Original Article

Effectiveness of Infliximab and Adalimumab in Iraqi patients with ulcerative colitis – Real-World Data

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ABSTRACT

Background: Ulcerative colitis can affect the quality of life and in some cases can cause life-threatening complications. Biologic drugs such as Infliximab (IFX) and Adalimumab (ADA) are anti-TNF-α, administered to patients for reducing colonic inflammation. This study aimed to evaluate the effect of IFX and ADA in patients with ulcerative colitis. **Methods:** One hundred patients who had previously diagnosed with UC at least 3 months had received treatment protocols prescribed by physicians in the GIT center and had received biological treatment (all patients received no previous TNF inhibitor). The patients were divided into two groups; The first group (70 UC patients) received Infliximab and the second group (30 UC patients) received Adalimumab. All patients were followed up for 6 months after the onset of biological agents. **Results:** The study included 100 UC patients, at baseline 45% of patients with endoscopy subscore 1, after 6 months only 26 of them (57.8%) remained with the same score, also 18 of them (40%) lowering their score to zero, only one patient had increased to three. Initially, 55% of patients had endoscopy subscore 2 and 3, after 6 months only 3 of them remained with the same score, the rest of them reduces at least one level. Infliximab showed slightly better conversion from moderate-severe Mayo endoscopic sub-score to mucosal healing (MH), 97.3%, compared to adalimumab (83.3%), but the difference between the two drugs was not significant. **Conclusions:** In this Real-World study, there was no significant difference between the most commonly used anti-TNF medications in the treatment of UC, namely infliximab and adalimumab, in their effect on reducing relapse rate and mucosal healing after 6 months follow-up.

Keywords: infliximab, adalimumab, ulcerative colitis, real-world data, relapse, mucosal healing

Introduction

Ulcerative colitis refers to an inflammatory bowel disease (IBD) that results in persistent inflammation and ulcers (lesions) in the large bowel. Ulcerative colitis affects the colon and the rectum. Symptoms appear over a long period [1]. There is no real reason for the occurrence of ulcerative colitis, although there is linkage to the immunity of the body [2].

Patients need awareness of inflammatory disease and anti-inflammatory remedies. [3, 4] Ulcerative colitis is an autoimmune condition which studied by many researchers. [5] However, inflammation of ulcerative colitis is due to the stimulation of white cells to eliminate the infection resulting in bacterial infection [6]. With infection dismissal, retaliation of the immune system proceeds, however, failure would result in a struggle for infections that are not existing leading to continuous inflammation [7].

Ulcerative colitis mainly begins in the rectum. It may stay in the rectum (ulcerative proctitis) or exceed contiguously, occasionally spreading wholly to the colon. Patients suffer from diarrhea, rectal bleeding, lower abdominal pain, and tenesmus

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(dire need to excrete the bowels however less little movement of stool). [8].

There is a lack of head to head randomized clinical trial (RCT) comparing both infliximab (IFX) and adalimumab (ADA) in the literature, most of these studies performed in Western countries [9-12], with few studies examined Asian populations. This study aimed to evaluate the effect of Infliximab and Adalimumab in patients with ulcerative colitis in the Real-world setting.

Methods

Study design

One hundred patients who had previously diagnosed with UC at least 3 months had received treatment protocols prescribed by physicians at the GIT center and had received biological treatment (all patients received no previous TNF inhibitor). The patients were divided into two groups; The first group (70 UC patients) received Infliximab and the second group (30 UC patients) received Adalimumab. All patients were followed up for 6 months after the onset of biological agents.

Study setting

The study was conducted at the Baghdad Medical City – Gastroenterology and Hepatology Training Hospital in Baghdad/Iraq. The study was conducted from December 2018 to July 2019.

Patients with congestive heart failure, viral hepatitis, active bacterial infection (e.g. tuberculosis [TB]), and pregnant women were excluded from the study.

Baseline assessment

Screening of all patients before the onset of TNF inhibitors includes a physical examination, endoscopic examination, Mayo subscore, and TB screening.

Participants

Adults between the ages of 18 – 70 years were eligible for inclusion, patients with mild to severe UC (based on Mayo subscore), patients who did not receive previous anti-TNF treatment.

