Efficacy and safety of infliximab on colonic mucosal healing in patients with moderate-to-severe ulcerative colitis

Khaled F. Mohamed[a,c], Ali A. Ismail[b,c], Elham A. Hassan[a], Haidi K. Ramadan[a], Madiha M. El-Attar[a]

[a]Department of Tropical Medicine and Gastroenterology, Faculty of Medicine, Assiut University, Assiut, [b]Department of Internal Medicine, Faculty of Medicine, Zagazig University, Zagazig, Egypt, [c]Gastroenterology Unit, Farwaniya Hospital, Kuwait City, Kuwait

Correspondence to Elham A. Hassan, MD, Department of Tropical Medicine and Gastroenterology, Assiut University Hospital, Assiut, Egypt
Tel: +20 100 296 3415; Fax: +20882333327; Postal Code: 71111;
e-mail: mam_elham75@yahoo.com

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Background
Infliximab (IFX), a monoclonal anti-tumor necrosis factor-α antibody, is commonly used for the treatment of moderate-to-severe inflammatory bowel diseases. No sufficient data are present for its role in the treatment of ulcerative colitis (UC) in our area. We studied the efficacy and safety profile of IFX in treating patients with refractory UC.

Patients and methods
This prospective study included 48 adult patients with refractory UC. They received IFX (5 mg/kg) intravenously at weeks 0, 2, and 6 at Farwaniya Hospital, Kuwait, between 2013 and 2016. Patients were followed-up for 12 weeks and re-evaluated for clinical and endoscopic response to therapy.

Results
With the exception of four patients who were excluded from the study because of serious side-effects, 44 patients completed the study. At week 12, clinical remission and colonic mucosal healing were achieved in 29 (65.9%) patients after initiating IFX treatment. Of these 29 responders, no relapse occurred. No serious adverse events or mortalities were recorded during the course of treatment among the studied patients treated with IFX.

Conclusion
IFX is a safe and efficient therapy that may be useful for induction of remission in patients with refractory UC.

Keywords:
infliximab, mucosal healing, refractory ulcerative colitis

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Introduction and aim

Ulcerative colitis (UC) is a relapsing inflammatory disorder of the colon, characterized by mucosal ulceration, rectal bleeding, persistent bloody diarrhea, and abdominal cramping, which often requires long-term therapy to maintain remission [1]. Pharmacological management of UC has relied mainly on 5-aminosalicylates, corticosteroids, and immunosuppressants; however, ~25% of patients fail these or other therapies and require treatment with immunomodulators, including infliximab (IFX), cyclosporin, and/or tacrolimus, and/or colectomy [2].

Mucosal healing (MH) in UC is the absence of friability, blood, erosions, and ulcers in all visualized segments of the gut mucosa [3]. Achieving MH may improve quality of life, prevent in inflammatory bowel disease (IBD) relapses, minimize hospitalizations, and alter the natural history of the disease to prevent complications such as colorectal cancer and need for surgery [4].

IFX is a chimeric monoclonal antibody (IgG1) that inhibits the proinflammatory activity of tumor necrosis factor-α and reduces histological inflammation in patients with UC [5].

Large, randomized controlled trials examining the effects of IFX in patients with UC have been carried out mainly in western countries ([6–9]). In Kuwait, such studies are lacking despite chronic UC being identified with increasing frequency with an incidence of 2.8 per 100 000 persons per year [10]. We aimed to assess the safety and efficacy of IFX therapy in achieving clinical remission and endoscopic colonic MH in patients with moderate-to-severe UC not responding to conventional therapy according to the Mayo score [11].

Patients and methods

Study design

This was a prospective, clinical, observational study carried out at the Gastroenterology Unit, Farwaniya (FAR) Hospital, Kuwait, during the period between February 2013 and August 2016. The study

was approved by the local Ethics Committee, and was conducted in accordance with the previsions of the Declaration of Helsinki. Informed written consent was obtained from all the participants before enrollment.

Study population

Forty-eight adult patients were enrolled from the outpatient clinics and the inpatient department of the Gastroenterology Unit of FAR Hospital, Kuwait. The patients had an established diagnosis of moderate-to-severe UC based on standard clinical, endoscopic (total Mayo score [11], 6–12 points with endoscopy subscore of at least 2), radiological, and histopathological criteria, they did not respond to full dose or could not tolerate conventional therapy such as corticosteroids and/or azathioprine or 6-mercaptopurine and/or 5-aminosalicylate-containing medications, and were eligible for IFX therapy.

Patients previously exposed to IFX or any other anti-tumor necrosis factor-α agents, those with positive tuberculin test or abnormal chest radiography or past history of tuberculosis, positive HBsAg or anti-hepatitis C virus, chronic, current, or opportunistic infections, abnormal kidney function or heart failure, indeterminate colitis, and other causes of colitis such as cytomegalovirus colitis, history of colectomy, hemorrhoids, pregnancy, or lactation were excluded from the study.

