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ORIGINAL ARTICLE

Clinical and biochemical response for treatment with anti-TNFα in Egyptian IBD patients: Zagazig University IBD Clinic experience

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ABSTRACT

The aim is to evaluate the clinical and biochemical response of treatment with anti-tumor necrosis factorα (anti-TNFα) therapy used for induction and maintenance of remission in Egyptian inflammatory bowel disease (IBD) patients who attended an IBD Clinic of the Internal Medicine Department, Zagazig University over a one year.

Methods A prospective cohort study included seventy-seven IBD patients; 40 ulcerative colitis (UC) and 37 Crohn's disease (CD) indicated for biological therapy. Patients were randomly assigned into either two treatment subgroups: (a) received Infliximab, or (b) received Adalimumab.

Results 51.95% (n=40/77) showed an initial significant improvement following induction of remission dose and completed the study. Clinical remission was maintained to week 52 in 37 patients. The reduction rate of fecal calprotectin from the baseline was higher for CD compared to UC patients (82.4% and 51.7%, respectively, p<0.001 for both). 14.29% of all patients were non-responders; 10.39% were referred for surgery, 15.59% discontinued treatment due to adverse effects, mostly infusion reactions as an anaphylactic reaction or late serum sickness-like symptoms.

Conclusion anti-TNFα therapy seems to deliver a beneficial clinical and laboratory response in severe, steroid-dependent, or refractory patients. The effect was more noticed CD than UC patients; however, longer follow-up periods and mucosal healing assessment are needed in further studies for our populations.

Keywords: Infliximab; Ulcerative colitis; Adalimumab; Serum Sickness, Crohn's Disease

INTRODUCTION

Recently, the awareness of the inflammatory bowel disease (IBD) diagnosis and management in Egypt and the Middle East is increasing. Starting a disease registry is highly crucial for IBD patients and establishing a specific unit for IBD is extremely essential for better diagnosis, treatment, and patients care, for this reason, the IBD Clinic has been established at our institute since 2017.

IBD is a chronic inflammatory disorder of the gastrointestinal tract that includes two subgroups; Crohn's disease (CD) and ulcerative colitis (UC). It is characterized by periods of remission and relapse; bowel movements may be up to 20 times per day with associated fecal urgency and incontinence. IBD is also associated with extra-intestinal manifestations, affecting joints, eyes, skin, bones, and organs because of the disease process [1].

In Egypt, a recent study observed a marked increase in the frequency of IBD diagnoses in the last 10 years. The study observed a ratio of 6:1 for UC to CD [2].

IBD endures a chronic relapsing condition that can negatively impact the quality of life and contribute to a significant cost to the health care system. Disease activity often fluctuates over time and therefore requires lifelong treatment [3].

The goals of treatment of IBD are the rapid induction and maintenance of steroid-free remission, prevention of complications of the disease itself and its treatment, and improving the patient's health-related quality of life [4].

Current non-surgical treatments for IBD typically include the administration of corticosteroids, 5-aminosalicylic acid (5-ASA) preparations, and immune-suppressive drugs like azathioprine. However, exclusively just 50% of patients achieve sustained remission with these drugs, and the treatment may cause many side effects [5].

Recently, biological therapies (biotechnologically manufactured TNF-α blockers) that target immune pathways have emerged as a novel therapeutic approach for the treatment of immune dysfunction-mediated diseases such as severe active forms of inflammatory bowel disease and in patients who do not respond adequately to conventional therapy with steroids or immunomodulators, and in many patients, enable the dose of steroids to be reduced [4].

We aimed at evaluating the clinical, laboratory outcome, and complications of anti-TNFα therapy used for the treatment of Egyptian IBD patients attended for follow-up at Zagazig university's IBD clinic.

Materials and Methods

Patients

This was an observational study, data were collected from a total of seventy-seven IBD patients (40 ulcerative colitis and 37 Crohn's disease) subjected to treatment with anti-TNFα therapy; attended for follow up over one year at our specialized IBD Clinic of the Internal Medicine Department, Gastroenterology and Hepatology Division, Zagazig University, Egypt

All patients were of Age ≥ 18 years with a confirmed diagnosis of UC or CD by colonoscopy and histopathological features and were eligible and indicated for biological therapy.

