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Evaluation the response to infliximab therapy in patients with ulcerative colitis and crohn's disease

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ABSTRACT

Aim of study: To evaluate effect of infliximab therapy in Iraqi patients with ulcerative colitis and Crohn`s diseases.
Patients & Methods: A clinical prospective follow up study conducted in Gastroenterology and Hepatology Teaching Hospital-Medical Complex in Baghdad city-Iraq through the period from 1st of July 2013 to 30th of April 2014 on sample of 32 patients with inflammatory bowel disease (19 ulcerative colitis patients and 13 Crohn`s diseases patients). The patients were in active disease and not responding to usual treatment. The patients were administered with an appropriate dose of Infliximab.
Results: The good response to Infliximab was reported in 42.1% of UC patients, partial response in 21.1% of UC patients and no response in 36.8% of UC patients. Mean Mayo score of UC patients before using Infliximab was significantly reduced after using Infliximab ($p<0.001$). The good response to Infliximab was reported in 61.5% of CD patients, partial response in 15.4% of CD patients and no response in 23.1% of CD patients. Mean CDI score of CD patients before using Infliximab was significantly reduced after using Infliximab ($p=0.001$). The side effects were minor that restricted to anemia in some cases.
Conclusions: The Infliximab is effective and safe treatment choice for moderate to severe cases of ulcerative colitis and Crohn`s disease.

Keywords: Ulcerative colitis, Crohn`s disease, Infliximab.

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INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) both are chronic relapsing inflammatory diseases of the gastrointestinal tract [1, 2]. The ulcerative colitis is continuous mucosal inflammation of the colon that begins from rectum, while the Crohn's disease might affect any part of gastrointestinal tract from mouth to the anus and it is identified with intermittent transmural mucosal inflammation [3]. Both UC and CD disorders are comparable to each other's in clinical presentations and in affecting gastrointestinal tract, [4] however, information on epidemiology, clinical course and risk factors for those two diseases in developing countries as compared to developed countries are scarce [5, 6]. The inflammatory bowel diseases are public all over the world, although, the higher incidence in northern regions of the world and in white populations [7] Risk factors associated with UC or CD might be related to difference in geographical or genetic reasons [8]. In Iraq, the UC was more common than CD, but both of them were prevalent among males more than females [9].

Generally, the medical treatment for ulcerative colitis and Crohn's diseases are mainly targeting the inflammatory mediators and these treatments are corticosteroids, aminosalicylates, immunomodulators and biological therapies like anti-tumor necrosis factor (TNF) therapies [3]. The Infliximab is a chimeric monoclonal immunoglobulin G1 (IgG1) antibody against TNF and it the common and first biologic treatment for inflammatory bowel diseases. It had fourteen days half-life and given intravenously after calculation of dose that based on weight [10]. Many randomized controlled trials and meta-analysis studies revealed that infliximab is very effective agent in treatment of ulcerative colitis and Crohn's diseases [11-14]. However, these anti-tumor necrosis factor agents are ineffective treatment for some patients with inflammatory bowel diseases who showed primary non-response (PNR). Primary non-response to anti-TNF drugs is defined as an absence of improvement for symptoms or clinical signs following induction phase that is followed stopping the treatment. Incidence of PNR occur among 10-40% of patients with inflammatory bowel diseases according to type of disease and different methodologies of clinical trials [15]. Secondary loss of response (SLR) occurs among patients who initially respond to anti-TNF treatment and could either stimulate strengthening or stopping treatment course in about 50% of patients after 12 months of treatment [16]. This SLR is also known deteriorating symptoms due to active phase of inflammatory bowel disease throughout administering of maintenance therapy among patients who previously had disease control after induction treatment. Additionally, there are many serious adverse reactions of anti-TNF treatments such as infection, dermatologic disorders and allergic reactions that needs stopping of treatment [16]. This study is aimed to evaluate effect of infliximab therapy in Iraqi patients with ulcerative colitis and Crohn's diseases.

