Original Article

Exploring treatment of inflammatory bowel disease with infliximab in the Middle East and Northern Africa: An analysis of the HARIR observational cohort study

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Abstract

Background: In 2017, inflammatory bowel disease, including Crohn's disease (CD) and ulcerative colitis (UC) affected more than 6.8 million people worldwide, with increased incidence in newly industrialized countries. Although treatment options were previously limited to symptom reduction, current approaches benefit from disease-modifying biologics. In this study, we aimed to explore disease characteristics, treatment, and outcomes of patients with CD or UC treated with infliximab or golimumab in routine clinical practice in the Middle East and Northern Africa.

Methods: HARIR was a prospective, observational, multicenter study (NCT03006198), in patients who were treatment naïve or who received two or fewer biologic agents. Observed data from routine clinical practice were presented descriptively.

Results: Data from 86 patients enrolled from five countries (Algeria, Egypt, Kuwait, Qatar, and Saudi Arabia) were analyzed, 62 with CD and 24 with UC. All patients received infliximab. Clinically meaningful efficacy data were observed only for the CD group (up to Month 3) due to limited patient numbers. Crohn's Disease Activity Index (CDAI) scores at Month 3 indicated a positive response to treatment (reduced score of ≥70 and ≥25% compared with baseline) for 14/48 (29.2%) patients; notably, 28/52 (53.8%) patients had CDAI score <150 at baseline. Rates of serious and severe adverse events (AEs) were low in both groups. The most common AEs were gastrointestinal disorders.

Conclusion: Infliximab treatment was well tolerated in this Middle Eastern and Northern African population, and a clinical response was observed for 29.2% of CD patients. Limited accessibility to biologics and concomitant treatments restricted study conduct.

Keywords: Crohn's disease, infliximab, ulcerative colitis, inflammatory bowel disease, biologics

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INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by non-infectious chronic inflammation and includes two main subtypes, Crohn's disease (CD) and ulcerative colitis (UC).[1] In 2017, IBD affected more than 6.8 million

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people worldwide,[1] and approximately 25% of patients presented with the disease before the age of 20 years.[2] Epidemiology data for IBD vary based on geographic region, environmental factors, and ethnic groups.[3,4] Notably, the incidence of IBD has increased in newly industrialized countries, whose societies have become more Westernized.[5,6]

Common symptoms of both CD and UC include diarrhea, rectal bleeding, abdominal pain, and weight loss.[7] Treatment options were previously limited to symptom reduction, primarily with anti-inflammatories, but current therapeutic approaches benefit from the use of disease-modifying biologics that target tumor necrosis factor (TNF).[2] TNF-α inhibitors modulate the expression of proinflammatory mediators and reduce the number of activated immune cells,[8] inducing complete intestinal mucosal healing and disease remission.[2,3] Currently approved biologics for IBD include four TNF-α inhibitors: infliximab, adalimumab, golimumab, and certolizumab pegol.[9,10] Besides patient and disease characteristics, there are several parameters that have an impact on the prescription of a first-line biologic agent, including efficacy and safety profile, specific country availability and labeling, and cost-effectiveness.[9] There is limited information regarding disease burden and standard-of-care treatment for IBD in the Middle East and Northern Africa, particularly for CD or UC patients treated with TNF-α inhibitors in these regions.

HARIR was a prospective, observational, multicenter cohort study to explore and describe the disease characteristics, treatment, and outcomes of patients enrolled in HARIR with CD and UC, who were treated with infliximab or golimumab in clinical practice in the Middle East and Northern Africa.

PATIENTS AND METHODS

HARIR study overview

This was a prospective, observational, multicenter study (NCT03006198) conducted between March 2016 and December 2018. Patients diagnosed with CD or UC as the major disease, who were treated with infliximab or golimumab in participating centers in the Middle East and Northern Africa, were included in this study. Treatment decisions and clinical management of patients were made at the discretion of the treating physician, per routine clinical practice; no medication was provided by the study sponsor.

The observational period for each patient was a maximum of two years after initial baseline data collection. Available data per clinical practice and, where permitted, patient-reported outcome (PRO) assessments were collected. The HARIR study was stopped prematurely due to slow recruitment, low number of participants, and high withdrawal rate (42.1%).

The study was conducted according to the applicable regulatory requirements, including study protocol (and amendment) review by an independent ethics committee and written informed consent from participants or their legally acceptable representatives.