Exclusion criteria

Patients with a history of previous lymphoma or malignancy, patients with severe infection, heart failure, multiple sclerosis, demyelinating disorders, immunodeficiency, positive tuberculin test or abnormal chest radiography or history of tuberculosis, positive HBsAg or anti-hepatitis C virus, pregnancy, lactation, and patients with other causes of their disease execration as Clostridium difficile or CMV infection

Methods

All selected patients were subjected to detailed medical history (including sociodemographic and general characteristics of the patients, detailed symptoms for diarrhea, crampy abdominal pain, rectal bleeding, tenesmus, rectal urgency, weight loss, family history of IBD, special habits, and associated co-morbidities) and thorough physical examination.

Written informed consent was obtained from all participants, the study was approved by the research ethical committee of the Faculty of Medicine, Zagazig University (IRB#2682). The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Assessment of disease activity at week 0 and week 52

Clinical assessment through clinical activity scoring

Partial Mayo scoring [6] that categorizes the severity of UC to remission, mild, moderate, or severe activity depending on stool frequency, rectal bleeding, and physician's global assessment.

Harvey-Bradshaw activity index [7] that categorizes the activity of CD into remission, mild, moderate, or severe disease depending on general well-being, abdominal pain, palpable mass, bowel habits, and presence of complications as anal fissure and fistula.

Biochemical assessment

Done at 1st diagnosis, following induction of remission and during the period of follow up every 3 months up to 1 year, including CBC,

Inflammatory markers (ESR and CRP), fecal calprotectin, and stool examination.

Imaging assessment at week 0

Disease severity, extension, activity, and complications were evaluated through endoscopy, biopsy, and histopathology, X-ray erect abdomen, or CT, and MRI enterography. Endoscopic evaluation for disease activity at week 0 was done coinciding with the Mayo Endoscopic subscore [6] for UC patients and simple endoscopic severity for Crohn's disease (SES-CD) [8] for CD patients.

Treatment protocols

Patients were subjected to either treatment subgroups:

Subgroup (a) included 40 patients (20 with UC and 20 with CD) who received infliximab (supplied as REMICADE® by Jansen pharmaceuticals) at a dose of 5mg/kg/dose at 0, 2, 6 weeks then every 8-weeks IV infusion over 2 hours. The dose was administered under observation in a specialized room for intravenous infusion.

Subgroup (b) included 37 (20 with UC and 17 with CD) patients who received adalimumab (supplied as HUMIRA® by AbbVie pharmaceuticals) at a dose of 160 mg then 80 mg after 2 weeks then 40mg every 2 weeks.

Patients were maintained on their azathioprine dose during treatment. Medications were supplied to some patients through Ministry of Health centers or health insurance; however, some patients received treatment at their own expense.

Assessment of Clinical and laboratory outcome

was done by collection of data following one year of treatment (week 54) and was evaluated by the same scoring systems and laboratory investigations previously described.

Clinical remission according to partial Mayo scoring was defined as score < 2. Clinical remission according to the Harvey-Bradshaw activity index was defined as a score < 5 points.

Biochemical remission was defined as normalization of inflammatory markers like CRP, ESR, improvement of anemia, and fecal calprotectin <200 mg/kg.

Endpoints

The primary endpoint represents the percentage of patients who achieved and maintained clinical remission and biochemical remission or significant response at week 52 of treatment with either infliximab or adalimumab.

The secondary endpoint is to detect the complications and compliance with therapy.

Statistical analysis

Data were collected, entered, and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences software (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp) for analysis. According to the type of data, qualitative data were represented as numbers and percentages; the quantitative data were represented by mean ± SD. The following tests were undertaken to test differences for significance; Chi-square test (X2) for qualitative variables and Student t-test for quantitative data. Paired t-test was used when appropriate. P-value was set at < 0.05 for significant results & < 0.001 for high significant result.

Results

Patient distribution throughout the study

Forty (51.9%) IBD patients showed an initial clinical and biochemical response following induction dose with anti-TNFα therapy at week 12 and completed the follow-up period while 37 (49.1%) patients discontinued the treatment due to varied causes (shown in Fig. 1). The characteristics of patients who completed the follow-up period are shown in Table 1.

Clinical outcome

A significant improvement for the abdominal pain severity and bloody diarrhea at week 52 of treatment with either infliximab (p = 0.02, 0.002 respectively) or adalimumab (p = 0.04, 0.002 respectively) in all patients with UC was achieved.

Similarly, a significant improvement for the abdominal pain severity, frequency of diarrhea, and bloody diarrhea at week 52 of treatment with either infliximab (p = 0.01, 0.02, 0.002 respectively) or adalimumab (p = 0.02, 0.04, 0.001 respectively) in all patients with CD was found. In addition, all patients with perianal fistulizing disease achieved

successful closure of fistulae in the infliximab group.