At baseline and after 12 weeks of initiation of IFX therapy (in the same day of colonoscopy), all patients were subjected to the following:

(1) Full clinical history taking and examination
(2) Complete blood analysis
(3) Liver function tests
(4) Serum urea and creatinine
(5) Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)
(6) Colonoscopy: all colonoscopies were performed at the Gastroenterology Unit, FAR Hospital, Kuwait, using Olympus scope (CF-FH260AZL; Olympus, Tokyo, Japan) by two experienced endoscopists IBD who were blinded to medications taken by the patients. The mucosal changes were assessed (at weeks 0 and 12) by the Mayo endoscopic subscore [12], calculated by consensus of the two endoscopists. In addition, the extent and location of the disease were recorded.

Infliximab therapy

In the absence of contraindications to IFX therapy, patients with refractory UC received IFX therapy as induction regimen within a week of baseline colonoscopy as follows: intravenous infusions of IFX at a dose of 5 mg/kg at weeks 0, 2, and 6. When a patient was not admitted, the dose was administered under observation in a specialized room for intravenous infusion at the Gastroenterology Unit in FAR Hospital.

Statistical analysis

All statistical analyses were performed using SPSS for windows version 16 (SPSS Inc., Chicago, IL. USA). Quantitative variables are described as means and standard errors. Comparison between means was carried out using paired and Student's *t*-tests. Numerical data are described as percentages. Multiple regression analysis was used to evaluate predictors of colonic MH. Statistical significance was considered when *P*-value was less than 0.05.

Results

Characteristics of the study population

Forty-eight UC patients who met inclusion criteria of the study were recruited. During the study, four patients discontinued IFX treatment and dropped out of the study – three of them developed serious IFX side-effects (first patient developed anaphylactic reaction, the second had generalized vitiligo at week 9 of IFX therapy, and the third patient had abnormal lymphocytosis at week 10), and the fourth patient discontinued therapy because he developed toxic megacolon after the first dose of IFX and underwent surgical colectomy. This was not considered as an adverse effect of IFX therapy; therefore, the remaining 44 patients completed the study. Their sociodemographic and clinical characteristics before start of IFX administration (week 0) are summarized in Table 1. The majority of patients were males (59.1%), and their mean age was 32.6 ± 1.6 years. Regarding colonic lesions, left-sided colitis was present in 61.4% (in 27 patients), and pancolitis was present in 38.6% (in 17 patients).

On receiving IFX, all studied patients had significantly lower Mayo score (4.4 ± 0.6 vs. 9.3 ± 0.22, $P < 0.001$) and endoscopic subscore (0.97 ± 0.2 vs. 2.4 ± 0.1, $P < 0.001$) at week 12 compared with their variables at the beginning of the treatment (week 0) (Table 2).

Assessment of mucosal healing in patients with moderate-to-severe ulcerative colitis after infliximab administration

At week 12 of IFX therapy, 29 (65.9%) patients achieved MH (group 1, endoscopic subscore of mayo score<1) compared with 15 (34.1%) patients who failed to achieve MH (group 2, endoscopic subscore>1). The two groups showed no significant differences in laboratory and endoscopic findings at week 0 of IFX therapy;

however, significant improvement was found in these variables at week 12 in patients with MH (group 1) compared with those without MH (group 2) except for hemoglobin (Table 3 and Fig. 1).

Risk factor analysis for mucosal healing

When multiple regression analysis was performed, none of the predictive factors (age, sex, white blood cell, ESR, CRP, Mayo score, endoscopic subscore, and fecal calprotectin) in week 0 could predict MH at week 12 of IFX therapy (Table 4).

Table 1 Sociodemographic, clinical, laboratory, and endoscopic characteristics before start of infliximab administration (week 0)

Variable (at week 0)	UC patients (*n*=44)
Age range (years, mean±SE)	16-60 32.6±1.6
Sex (*N* (%))	
Males	26 (59.1)
Females	18 (40.9)
WBC (mean±SE) (μl)	8.7×10^3±0.5
ESR (mean±SE) (mm/h)	35±2.9
CRP (mean±SE) (mg/l)	35.5±4.1
Hb (mean±SE) (g/dl)	11.65±0.27
Mayo score (*N* (%))	
Moderate cases	28 (63.6)
Severe cases	16 (36.4)
Mayo score	9.34±0.22
Colonoscopic lesions (*N* (%))	
Left-sided colitis	27 (61.4)
Pancolitis	17 (38.6)
Endoscopic subscore	2.36±0.7

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; UC, ulcerative colitis; WBC, white blood cell.