Patient population

Eligible patients were aged between 18 and 65 years with a confirmed diagnosis of CD or UC. Patients were included in the study for one disease only, with infliximab or golimumab treatment initiation planned at the time of study enrollment and started within 30 days of enrollment. Prior to enrollment, patients were either naïve to the products under study or had received no more than two different biologic agents before enrollment. Patients were not eligible if they (1) previously received study therapy and started the same therapy a second time; (2) were currently enrolled in an investigational study; or (3) received an investigational drug or used an invasive investigational medical device within 30 days prior to baseline data collection. Patient participation in other non-interventional studies at the same time was generally permitted.

Study outcomes

Efficacy outcomes were defined for each pathology. For CD, clinical response was considered as a reduction of Crohn's Disease Activity Index (CDAI) score of ≥70 points and ≥25% versus baseline. Clinical remission was assessed using two measures: (1) CDAI score <150 points; (2) Harvey-Bradshaw Index (HBI) score <5 points. For UC, clinical response was considered as a decrease from baseline in total Mayo score of ≥30% and ≥3 points, and a decrease in rectal bleeding subscore to 0 or 1 point. Clinical remission was based on a total Mayo score ≤2 points and no individual subscore >1 point. Change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) score was also measured for both CD and UC groups.

Safety outcomes included all adverse events (AEs), regardless of seriousness or potential causal relationship, which were recorded in the case report form and in the patient's source medical records, and were followed up in accordance with clinical practice. Safety events of interest included, but were not limited to, overdose of a product, exposure to a product from breastfeeding; suspected abuse/misuse of a product; inadvertent

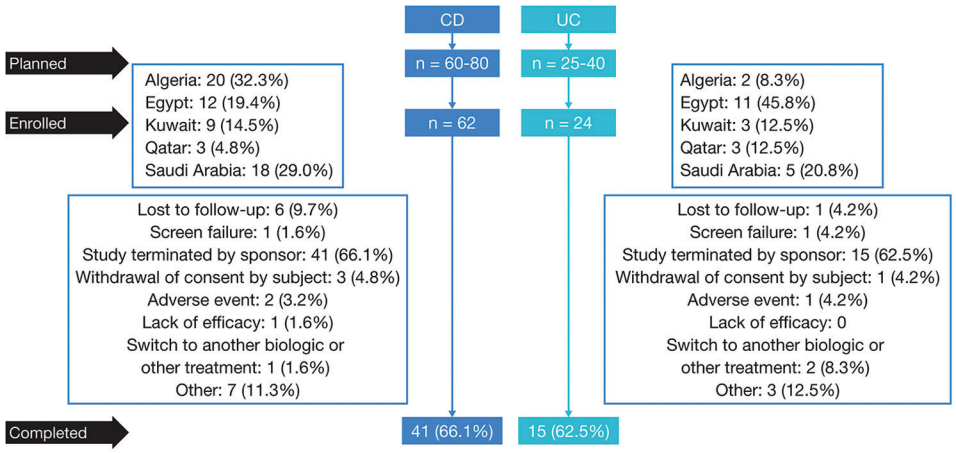

Figure 1: Patient disposition. CD, Crohn's disease; UC, ulcerative colitis

or accidental exposure to a product; any failure of expected pharmacologic action of a product; unexpected therapeutic or clinical benefit from use of a product; or medical error involving a product.

Medical resource utilization and health economics data were documented by the participating physician or site, for all patients throughout the study. Data for collection included the number of hospitalization days, number and duration of medical care encounters, outpatient medical encounters and treatments, primary reason/diagnosis associated with medical resource use, or for patients receiving treatment with golimumab, ease of use of self-injection device or the need for external support.

Data sources and collection

Where available in the patient's source medical records, demographic data and patient information; medical history, including diagnosis, type and current characteristics of CD or UC; previous and current therapies for CD or UC; comorbidities; and concomitant medications were documented at baseline.

During the observational period, three months (±2 months) after treatment initiation, within one month of each change in treatment (dose change, treatment optimization, or resumption of treatment following interruption) where applicable, and approximately six months after the previous data collection, the following were documented by the participating physician for all patients: patient information; study treatment dosage, duration, and reason for discontinuation (if applicable); measures of clinical response and effectiveness and PRO assessments (where available); AEs; concomitant medications; vital signs; and medical resource utilization.