According to partial Mayo scoring and Harvey-Bradshaw activity index, maintained clinical remission with significant improvement of scoring among 37 IBD patients at week 52 of treatment with either infliximab or adalimumab was obtained ($p < 0.05$) (Table 2).

Biochemical outcome

In patients with UC and CD, after 1 year of treatment by either infliximab or adalimumab, a significant drop in platelets count, ESR, CRP, number of RBC'S and pus cell in stool and fecal calprotectin concentration was found, while there was a significant increase in Hb concentration ($p < 0.05$) (Table 3 and 4).

The reduction rate of fecal calprotectin from the baseline was higher for CD compared to UC patients (82.4% and 51.7%, respectively, $p<0.001$ for both) (shown in Fig. 2)

Endpoints

As regards primary endpoint, per-protocol clinical remission rates at week 52 of treatment with infliximab and adalimumab were 86.3 % (19/22) for UC patients, 100% for (18/18) CD patients while the intention-to-treat remission rates were 48% (19/40) in UC patients and 49% (18/37) in CD patients (supplementary figure)

As regards biochemical remission, despite that all patients in the current study achieved significant biochemical response with anti-TNFα, remission was observed more in patients with CD than in UC as noticed by normalization of all inflammatory markers at weeks 52 of treatment (Table 3 and 4).

For the secondary endpoint, 37 IBD patients stopped treatment and follow-up due to varied causes (Fig. 1), 12 patients (15.5%) experienced complications and adverse effects that mandates treatment discontinuation, mostly an anaphylactic reaction or late serum sickness-like symptoms (10 patients), dermatological troubles as severe eczema (one patient), and development of T.B reactivation (one patient). No mortalities were reported during the study.

Mild to moderate adverse effects as arthropathy or neuropathy (4 cases), dermatological complications as urticarial rash, itching, and pain at the infusion or injection site were reported in 7 patients that didn't necessities treatment discontinuation.

Infliximab versus Adalimumab

Patients with UC treated with adalimumab displayed significantly more reduced values of ESR at week 52 of treatment than those treated with infliximab ($p = 0.03$) (Table 5), however, no significant difference between them regarding other parameters was obtained ($p > 0.05$).

Similarly, patients with CD treated with adalimumab displayed no significant difference compared to those treated with infliximab regarding different parameters ($p > 0.05$). In addition, no superiority of either drug regarding clinical remission was found ($p > 0.05$) (Table 5).

Despite the reduction rate of fecal calprotectin from the baseline being higher for adalimumab compared to infliximab, the difference was non-significant ($p > 0.05$) (Table 5).

Table (1) Demographic, clinical and endoscopic characteristics of enrolled subjects who completed the study follow-up period.

Characteristics	UC (22)	CD (18)
Age (y)	44.9 ± 12.18	45.75 ± 11.88
Male	13 (59)	10 (55.5)
Female	9 (41)	8 (44.5)
Residence		
Rural	10 (45.4)	8 (44.4)
Urban	12 (54.6)	10 (55.6)
Smoking history		
Yes	10 (45.4)	8 (44.4)
No	12 (54.6)	10 (55.6)

Characteristics	UC (22)	CD (18)
Family history		
Yes	7 (31.8)	5 (27.7)
No	15 (69.2)	13 (73.3)
Duration of illness (y)	7.85±2.9	11.45± 3.3
Bloody Diarrhea		
Yes	22 (100)	5 (27.7)
No	0 (0)	13 (73.3)
Diarrhea severity		
Mild	11 (50)	5 (27.7)
Moderate	7 (31.8)	8 (44.6)
Severe	4 (18.2)	5 (27.7)
Abdominal pain severity		
No	12 (54.5)	5 (27.8)
Mild	3 (13.6)	4 (22.2)
Moderate	4 (18.2)	5 (27.8)
Severe	3 (13.6)	4 (22.2)
Indications of biological treatment		
Steroid-dependent	11 (50)	5 (27.8)
Steroid- refractory	8 (36.3)	4 (22.2)
Acute severe colitis (ASC)	3 (13.6)	-
Fistulizing CD (perianal) (B1p)	-	5 (27.8)
Steroid- intolerant active luminal disease	-	4 (22.2)
Endoscopic features*		
Pancolitis (E3)	15 (68.1)	-
Left side colitis (E2)	4 (18.1)	-
Proctosigmoiditis (E1)	3 (13.8)	-
Terminal Ileitis and colitis (L3)	-	10 (55.5)
Chron's colitis (L2)	-	3(16.8)
Terminal ileitis (L1)	-	4 (22.2)
Upper GIT plus ileocolonic involvement (L3+L4)	-	1 (5.5)
Endoscopic scores		
SES-CD [a] (mean ± SD)	-	13.9±4.6
Mayo endoscopic subscore (mean ± SD)	2.8±0.4	-