Table 2 Comparison between laboratory and endoscopic findings at week 0 and week 12 of infliximab administration among the studied patients

	Week 0	Week 12	*P*
WBC (μl)	8.7×10^3±0.52	8.1×10^3±0.38	0.18
Hb (g/dl)	11.65±0.27	11.57±0.26	0.3
ESR (mm/h)	35.2±2.9	32.9±2.5	0.07
CRP (mg/l)	35.5±4.1	37.8±5.6	0.59
Mayo score	9.3±0.22	4.4±0.6	<0.001
Endoscopic subscore	2.4±0.1	0.97±0.2	<0.001

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; WBC, white blood cell.

Finally, we illustrate the endoscopic lesions of some patients with moderate-to-severe UC before the start of IFX treatment (week 0) and colonic MH after (week 12) IFX treatment in Fig. 1.

Infliximab safety evaluation

Apart from the four previously mentioned patients who discontinued IFX therapy, most of the side-effects of IFX were mild to moderate and did not mandate therapy discontinuation. During the study, seven (7/44, 15.9%) patients developed mild-to-moderate IFX side-effects, and five patients developed skin urticarial rash, itching, mild pain at the infusion site, and fever due to IFX infusion. The other two patients developed mild, asymptomatic alanine aminotransferase elevations (90 and 75 U/l, respectively) after the first dose of IFX and returned to normal levels at week 6. No relapses or mortalities were reported during the study.

Discussion

The overall aim of this study was to evaluate the safety and efficacy of IFX induction therapy in achieving clinical remission and endoscopic colonic MH in patients with moderate-to-severe UC who did not respond to conventional therapy according to the Mayo score.

This study evaluated only short-term (90 days) response to IFX in patients with UC, because almost always long-term remission is established in this time period. When a patient does not respond after three drug infusions, it is predicted that he or she will not respond to further doses and therapy is discontinued and switched to other therapeutic methods ([13,14]).

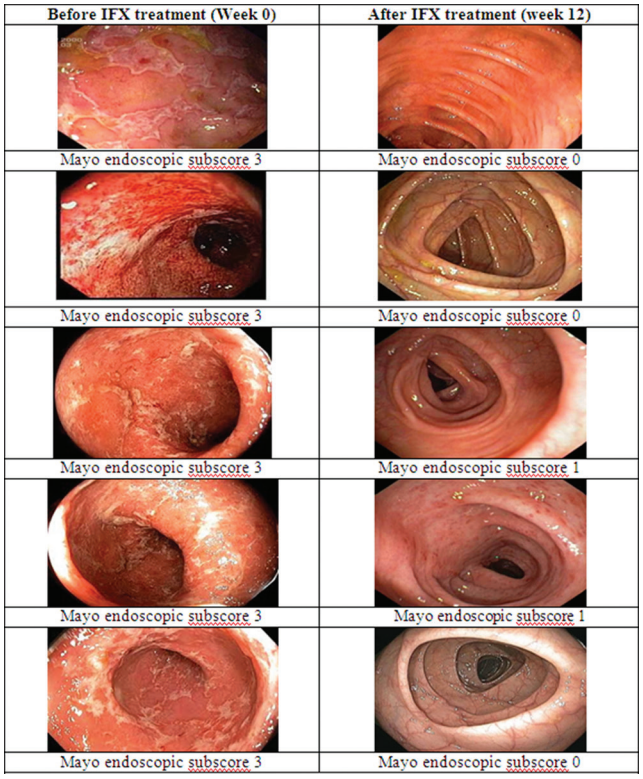
In our study, MH was achieved in 65.9% of patients who received three doses of IFX and completed the study without serious side-effects. These results are similar to that of Active Ulcerative Colitis Trials 1 and 2 (ACT1 and ACT2), which found a response rate to IFX between 45 and 69% [12]. However, our findings were higher than that of Sands *et al.* [15], who

Table 3 Comparison between patients with and without mucosal healing with regard to laboratory and endoscopic findings at week 0 and 12 of infliximab administration

	Week 0 of IFX therapy			Week 12 of IFX therapy		
	Group 1	Group 2	*P*	Group 1	Group 2	*P*
WBC (μl)	7.8×10^3±0.57	10.5±0.1	0.08	7.3×10^3±0.3	9.6×10^3±0.8	0.003
Hb (g/dl)	11.95±0.27	11.04±0.5	0.11	11.9±0.3	10.9±0.4	0.07
ESR (mm/h)	31.9±3.5	41.6±5	0.12	28.9±2.4	40.7±5.1	0.024
CRP (mg/l)	29.9±5.3	46.2±5.7	0.06	26.3±4	60±12.9	0.003
Myoscore	9±0.29	9.9±0.28	0.060	1.7±0.2	9.6±0.2	<0.001
Endoscopic subscore	2.3±0.1	2.5±0.1	0.097	0.2±0.08	2.4±0.13	<0.001

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; IFX, infliximab; WBC, white blood cell.