Patients and Methods

The design of current study was a clinical prospective follow up study conducted in Gastroenterology and Hepatology Teaching Hospital-Medical Complex in Baghdad city-Iraq through the period from 1st of July 2013 to 30th of April 2014. The study population was patients with complicated UC and CD admitted to Gastroenterology and Hepatology Teaching Hospital. Adults (age>18 years), complicated UC or CD not responded to usual treatments were the inclusion criteria. The exclusion criteria were younger age (less than 18 years), mild cases of UC or CD, responding to usual treatment and patients refused to participate. A sample of

32 patients with inflammatory bowel disease admitted to Gastroenterology and Hepatology Teaching Hospital (19 UC patients and 13 CD patients) and eligible to inclusion and exclusion criteria was taken. The ethical considerations were obtained according Helsinki Declaration regarding ethical approval of Health authorities, oral informed consent of patients, responsibility on continuing treatment, withdrawal on side effects and confidentiality of data.

A detailed questionnaire (CDAI, Mayo score) had been prepared and filled in by researcher through an interview with the patients. For all eligible patients, we collected demographic data, baseline characteristic of UC and CD, the clinical outcomes, and adverse events of infliximab treatment.

The studied patients should have active disease with a Mayo score [17] of ≥ 6 and moderate-to-severe inflammation on colonoscopy despite concurrent treatment with corticosteroid and/or immunomodulators. Regarding indications for infliximab, patients were classified as acute severe UC if he/she had severe disease (according to Truelove-Witts' score and/or Mayo score) requiring admission for proper treatment.

So, most cases diagnosed depend on correlation the sign and symptoms with radiological and endoscopic finding, obstruction and narrowing exclude.

Questionnaire (Mayo score [17], CDAI [18] had be prepared and filled in by the investigator through an interview with the patients; Hb, CRP, ESR, Tubercline test and CXR (to exclude TB), Colonoscopy were done for every eligible patient. The Mayo score was measured according to Ulcerative Colitis Disease Activity Index (Mayo Score) [17], while the Crohn's Disease Activity Index (CDAI) was also measured according an appropriate scale [18]. Treatment regimen was scheduled therapy, defined as a three-dose infliximab 5mg/Kg (2 hr. infusion periods) at 0, 2, and 6 weeks, followed by regular 8-weekly infusions thereafter.

Clinical Outcome Evaluation

For the evaluation of disease activity and the response to infliximab therapy, CDI, Mayo score or partial Mayo score (Mayo score without endoscopy) was determined before the first infusion of infliximab and afterthird dose of treatment, as well as the last follow-up visit. We also determined C reactive protein (CRP), erythrocyte sedimentation rate (ESR), and other laboratory data. In all patients who had undergone follow-up endoscopy, we assessed whether mucosal healing was achieved or not. Clinical response was defined as a decrease from baseline in the total Mayo score of at least 3 points, while for patients whom their response were below 3 points defined as partial response.

The data collected were analyzed statistically by Statistical Package of Social Sciences software version 22. The chi square test was applied for analyzing the data as suitable. Paired t-test was used to compare two consecutive means. Level of significance (p value) was regarded statistically significant if it was 0.05 or less.

Results

This study included 32 patients with inflammatory bowel disease (19 UC patients and 13 CD patients). Mean age of UC patients was (29.9 years) with predominance of male gender (52.6%) as compared to female gender (47.4%). The common presenting complaint of UC was bloody diarrhea (94.7%), followed by abdominal pain (52.6%) and weight loss (15.8%). Positive family history of UC was present among 3 (15.8%) patients with negative surgical history and the extra-intestinal manifestations were detected among 68.4% of UC patients. Positive CRP was detected for 52.6% of UC patients. Colonoscopy grading before using Infliximab showed moderate colitis (21.1%) and severe colitis (78.9%), while after using Infliximab, the colonoscopy grading showed normal findings (42.1%), mild colitis (31.6%), moderate colitis (5.3%) and severe colitis (21.1%). The good response to Infliximab was reported in 42.1% of UC patients, partial response in 21.1% of UC patients and no response in 36.8% of UC patients. The side effects of Infliximab were restricted on anemia only (10.5%). (***Table 1***) As shown in (***Table 2***); mean Mayo score of UC patients before using Infliximab was (9.32) which was significantly reduced to (6.11) after using Infliximab ($p<0.001$).

