–49.97, $p = 0.031$) were associated with drug change in UC but not in CD patients. All the above predictors of drug change in CD have previously been reported to be high-risk features of the disease and surrogate markers for drug resistance [42, 44]. Furthermore, the association between using vedolizumab and lower odds of drug change in UC reflects the drug's durability, consistent with previously published studies [45].

Given the limitations surrounding the study design and sample size, our results require further validation by large, prospectively conducted randomized controlled

trials. Despite the rules mentioned above, our study provides insightful information as it is the first study to report patterns of biologic persistence and sequencing in Saudi patients diagnosed with IBD.

Conclusions

Despite introducing several new biologics for managing IBD, TNFα inhibitors remain the first and second choice for patients with IBD, both CD and UC. Multiple predictors of drug change over time exist for both diseases. Starting vedolizumab as the first biologic for UC is associated with a lower risk of drug change.

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Statement of Ethics

The KAU Hospital Research Ethics Committee granted ethical approval before the initiation of the study (#480-17). Written informed consent from participants was not required in accordance with local/national guidelines.

Conflict of Interest Statement

Mahmoud Mosli has served as a speaker for Janssen, AbbVie, Pfizer, Takeda, Hikma, Ferring, Sandoz, and Organon; he also served as an advisory board member for AbbVie, Hikma, Janssen, Pfizer, Takeda, Amgen, BMS, Novartis, Ferring, Organon, Sanofi, Sandoz, and Falk.

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Author Contributions

Mahmoud Mosli designed the study, collected the data, analyzed and interpreted the data, and wrote and finalized the manuscript.

Data Availability Statement

The data supporting this study's findings are not publicly available because they contain information that could compromise the privacy of research participants but are available from M.M. upon reasonable request.

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