Data collection

Detailed history regarding the following points was taken:

1. The type of biological treatment according to the treatment protocol schedule.
2. Response (including remissions and relapses) these parameters were calculated and compared before and after the start of treatment (clinically and colonoscopically)
3. Any symptoms that indicate side effects

Patients were examined for signs of fever, tachycardia, pallor, abdominal pain, blood on rectal exam, joints' inflammation and diarrhea with or without blood. These physical symptoms and complications may present related to UC reported and studied before and after the biologic treatment.

Treatment protocol

Infliximab IFX (REMICADE® brand name of Janssen CarePath Company) at the recommended dose of 5 mg/kg intravenous infusion with induction regimen at 0, 2 and 6 weeks followed by a 5 mg/kg maintenance regimen every 8 weeks for 1 year or accordingly.

Adalimumab (HUMIRA® brand name of Abbvie Company) subcutaneously with a recommended dose regimen of 160 mg initially on day 1 (given on a single day or split over two consecutive days), followed by 80 mg two weeks later than 40 mg every two weeks.

Evaluation of study parameters

Relapse: relapse UC (flare) is an acute worsening of the symptoms of bowel inflammation. Disease relapse was diagnosed clinically and endoscopically by the Mayo sub-score with the exclusion of other causes of relapse, i.e. infection and interruption of treatment [13].

Clinical relapse symptoms include cramps or abdominal pain that can't be managed by ordinary antispasmodic or pain killer drugs ,bloody stool, dehydration, diarrheal symptoms, decrease appetite leading to loss of weight, and abnormal bowel motion. These symptoms and others are evaluated and compared between groups before and after 6 months of treatment.

Mayo Endoscopic sub-score

This score was used to assess mucosal healing (MH) [14], then recorded by specialists and compared to before and after 6 months of treatment, for severity grade (see Table 1) [13]. MH is defined as a score of 0 or 1 [14].

Table 1: Mayo endoscopic sub-scores [13]

Grading	Disease Activity	Finding
0	Inactive	Normal
1	Mild	Mild friability, erythema and loose of vascular pattern
2	Moderate	Erosions, absent of vascular pattern, marked erythema and friability
3	Severe	Spontaneous bleeding and ulceration