Figure 1



Endoscopic lesions of moderate-to-severe ulcerative colitis before (week 0) and after (week 12) infliximab treatment.

Table 4 Logistic regression analysis for predictors of mucosal healing

Predictive factor at week 0 of IFX therapy	*P*
Age	0.89
Sex	0.17
WBC	0.46
ESR	0.41
CRP	0.78
Mayo score	0.35
Endoscopic subscore	0.75

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IFX, infliximab; WBC, white blood cell.

found a treatment success of IFX therapy in 50% of patients with UC but with similar good safety profile and no significant side-effects.

Our results are in contrast with the study by Probert *et al.* [16], who carried out a randomized placebo controlled trial with IFX (5 mg/kg) for the treatment of glucocorticoid-resistant UC. Remission was achieved in 3/11 (27%) patients initially treated with IFX and in 1/9 (11%) patients treated with placebo. Therefore, their study did not support the use of IFX in the management of moderately active glucocorticoid-resistant UC.

Several studies have obtained mixed results, with rate of response ranging from 13 to 69% ([12,15–17]). These different rates of MH may be attributed to different definitions of MH, different study designs, different timing of endoscopy evaluations, differences in sample size, demographic variation, and duration of therapy. In addition, genetic predispositions may have an important role in response to IFX in UC patients [18].

In recent years, after the use of biological agents for the treatment of UC, MH has emerged as the goal for therapy to achieve long-term remission and to change the natural course of UC. Thus, it is essential to monitor thoroughly the disease activity [19]. MH can alter the course of UC disease as it is associated with less flares, reduced rates of hospitalizations, low rates of colorectal cancer and surgeries, and improved quality of life; therefore, MH is regarded as one of the most important goals in the treatment of IBD ([20–22]).

IFX contributes to MH by acting directly at the intestinal mucosal level and indirectly affecting epithelial cell migration and proliferation by acting on both fibroblasts and leukocytes. IFX-treated colonic mucosal biopsies displayed a better histological appearance, reduced inflammation with an increase in E-cadherin, phospho-ERK, and apoptosis [23]. Barbara *et al.* [24], reported that IFX is effective for the maintenance of remission and is steroid sparing in patients who are unable to maintain remission without steroid therapy or are intolerant to immune-suppressive agents; hence, IFX is the primary biological agent used in the treatment of moderate-to-severe UC.

According to our results, IFX had an excellent safety profile. Only four patients dropped out of the study – three (6%) out of 48 patients developed significant adverse effects (one developed solar anaphylactic reaction, one developed vitiligo, and one developed abnormal lymphocytosis, and the patients refused to continue drug administration), and the fourth patient of our cohort discontinued therapy because he developed toxic megacolon and underwent surgical colectomy; therefore, it was not regarded as discontinuation due to IFX adverse effect.

In our study, other side-effects of IFX were mild to moderate and did not mandate therapy discontinuation. We observed this in only seven patients – five cases with allergic reactions, including skin urticarial rash, itching, and mild pain at the infusion site, and two patients developed mild asymptomatic alanine aminotransferase elevations (90 and 75 U/l, respectively) after the first dose of IFX that returned to normal levels at week 6. No relapses or mortalities were reported during this study. Our findings are compatible with several studies. Zabana *et al.* [25], concluded that IFX therapy is safe when the recommended preventive measures are implemented, with a rate of serious adverse effect less than 10%.

Therefore, according to our study, IFX therapy appears to be efficient and relatively safe for UC patients. However, the use of IFX requires careful screening and close patient monitoring to identify patients at risk and the infrequent but sometimes serious complications. In addition, it is of great importance to continue treatment for those who show positive response only, owing to its high cost and its risk for developing of severe adverse effect [26].

In the present study, multiple regression analysis showed that none of these parameters – white blood cell, ESR, CRP, Mayo score, endoscopic subscore, and fecal calprotectin –at the beginning of IFX therapy could significantly predict MH at week 12 after IFX administration. In contrast, in a study by Lee *et al.* [27], severe disease, no history of immunomodulator therapy, hemoglobin greater than or equal to 11.59 mg/dl, and high baseline CRP were independent predictors of good response to IFX therapy. This may be because of the small number of UC patients in our study and a variable study design.

The limitations of our study included its small sample size and single-center design. Further multicenter, large-sized prospective studies are needed to confirm these findings.

In conclusion, patients with moderate-to-severe active UC treated with IFX for were more likely to show a clinical response and MH at week 12 of IFX therapy with a few serious adverse effects.

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Conflicts of interest
There are no conflicts of interest.

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