Regarding CD patients, the mean age of them was (30.49 years) with predominance of male gender (61.5%) as compared to female gender (38.5%). The main presenting complaint of UC was abdominal pain (84.6%), followed by diarrhea (69.2%) and weight loss (23.1%). No positive family history of CD was detected, while positive surgical history was reported among 38.5% of CD patients. Colonoscopy grading before using Infliximab for CD patients showed mild colitis (7.7%), moderate colitis (30.8%) and severe colitis (61.5%), while after using Infliximab, the colonoscopy grading showed normal findings (69.2%), mild colitis (7.7%), moderate colitis (15.4%) and severe colitis (7.7%). Positive CRP was detected for 69.2% of CD patients. The good response to Infliximab was reported in 61.5% of CD patients, partial response in 15.4% of CD patients and no response in 23.1% of CD patients. The side effects of Infliximab were restricted on anemia only (7.7%). (***Table 3***)

As shown in (***Table 4***); mean CDAI score of CD patients before using Infliximab was (315.7) which was significantly reduced to (144.9) after using Infliximab ($p=0.001$). As shown in (***Table 5***); no significant difference was observed between patients with UC and patients with CD regarding response to Infliximab treatment ($p=0.55$). As shown in (***Table 6***); no significant difference was observed between different response to Infliximab for patients with UC and patients with CD regarding CRP ($p=0.19$, $p=0.58$, respectively).

Discussion

In present study, 42.1% of UC patients had good response and 21.1% had partial response to Infliximab therapy. These findings are comparable with five uncontrolled studies [19-21] which found that early response rates of UC patients to infliximab treatments were ranged between 59–67%, while higher response rates of 78–97% were detected by other multicenter retrospective surveys [22, 23]. However, another randomized, controlled trials [24] revealed that about two-thirds of UC patients had clinical response to infliximab. The differences in response rates between different studies might be related to discrepancies in patients' factors (treatment indications, disease severity, and need for hospitalization), treatment regimens and differences in study methodology. Current study findings are consistent with results of Mohammed et al [25] study in Iraq which reported a significant effectiveness of Infiliximab in reducing relapse rate and mucosal healing after 6 months follow up. Our results showed the mean mayo score prior to infliximab administration was (9.3) which declined after treatment

by infliximab to (6.1) with significant difference. This finding is similar to results of retrospective multicenter study that involved 16 tertiary teaching hospitals in South Korea [26] in which, found that Mayo score significantly decreased from (9.9) to (4.1) after induction therapy by Infiximab.

Regarding the response to infliximab in patients with CD, eight patients (61.54%) had good response, partial response was found in two patients (15.38%) and the remaining three patients (23.8%) had no response. Additionally, the mean CDAI before using infiximab was (315.7) and after using infliximab was reduced to (144.9) with significant difference. This finding is consistent with previous Canadian study by Van dullemen et al [31], which found rapid improvement in symptoms within four weeks of receiving Infiliximab with mean decrease in CDAI score [27]. Our results regarding the benefit of infliximab in active CD patients was consistent with Ford et al study [28] in USA which demonstrated that biological drugs are highly effective than placebo in inducing remission in moderate to severely active CD and decreasing CDAI score less than 150 points. Our study showed that three (23.08%) CD patients had no clinical response, a finding that is consistent with many previous literatures [29, 30] which found that remission of CD was not achieved in 71.5 % of CD patients treated anti-TNF α antibodies as compared to 80.7% of patients administered by placebo.