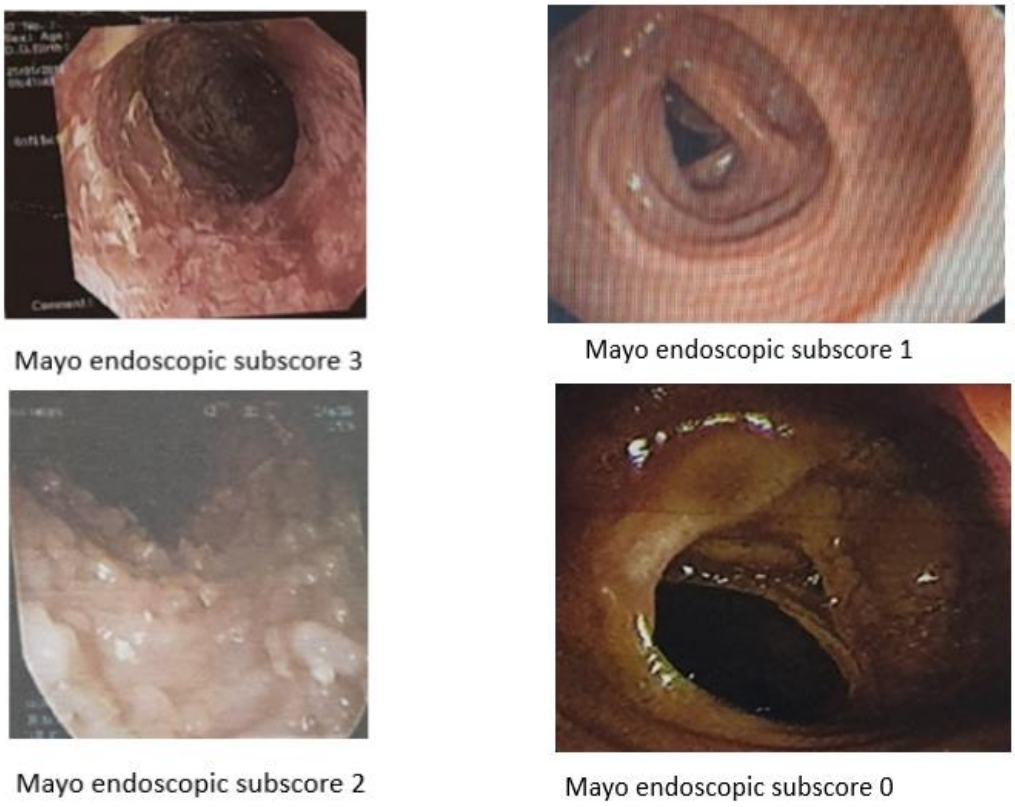

Figure 1: endoscopic images

Ethical approval

All procedures in the study are following the ethical standards of the institutional research committee at the Faculty of Medicine – University of Baghdad (Code: 2019/0263) and with the 1964 Helsinki declaration and subsequent amendments.

Informed consent

Written Informed consent was obtained from all study participants separately.

Statistical analysis

Wilcoxon Median rank test, logistic regression were used to calculate odds ratios (OR) and 95% confidence intervals were used for statistical analysis. GraphPad Prism version 8.0.0 used for statistical analysis, p-value <0.05 was considered significant.

Results

The study included 100 UC patients, mean age 34.2 ± 12.1 years, with slightly higher female subjects, 70% of them received IFX, and 30% received ADA, as shown in Table 2.

Table 2: Evaluation of patient clinical data

Variable	Value
Number	100
Age (Mean ± SD)	34.2 ± 12.1
Gender, n (%)	
Female	55 (55%)
Male	45 (45%)
Drugs, n (%)	
Infliximab	70 (70%)
Etanercept	30 (30%)

At baseline, 45% of patients had endoscopy subscore 1, after 6 months only 26 (57.8%) remained with the same score, also 18 of them (40%) reduced their score to zero, and only 1 patient had increased to 3. Initially, 55% of patients had endoscopy subscore 2 and 3, after 6 months only 3 of them remained with the same score, the rest of them reduce at least one level, as shown in Table 3.

Table 3: Assessment of the Mayo endoscopic sub-score

Baseline	After 6 months			
	Inactive	**Mild**	**Moderate**	**Severe**
		All patients		
Mild	18 (40%)	26 (57.8%)	0 (0%)	1 (2.2%)
Moderate	15 (60.0%)	8 (32.0%)	2 (8.0%)	0 (0%)
Severe	22 (73.3%)	6 (20.0%)	1 (3.3%)	1 (3.3%)
		Infliximab		
Mild	13 (39.4%)	20 (60.6%)	0 (0%)	0 (0%)
Moderate	12 (60.0%)	7 (35.0%)	1 (5.0%)	0 (0%)
Severe	12 (70.6%)	5 (29.4%)	0 (0%)	0 (0%)
		Adalimumab		
Mild	5 (41.7%)	6 (50.0%)	0 (0%)	1 (8.3%)
Moderate	3 (60.0%)	1 (20.0%)	1 (20.0%)	0 (0%)
Severe	10 (76.9%)	1 (7.7%)	1 (7.7%)	1 (7.7%)

Infliximab showed slightly better conversion from moderate-severe Mayo endoscopic sub-score to mucosal healing (MH), 97.3%, compared with adalimumab (83.3%), however, the difference did not appear to be significant between the two drugs, as shown in Table 4.

Table 4: Evaluation of the effect of the medication on mucosal healing

Baseline	After 6 months		OR (95%CI)	p-value
	MH	**Moderate to severe**		
		All patients		
Mild	44 (97.8%)	1 (2.2%)	3.451 (0.372-32.033)	0.276
Moderate to severe	51 (92.7%)	4 (7.3%)		
		Infliximab		
Mild	33 (100%)	0 (0%)	-	0.999
Moderate to severe	36 (97.3%)	1 (2.7%)		
		Adalimumab		
Mild	11 (91.7%)	1 (8.3%)	2.200 (0.201-24.086)	0.518
Moderate to severe	15 (83.3%)	3 (16.7%)		

OR: odds ratio, CI: confidence interval

There was a significant decrease in the relapse rate (both drugs reduced the relapse rate to a similar degree), as shown in Table 5.