Safety data collection began when the treatment under study commenced, and included all AEs that occurred within 90 days after a patient's last use within the study.

Statistical analysis

As this was an exploratory observational study, no formal calculation of sample size was performed. Based on market research, the study was expected to include between 60 and 80 patients diagnosed with CD and 25 and 40 patients diagnosed with UC. Each cohort was analyzed if it included at least 15 patients. All analyses were descriptive in nature using descriptive statistics; no hypotheses were tested.

Table 1: Patient baseline characteristics

	Crohn's Disease *n*=62	Ulcerative Colitis *n*=24
Age, years, mean (SD)	32.7 (11.5)	29.6 (9.4)
Sex, female, *n* (%)	33 (53.2)	14 (58.3)
Weight, kg, mean (SD)	60.7 (14.3)	63.2 (20.2)*
BMI, kg/m^2, mean (SD)	22.3 (5.5)†	23.8 (5.7)*
Employment, *n* (%)*		
Full time	13 (21.0)	7 (30.4)
Part time	5 (8.1)	3 (13.0)
Homemaker/housewife	10 (16.1)	4 (17.4)
Student; not working	14 (22.6)	5 (21.7)
Student; working	2 (3.2)	0
Unemployed	11 (17.7)	2 (8.7)
Self-employed	1 (1.6)	1 (4.3)
Retired	3 (4.8)	0
Not given	1 (1.6)	1 (4.3)
Long-term sickness/disabled	2 (3.2)	0
Any prior biologic use, *n* (%)	3 (4.8)	8 (33.3)
Adalimumab	3 (4.8)	8 (33.3)
Duration of use, total		
<1 year	2 (66.7)	3 (37.5)
≥1 and <3 years	1 (33.3)	5 (62.5)
Reason for discontinuation		
Lack of efficacy	1 (33.3)	6 (75.0)
Financial	1 (33.3)	2 (25.0)
Other	1 (33.3)	0
Severe arthropathy	1 (33.3)	0

Intent-to-treat analysis set for safety. *n=23 for ulcerative colitis group; †n=61 for Crohn's disease group. BMI, body mass index; SD, standard deviation

Table 2: On-study treatment

	Crohn's Disease *n*=62	Ulcerative Colitis *n*=24
Line of infliximab treatment, *n* (%)		
First line	59 (95.2)	16 (66.7)
Second line	3 (4.8)	8 (33.3)
Time from previous treatment, weeks, mean (SD)	199.0 (182.6)	34.5 (39.6)
Start dose of infliximab, mg/kg, mean (SD)	5.0 (0.2)	5.0 (1.2)
Duration of infliximab exposure, days, mean (SD)	388.9 (198.0)	291.2 (165.9)
Number of injections, mean (SD)	8.6 (3.7)	7.0 (3.7)
Time to treatment stop based on Kaplan-Meier estimates, weeks*†, median (95% CI)	NE (69.4, NE)	71.1 (44.7, NE)
Infliximab dose adjustment between baseline and treatment stop†, *n* (%)	4 (6.5)	5 (20.8)
Reason for dose adjustment		
Lack of efficacy	2 (50.0)	3 (60.0)
Adverse event	1 (25.0)	0
Other	1 (25.0)	2 (40.0)
Dose increased by doctor for treatment adjustment	0	1 (20.0)
Patient under subtotal colectomy and end ileostomy	0	1 (20.0)
Weight-based dose adjustment	1 (25.0)	1 (20.0)
Concomitant DMARDs and NSAIDs use, *n* (%)	13 (21.0)	7 (29.2)
Immunosuppressants	12 (19.4)	6 (25.0)
Azathioprine	12 (19.4)	6 (25.0)
Mycophenolate mofetil	0	1 (4.2)
Intestinal anti-inflammatory agents	1 (1.6)	3 (12.5)
Other concomitant medication use, *n* (%)	11 (17.7)	9 (37.5)
Systemic corticosteroids	2 (3.2)	5 (20.8)
Hydrocortisone	1 (1.6)	2 (8.3)
Prednisolone	1 (1.6)	2 (8.3)
Methylprednisolone	0	1 (4.2)
Beta-lactam antibacterials	2 (3.2)	3 (12.5)
Ceftriaxone	1 (1.6)	2 (8.3)
Cefoperazone sodium	0	1 (4.2)
Cefotaxime	0	1 (4.2)
Cefotaxime sodium	1 (1.6)	0
Antiemetics	2 (3.2)	0
Ondansetron	2 (3.2)	0
Non-steroidal anti-inflammatory and antirheumatic agents	0	1 (4.2)
Ketoprofen	0	1 (4.2)
Belladonna and derivatives	0	1 (4.2)
Hyoscine butylbromide	0	1 (4.2)
Iron preparations	0	1 (4.2)
Quinolone antibacterials	3 (4.8)	1 (4.2)
Ciprofloxacin	3 (4.8)	0
Levofloxacin	0	1 (4.2)
Other antibacterials	5 (8.1)	2 (8.3)
Linezolid	0	1 (4.2)
Metronidazole	5 (8.1)	1 (4.2)