Values are presented as mean±SD or number (%). [a:] simple endoscopic severity - Chron's disease. ASC; Acute severe colitis * According to The Montreal classification of inflammatory bowel disease. All Chron's patients had non-stricturing non-penetrating disease (B1).

Table (2) Clinical Outcome of anti-TNFα therapy in UC and CD patients at the end of 1-year Follow up

	Mild			moderate			Severe			Remission		
	Week 0	Week 52	P	Week 0	Week 52	P	Week 0	Week 52	P	Week 0	Week 52	P
UC (a) (N=12)	0 (0)	2(16.7)	0.4	3(25)	0 (0)	0.5	9(75)	0 (0)	<0.001*	0 (0)	10(83.3)	<0.001*
UC (b) (N=10)	0 (0)	1(10)	0.56	2(20)	0 (0)	0.431	8(80)	0 (0)	<0.001*	0 (0)	9 (90)	<0.001*
CD (a) (N=10)	0 (0)	0 (0)	1	2(20)	0 (0)	0.431	8(80)	0 (0)	<0.001*	0 (0)	10(100)	<0.001*
CD (b) (N=8)	0 (0)	0 (0)	1	2(25)	0 (0)	0.061	6(75)	0 (0)	0.001*	0 (0)	8(100)	0.001*

Values are presented as number (%) * significant value**.** UC; Ulcerative colitis, CD; Chron's disease.

Clinical remission for UC patients according to partial Mayo scoring was defined as score < 2.

Clinical remission for CD patients according to the Harvey-Bradshaw activity index was defined as a score < 5 points.

Table (3) Biochemical outcome of anti-TNFα therapy in UC patients at the end of 1-year follow-up

	UC (a)			UC (b)		
	Week 0	Week 52	P-value	Week 0	Week 52	P-value
Platelets (10^3/µL)	356.2 ± 46.2	301 ± 32.9	0.007*	355.8±17.2	293 ± 36.4	<0.001*
HB (g/dl)	10.6 ± 1.9	12.97 ±1.2	0.005*	11.22 ± 2.3	13.69 ± 1.1	0.008*
WBCs (10^3/µL)	9.4 ± 1.7	8.2 ± 1.7	0.142	9.33 ± 1.6	8.13 ± 1.6	0.130
ESR (mm/h)	38.8 ± 10.5	11.6 ± 2.3	<0.001*	27.6 ± 6.9	9.3 ± 2.3	<0.001*
CRP (mg/L)	10.9 ± 0.9	9.7 ± 1.2	0.029*	11.3 ± 1.4	10 ± 0.8	0.026*
Pus in stool [a]	81 ± 15.7	7.2 ± 5.9	<0.001*	79 ± 15.2	4.2 ± 1.0	<0.001*
Blood in stool [a]	87.5 ± 16.7	5.2 ± 1.0	<0.001*	83 ± 16.1	4.2 ± 1.7	<0.001*
Calprotectin(mg/kg)	1027.2 ± 95.0	514.9 ± 96.9	<0.001*	932.3±54.5	424.3 ± 52.9	<0.001*

Values are presented as mean±SD.* significant value, [a] per HPF, HB; hemoglobin, WBC'S; white blood cells, ESR; erythrocytic sedimentation rate, CRP; C- reactive protein

Table (4) Biochemical outcome of anti-TNFα therapy in CD patients at the end of 1-year follow-up