Table 5: Evaluation of the effect of treatment with a biological agent on the relapse rate of patients with UC

Variables	Baseline	After 6 months	p-value
All patients	1 (1 – 1)	0 (0 – 1)	<0.001
Infliximab	1 (1 – 1)	0 (0 – 1)	<0.001
Etanercept	1 (1 – 1)	0 (0 – 1)	0.023

Data presented as median (IQR)
IQR: interquartile range (25^{th} – 75^{th} percentile)

Palpitation was the most common side effect caused by IFX during the study, followed by blurred vision, while headache was the most common side effect affect patients received ADA, the rest of the side effects are illustrated in table 6.

Table 6: side effect of drugs

	Infliximab (70 cases)	Adalimumab (30 cases)
Palpitation	10 (14.3%)	3 (10.00%)
Blurred vision	8 (11.42%)	1 (3.33%)
Headache	5 (7.14%)	5 (16.66%)
Nausea	5 (7.14%)	0
Fever	5 (7.14%)	2 (6.66%)
Weakness	4 (5.71%)	0
Cough	4 (5.71%)	1 (3.33%)
Dizziness	2 (2.85%)	0
Shortness breath	2 (2.85%)	0
Hypotension	1 (1.42%)	0
Abdominal pain	1 (1.42%)	3 (10.00%)
Vomiting	1 (1.42%)	0
Muscles aches	0	2 (6.66%)
Skin rash	0	1 (3.33%)
TB infection	0	1 (3.33%)

Discussion

Anti-TNF therapy is one of the most effective agents for UC. They are used when the other treatment fails to improve the signs and symptoms of the disease, by blocking the activity of TNF, a substance that causes immune-system diseases and inflammation [15]. Limited observational studies are comparing the effectiveness of anti-TNF agents on IBD [16].

In the present study, the number of relapses decreased significantly for both IFX and ADA from baseline to 6 months of treatment, but there was no significant difference in the number of relapses treated with IFX or ADA after 6 months of therapy (median relapse was 0 for both IFX and ADA).

In Ananthakrishnan et al., they show moderate symptomatic improvement for IFX compared to ADA [17]. In Sandborn et al. study, both drugs were effective for the management of moderate-severe UC patients with no significant difference between the two drugs [18]. Other studies reported similar findings [9-12], most of these studies have been reported from Western countries. Few studies performed in Asia that compared both medications, in a recent study (2020) Han et al. examined 862 UC patients, 630 patients receiving IFX 232, and also ADA, There was no significant difference between the two drugs, despite both were clinically effective in treating UC [19]. Several meta-analyses indirectly compared these two anti-TNF, their result was in agreement with our findings [20-22].

In the present study, after 6 months of treatment, most UC patients achieved or maintained 95% mucosal healing. Infliximab showed slightly better conversion from moderate-severe Mayo endoscopic sub-score to mucosal healing (MH), 97.3%, compared with adalimumab (83.3%), however, the difference between the two drugs did not appear to be significant.

contrary to these studies, two meta-analyses showed that IFX is better than ADA, Danese et al. showed that IFX is better in inducing and maintaining remission in UC [23], Cholapranee et al. showed that IFX is better in inducing mucosal healing in UC [24]. These findings were somewhat similar to our findings.

There is a decrease in the number of relapses using biologic agents because these biologic agents bind with high affinity to TNF-α (a key proinflammatory cytokine in UC patients), neutralizing its biologic activity. Thus, these two agents are effective for maintaining clinical remission [25].

Study limitation

The small sample size of this study is a potential bias, in addition, the short duration of prospective follow-up (i.e. six months) also limits the number of events observed by the researcher.

Conclusion

In this Real-World study, there was no significant difference between the most commonly used anti-TNF medications for the

treatment of UC, namely infliximab and adalimumab, in their effect on decreasing relapse rate and mucosal healing after 6 months of follow-up.

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