Intent-to-treat analysis set for safety; all patients received infliximab. *Confidence intervals were computed using Brookmeyer and Crowley method based on log-log transformation on survival. †The time to treatment stop might be underestimated because only the stop reason of "study terminated by sponsor" was considered as censored; all other reasons were considered as treatment stop even if they did not have clear evidence for treatment stop. CI, confidence interval; DMARD, disease-modifying antirheumatic drug; NE, not estimable; NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation

RESULTS

Patient disposition and baseline characteristics

Data from 86 patients enrolled from five countries (Algeria, Egypt, Kuwait, Qatar, and Saudi Arabia) were included in the analysis: 62 patients in the CD group and 24 patients in the UC group [Figure 1]. The low recruitment was attributed to the difficulty in accessing medication.

At baseline, the mean patient age was 32.7 and 29.6 years in the CD and UC groups, respectively, and just over half were female [Table 1]. Most patients had not received any prior biologic treatment (95.2% in the CD group and 66.7% in the UC group), with adalimumab being the only biologic used prior to the study [Table 1]. Approximately two-thirds of the patients completed the study. The main reason for patient withdrawal was the early termination of the trial after two years.

On-study biologic use

Infliximab was the only biologic received during the study and was the first line of treatment in 95.2% of patients with CD and in 66.7% of patients with UC [Table 2]. The mean (SD) infliximab treatment duration was 388.9 (198.0)

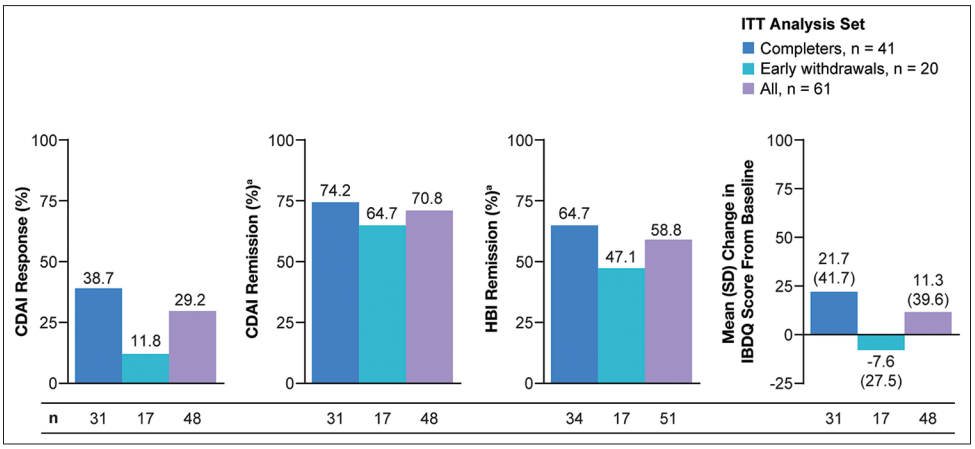

Figure 2: Treatment response for Crohn's disease at Month 3. CDAI response was defined as a reduction of CDAI score of ≥70 and ≥25% compared with the baseline; clinical remission was defined as CDAI score <150; remission was defined as HBI score <5; the IBDQ score ranged from 32 to 224, with a higher score indicating better health-related quality of life. [a]Note that 53.8% (28/52) of patients had a baseline CDAI score, indicating remission, accounting for the large proportion of patients showing remission at Month 3. CDAI, Crohn's Disease Activity Index; HBI, Harvey-Bradshaw Index; IBDQ, Inflammatory Bowel Disease Questionnaire; ITT, intent-to-treat; SD, standard deviation