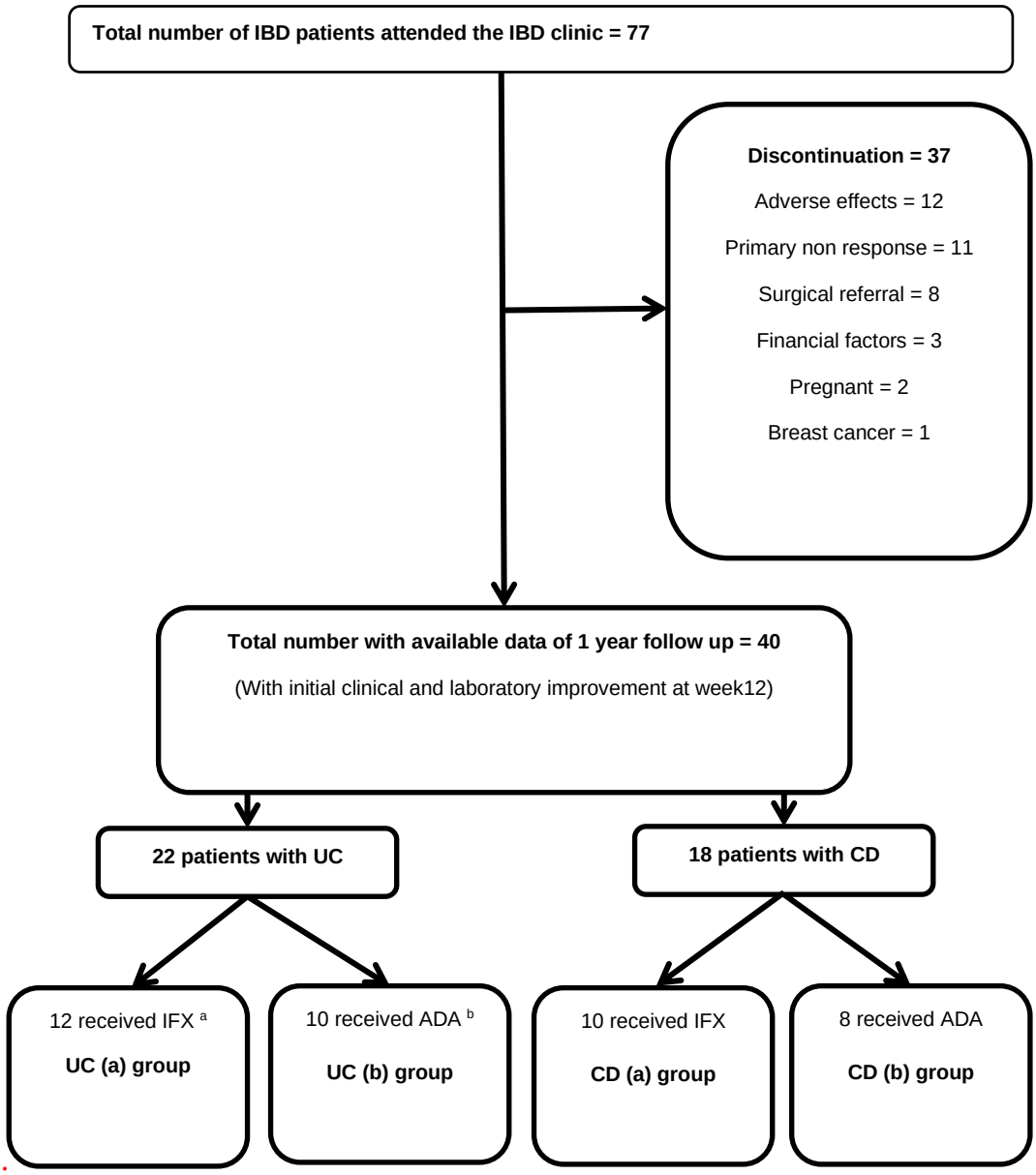
	CD (a)			CD (b)		
	Week 0	Week 52	P-value	Week 0	Week 52	P-value
Platelets (10^3/µL)	351.8±33.9	301 ± 32.9	0.003*	360 ± 61.5	292.7 ±36.5	0.008*
HB (g/dl)	11.28 ± 2.0	13.29 ±0.9	0.012*	11.27 ± 0.9	13.99 ± 0.6	<0.001*
WBCs (10^3/µL)	9.45 ± 1.5	8.85 ± 1.5	0.404	9.92 ± 1.5	9.32 ± 1.5	0.401
ESR (mm/h)	37.8 ± 10.5	10.2 ± 2.9	<0.001*	26.6 ± 6.9	8.3 ± 2.3	<0.001*
CRP (mg/L)	13.4 ± 1.8	5.9 ± 1.5	<0.001*	14.6 ± 1.6	6 ± 1.6	<0.001*
Pus in stool	12.8 ± 1.6	2.8 ± 0.7	<0.001*	11.5 ± 2.7	3.5 ± 1.0	<0.001*
Blood in stool	13.1 ± 3.5	3.1 ± 1.3	<0.001*	13.4 ± 3.3	3.4 ± 1.0	<0.001*
Calprotectin(mg/kg)	707.9 ±96.2	201.7 ±93.1	<0.001*	614.6 ±60	109.7 ± 52.0	<0.001*

Values are presented as mean±SD.* significant value., HB; hemoglobin, WBC'S; white blood cells, ESR; erythrocytic sedimentation rate, CRP; C- reactive protein

Table (5) Comparison between Infliximab and Adalimumab regarding clinical, biochemical outcome at week 52.