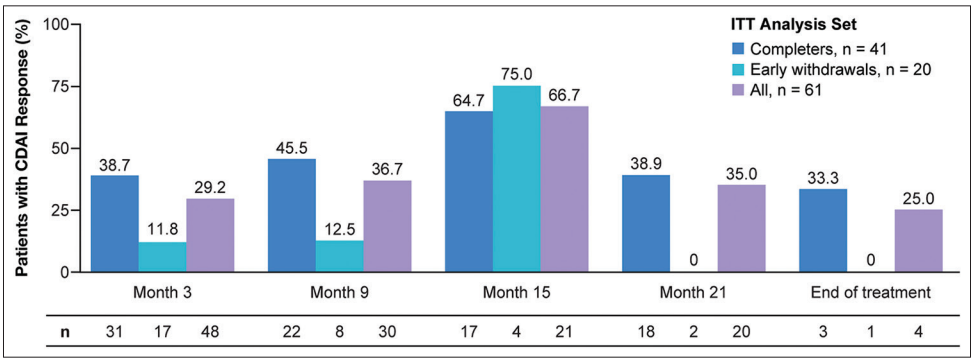

Figure 3: CDAI response for Crohn's disease. CDAI, Crohn's Disease Activity Index; ITT, intent-to-treat

and 291.2 (165.9) days in the CD and UC groups, respectively, with dose adjustments in 6.5% and 20.8% of patients, respectively [Table 2]. No patients switched study medication.

Efficacy in CD

Efficacy was analyzed only for the CD group, up to Month 3. Data were only considered meaningful up to Month 3 because of the small sample size at later follow-up visits and the high withdrawal rate. For the UC group, a lower-than-anticipated number of patients were enrolled, and therefore clinical response parameter results were not considered meaningful for this group.

In the CD group, CDAI scores at Month 3 indicated a positive response to treatment for 14/48 (29.2%) patients [Figure 2]; patient numbers were too low by Month 15 to consider responses [Figure 3]. Clinical remission (CDAI score <150) was achieved for 34/48 (70.8%) patients [Figure 2]; notably, 28/52 (53.8%) patients were at clinical remission at baseline, accounting for the large proportion of patients showing remission at Month 3 compared with the proportion of patients with a positive CDAI response to treatment. At Month 3, 30/51 (58.8%) patients with CD had an HBI score < 5, also indicating remission. In terms of PRO, the mean (SD) change from baseline in IBDQ score at Month 3 was an improvement of 11.3 (39.6) points [Figure 2].

Safety

AEs were reported by 16/62 (25.8%) and 9/24 (37.5%) patients in the CD and UC groups, respectively, and considered related to infliximab treatment for 6 (9.7%) and 4 (16.7%) patients [Table 3]. The most common AEs were gastrointestinal disorders (10 [16.1%] and 4 [16.7%] patients in the CD and UC groups, respectively).

The rates of AEs leading to discontinuation were low (<5% of patients in both groups) and were mostly unrelated to infliximab treatment; 1 (1.6%) patient with CD was discontinued due to an infliximab-related AE [Table 3].

Table 3: Safety summary

	Crohn's Disease *n*=62	Ulcerative Colitis *n*=24
Any AE	16 (25.8)	9 (37.5)
Any infliximab-related AE	6 (9.7)	4 (16.7)
Any SAE	8 (12.9)	4 (16.7)
Any infliximab-related SAE	5 (8.1)	1 (4.2)
Any severe AE	7 (11.3)	5 (20.8)
Any AE leading to withdrawal of infliximab	2 (3.2)	1 (4.2)
Any infliximab-related AE leading to withdrawal of infliximab	1 (1.6)	0
Any AE leading to permanent discontinuation of study	2 (3.2)	1 (4.2)
Any infliximab-related AE leading to permanent discontinuation of study	1 (1.6)	0
Death	1 (1.6)	0

Intent-to-treat analysis set for safety. For the summary of the number of patients, a patient was counted only once even if he/she reported more than one event. AE, adverse event; SAE, serious AE

Serious AE (SAE) rates were low, with 8 (12.9%) and 4 (16.7%) patients in the CD and UC groups reporting these; infliximab-related SAEs were reported by 5 (8.1%) and 1 (4.2%) patient, respectively [Table 3]. Diarrhea (2 [3.2%] patients in the CD group) was the only SAE occurring in more than 1 patient in either group. Severe AEs were experienced by 7 (11.3%) and 5 (20.8%) patients in the CD and UC groups, respectively, and gastrointestinal disorders were most frequently reported (6 [9.7%] and 2 [8.3%] patients). There was 1 death reported in the CD group (unrelated to treatment) [Table 3].

Medical resource utilization

The mean numbers of hospitalization days for CD and UC groups were 1.1 and 0.7, respectively [Table 4]. Patients with UC had a mean number of social service visits of 0.1; no patients with CD had these visits [Table 4]. The mean number of visits to an outpatient hospital/office for CD and UC groups were 0.8 and 1.3, respectively [Table 4]. In both groups, the most common tests/procedures were blood chemistry and blood differential [Table 4].

DISCUSSION

The HARIR observational study was conducted to explore and describe the disease characteristics, treatment, and outcomes of patients with CD and UC treated with infliximab and golimumab, in clinical practice in the Middle East and Northern Africa. This was the first attempt to track the effectiveness and safety of biologics in these regions.

The study was terminated early after two years due to the low number of patients participating, high patient withdrawal, and differences in the duration of observations among indications. Availability of only some research instruments at sites and incomplete study instruments for indication groups could account for even smaller indication/treatment cohort sample sizes. Further, no patients took golimumab as there was a delay in the formulary addition and local reimbursement, preventing analysis of this treatment. It is uncertain why there was a lower-than-expected recruitment of patients into this study and why there were fewer patients with UC than CD. A replacement of infliximab originator by a biosimilar led to patient withdrawal; it could be speculated that this was due to patient preference for the infliximab originator.

Due to limited data, effectiveness of infliximab could only be analyzed for the CD group (up to Month 3). A clinical response to infliximab was observed for 29.2% of patients in the CD group at Month 3. Clinical remission as assessed by CDAI was seen in 70.8% of patients, and HBI scores indicated remission in 58.8% of patients. The mean (SD) change from baseline in IBDQ score was an improvement of 11.3 (39.6) points. At baseline, 28 of 52 (53.8%) patients already had a CDAI score indicating remission (score of <150), accounting for the larger proportion of patients with CDAI scores showing remission, compared with the proportion showing a positive response to treatment at Month 3.

Treatment with infliximab for CD and UC was well tolerated in this Middle Eastern and Northern African population. The most common AEs, SAEs, and severe AEs were gastrointestinal disorders.

Medical resource utilization was low for both disease groups.

Table 4: Medical resource utilization

	Crohn's Disease *n*=61	Ulcerative Colitis *n*=23
Number of hospitalization days, mean (SD)	1.1 (7.8)	0.7 (1.8)
Number of home care nurse visits, mean (SD)	0	0
Number of social services visits, mean (SD)	0	0.1 (0.4)
Number of outpatient hospital/office visits, mean (SD)	0.8 (1.7)	1.3 (2.4)
Patients who received tests/procedures, *n* (%)		
Joint fluid aspiration	0	1 (4.3)
MRI	2 (3.3)	1 (4.3)
CT	2 (3.3)	1 (4.3)
US	1 (1.6)	1 (4.3)
X-ray	0	3 (13.0)
Colonoscopy	3 (4.9)	1 (4.3)
Blood differential	4 (6.6)	3 (13.0)
Blood chemistries	5 (8.2)	5 (21.7)
Serology (including immunological investigations)	2 (3.3)	2 (8.7)
Other	1 (1.6)	0

Intent-to-treat analysis set for safety. CT, computed tomography; MRI, magnetic resonance imaging; SD, standard deviation; US, ultrasonogram

In conclusion, the conduct of the study was restricted by limited accessibility to biologics and concomitant treatments in the Middle East and Northern Africa. In the small population of CD and UC patients studied, treatment with infliximab was well tolerated and a clinical response was observed for 29.2% of CD patients.

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Conflicts of interest

Dr Othman Alharbi: None

Professor Waleed Hamed: None

Professor Osama Salem: Participated in advisory boards and received honorarium from Janssen, AbbVie, Takeda, and Pfizer

Mohamed Sharaf: Full-time employee of Janssen

Catherine Taylor: Full-time employee of Janssen

Ahmed Besar: Full-time employee of Janssen

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