	UC (a)	UC (b)	P-value	CD (a)	CD (b)	P-value
Clinical remission	10 (83.3)	9 (90)	0.67	10 (100)	8 (100)	1
Platelets	301±32.8	293 ±36.4	0.17	301 ±32.9	292.7 ± 36.5	0.61
HB	12.97±1.2	13.69±1.1	0.202	13.29±0.9	13.99 ± 0.6	0.07
WBCs	8.2 ± 1.7	8.13 ± 1.6	0.92	8.85 ± 1.5	9.32 ± 1.5	0.49
ESR	11.6±2.3	9.3 ± 2.3	0.03*	10.2 ± 2.9	8.3 ± 2.3	0.15
CRP	9.7 ± 1.2	10 ± 0.8	0.50	5.9 ± 1.5	6 ± 1.6	0.89
Pus in stool	7.2 ± 5.9	4.2 ± 1.0	0.35	2.8 ± 0.7	3.5 ± 1.0	0.10
Blood in stool	5.2 ± 1.0	4.2 ± 1.7	0.1	3.1 ± 1.3	3.4 ± 1.0	0.59
% of Calprotectin drop	49.9%	54.1%	0.84	71.6%	82.2%	0.6

Values are presented as mean±SD or number (%), * significant value., HB; hemoglobin, WBC'S; white blood cells, ESR; erythrocytic sedimentation rate, CRP; C- reactive protein



IFX; infliximab, ADA; adalimumab

Fig. 1.Flow chart of patients' distribution throughout the study

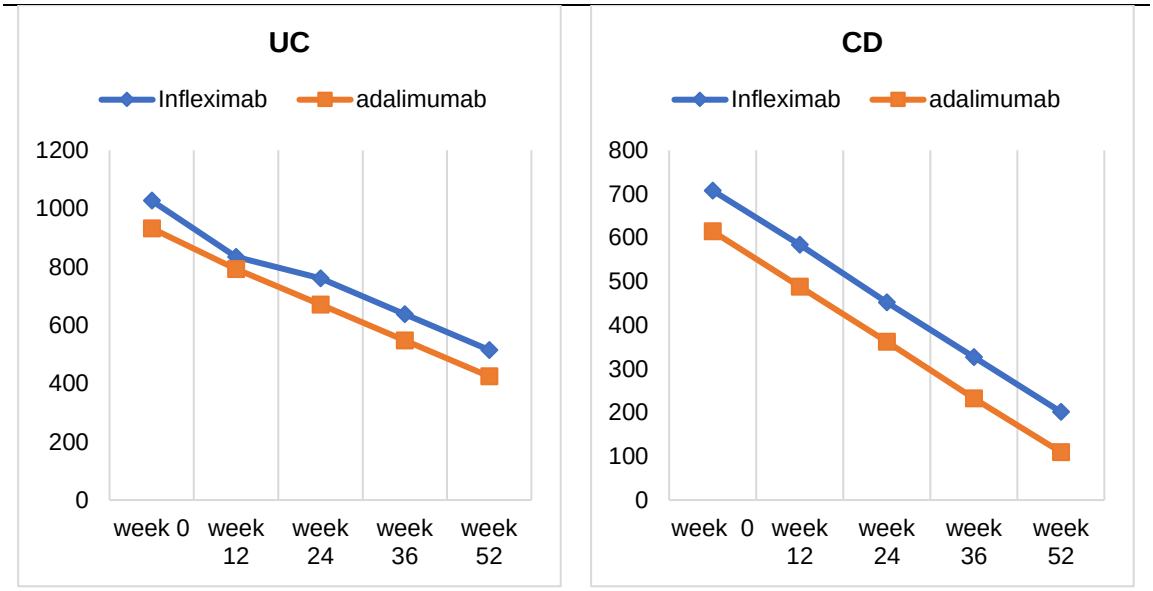


Fig. 2. Fecal calprotectin concentrations (mg/kg) throughout the duration of the study.

Discussion/Conclusion

Biological therapy with monoclonal antibodies to TNF-α, such as infliximab and adalimumab, has been included in the treatment of IBD, beginning with CD in 1998 [9] and extending to UC in 2005[6].

Indications for biological treatment in the current study; for the UC group, 50% were steroid-dependent despite the use of immunosuppressive medications, 35% were steroid-refractory and 15% of patients had acute severe colitis. In CD patients, indications were a fistulizing disease in 30%, steroid intolerant active luminal disease in 20%, steroid-dependent in 30%, and steroid-refractory in 20% of cases. Near similar indications were reported in many studies [10-12].

In UC patients treated with infliximab, early clinical response occurred in 60% (n= 12/20) of cases and 50% (n= 10/20) maintained clinical remission by week 52, a nearly similar rate was gained by Rutgeerts et al (6) (45 and 40%) after induction and by week 52 respectively, they reported that patients who had a clinical response or who were in clinical remission at each time were considered to have a sustained clinical response or to be in sustained clinical remission. On the contrary, Lehtola et al [12] reported a low response rate of only 29% at 2 years follow-up periods.

In UC patients treated with adalimumab (ADA) early, clinical response occurred in 50% (n= 10/20) of cases and 45% (n= 9/20) maintained clinical remission by week 52, similar to our results Tursi et al [13] reported that clinical remission was maintained in 45.8%, also Bálint et al [14] reported favorable efficacies of short- and long-term ADA treatment for patients with UC.

Infliximab treatment for CD patients achieved 50% (n=10/20) clinical remission by week 52, near similar results were reported by Hanauer et al [15] in the ACCENT I trial and by Papadakis et al [16] (58% and 54% respectively); while adalimumab achieved 47% (n=8/17) clinical remission at week 52. Hanauer et al [17] reported a 50% clinical response at week 52 however, in Sandborn et al [18] study, the clinical response rate was 77%.

In the current study, a comparison between infliximab and adalimumab as regards clinical response and remission revealed no significant difference at week 52. To our knowledge, no study performed a direct head-to-head comparison between them but the indirect comparison in the field of clinical response showed that in patients with UC, no significant difference between them during the induction phase (6–8 weeks) or maintenance phase (up to 52–54 weeks) [19-21] and this was in agreement with our results.

For patients with CD, studies have reported conflicting results, with some observed infliximab to be superior overall or in certain subpopulations and others reporting no difference [22-24]. Kestens et al [25]

demonstrated similar clinical response rates at 1 and 2 years between infliximab and adalimumab. Similar results were observed in other studies [26,27] and this was moreover been in accordance with our results.

The current study revealed a significant reduction in ESR, CRP, fecal calprotectin (FC) level, RBC's, and pus in the stool, in addition to a significant increase in HB level following 1 year of treatment with TNF-α inhibitors. In accordance with our results Lehtola et al [12], Joergensen et al [28], and Bouhnik et al [29] demonstrated a significant effect of biological treatment on these different laboratory variables.

Reduction rates of FC from the baseline in UC patients were 50.13% and 53.34% with infliximab and adalimumab treatment respectively while in CD patients were 77.26% and 87.63%, respectively. In CD the average reduction of fecal calprotectin was 82.45%, and 51.74% in UC from the baseline level. Nearly similar reduction rates (77 and 41% for CD and UC respectively) were reported by Lehtola et al [12] and Joergensen et al [27], this may indicate that treatment with anti-TNFα therapy may exert a superior effect for CD than UC patients.

Fecal calprotectin level is considered the most reliable, sensitive, and specific indicator for grave lesions CD and UC [30]. In clinical practice, Sipponen and Kolho [31] reported that one indication of mucosal healing during TNF-α blocking therapy is either normalization or at least a 75% decrease in calprotectin level.

The current study revealed that FC levels were significantly more reduced in IBD patients managed with adalimumab compared to infliximab at week 52 and therefore this may indicate that adalimumab may exert a superior effect than infliximab.

The superiority of adalimumab in the current study can't be guaranteed because of the steady low dose used for infliximab in our population owing to limited resources. In fact, in a recent survey of IBD specialists, 76% reported that they used more frequent or higher doses of infliximab for the treatment of severe UC [32]. The reason for this is likely that a severely inflamed colon, which can lead to significant fecal losses of infliximab [33] coupled with a low serum albumin level leads to lower serum infliximab levels as compared with patients with moderate UC [34].

Reduction in CRP levels in treated patients indicates the clinical response which may be associated with mucosal healing [29]. CRP levels were significantly decreased in both patients with CD and UC patients but with a more significant drop in CD patients, similar results obtained by other studies [28,29], however, Lehtola et al [12] reported a notable significant drop in CRP levels in patients with CD and non-significant drop in patients with UC.

It should be considered that the laboratory variables do not correlate straight with the clinical state and they may be altered also for other reasons not associated with IBD [12]. The gold standard for evaluating the degree of mucosal inflammation and disease activity remains endoscopy [35]. The goal of medical therapy for IBD patients in addition to clinical remission is to obtain deep mucosal remission [36].

14.29% of patients were non-responders to biological induction treatment in the current study. Papadakis et al [16] in their study reported that 15% of patients were non-responders to biological therapy while Yanai and Hanauer [37] reported that approximately one-third of patients with active IBD obtained no response to infliximab induction therapy.

Theede et al [10] reported that primary non-response for induction treatment doesn't exclude a long-term effect in CD patients. Treatment escalation may be needed as a shortening of the interval or increasing the dose and if there is no response by maintenance treatment, the treatment should be stopped.

Unavailability of enough resources, the significant cost of medications, and due to the prediction, that when a patient does not respond after three-drug infusions, he or she will not respond to further doses [38], these factors hinder maintaining therapy in our initial non-responding patients and these patients stopped treatment, follow up and were shifted to other treatment options.

In UC patients, however, for an incomplete/missing response or worsening, the

biologic therapy is discontinued, and surgery is offered [39].

The current study reported that 10.39% of patients discontinued the treatment due to the need for surgery, nearly similar results (17%) were reported by Sandborn et al [39], while Lehtola et al [12] reported that 30% of patients referred for surgery.

The biologic treatment has been proved to be a paradigm shift in IBD medical treatment. However, it does not appear that the role of surgery in IBD care had been reduced, with only minor decreases in surgical rates in preceding years. Anti-TNFα therapy may delay the necessity for surgery especially in UC patients [40].

15.59% (12/77) of all patients discontinued treatment due to adverse effects of treatment, in the ACCENT I trial CD patients treated with infliximab, only 9% of all patients stopped the treatment due to side effects [17] which was significantly less than that gained by Lehtola et al [12] (32%) while 16% of UC patients discontinued the treatment, which almost equals to the retrospective study of Baki et al [41].

Biological therapy is safe when the recommended preventive measures are implemented, with a rate of critical adverse events less than 10% [13] however; these agents are associated with certain toxicities and should therefore solely be used in patients who require the treatment. Physicians need to observe and examine patients receiving biological therapy regularly.

In conclusion, given these preliminary results, anti - TNF therapy seems to deliver a significant clinical and biochemical response in our patients who are steroid-dependent or refractory or have severe or complicated IBD with a few profound adverse effects, the effect is more noticed in patients with CD than UC as assessed with a more considerable drop of fecal calprotectin levels from the baseline values, however, mucosal remission evaluation through endoscopy remains the standard of care for IBD patients, thus longer follow-up periods and further multi-center studies are needed in our populations.

Limitation of the study

1- Endoscopic assessment for mucosal healing was one of the limitations of the current study due to the unavailability of follow-up endoscopic data for all patients.

2- Unavailability of therapeutic drug monitoring (TDM) at time of study in our institution that may affect treatment decisions represent another limitation.

Author Contributions

Afifi F. Afify, Fady M. wadea: design of the work. Afifi F. Afify, Fady M. wadea, Mohamed A. Gado: data collection, data analysis, interpretation, and drafting the article. Mohamed A. Gado, Fady M. wadea: statistical analysis. Maha K. Gohar: laboratory investigations, drafting the article. All authors involved in critical revision of the article, and final approval of the version to be published.

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adverse events for anti-TNF in studied patients

Adverse effects	Number of patients	%	Discontinuation
An anaphylactic reaction or late serum sickness-like symptoms	10 (77)	12.9	Yes
severe eczema	1 (77)	1.29	Yes
T.B reactivation	1 (77)	1.29	Yes
arthropathy	3 (77)	3.89	No
neuropathy	1 (77)	1.29	No
urticarial rash, itching	3 (77)	3.89	No
pain at the infusion or injection site	4 (77)	5.19	N0
Death	0 (77)	0	-

Per – protocol analysis (PPA) versus intension to treat analysis (ITT) for clinical outcome of treatment with biologics