Regarding comparison between UC and CD patients in response to infliximab there was no significantly different and 36.8% UC colitis patients in compared to 23.1% CD patients had no responded to infliximab treatment, so despite the proven efficacy of infliximab in the maintenance setting, loss of response is a real problem although it was within range of many previous literature (11-54%) [31]. Present study showed only minor side effects restricted to anemia that is treated by either blood transfusion or iron supplements. This finding coincides with results of Mir et al [32] study in USA which found minor side effects of Infliximab restricted with some cases of anemia. Our study concluded that Infliximab biological therapy is effective and safe treatment choice for moderate to severe cases of ulcerative colitis and Crohn's diseases. Primary non-response to Infliximab was not different between ulcerative colitis and Crohn's diseases.

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Tables

Table 1: General characteristics of Ulcerative Colitis patients.

Variables	Category	No.	%
Age mean±SD (29.9±10.1 years)			
Gender	• Male	10	52.6
	• Female	9	47.4
Presenting Complaints	• Bloody Diarrhea	18	94.7
	• Abdominal Pain	10	52.6
	• Weight Loss	3	15.8
Positive Family History		3	15.8
Positive Surgical History		0	0.0

Presence of extra-intestinal manifestations		13	68.4
Positive CRP		10	52.6
Colonoscopy grading before using Infliximab	• Normal	0	0.0
	• Mild Colitis	0	0.0
	• Moderate Colitis	4	21.1
	• Severe Colitis	15	78.9
Colonoscopy grading after using Infliximab	• Normal	8	42.1
	• Mild Colitis	6	31.6
	• Moderate Colitis	1	5.3
	• Severe Colitis	4	21.1
Response to Infliximab	• Good Response	8	42.1
	• Partial Response	4	21.1
	• No Response	7	36.8
Side effects	• No	2	10.5
	• Anemia	17	89.5
Total		**19**	**100.0**

Table 2: Mean Mayo score for ulcerative colitis group in relation to infliximab use.

Relation to Infliximab	**No.**	**Mayo Score**		**Paired t-test**	**P value**
		Mean	**SD**		
• **before using Infliximab**	19	9.32	1.734	5.846	**< 0.001***
• **after using Infliximab**	19	6.11	2.726		

**Significant.*

Table 3: General characteristics of Crohn's Disease patients.

Variables	**Category**	**No.**	**%**
Age mean±SD (30.4±11.2 years)			
Gender	• Male	8	61.5
	• Female	5	38.5
Presenting Complaints	• Abdominal Pain	11	84.6
	• Diarrhea	9	69.2
	• Weight Loss	3	23.1
Positive Family History		0	0.0
Positive Surgical History		5	38.5
Colonoscopy Grading before using Infliximab	• Normal	0	0.0
	• Mild Colitis	1	7.7
	• Moderate Colitis	4	30.8
	• Severe Colitis	8	61.5
Colonoscopy Grading after using Infliximab	• Normal	9	69.2
	• Mild Colitis	1	7.7
	• Moderate Colitis	2	15.4
	• Severe Colitis	1	7.7
Positive CRP		9	69.2
Positive History of Smoking		6	46.2

Response to infliximab	• Good Response	8	61.5
	• Partial Response	2	15.4
	• No Response	3	23.1
Side effects	• No	12	92.3
	• Anemia	1	7.7
Total		**13**	**100.0**

Table 4: Mean CDI score for Crohn's disease group in relation to infliximab use.

Relation to Infliximab	**No.**	**CDAI Score**		**Paired t-test**	**P value**
		Mean	**SD**		
• **before using Infliximab**	13	315.7	138.1	4.312	**0.001***
• **after using Infliximab**	13	144.9	91.3		

**Significant.*

Table 5: Distribution of sampled patients according to study group and to response to infliximab.

Response to Infliximab	**Ulcerative Colitis**		**Crohn's Disease**		**X^2**	**P value**
	No.	**%**	**No.**	**%**		
• Good Response	8	42.1	8	61.5		
• Partial Response	4	21.1	2	15.4	1.18	0.55*
• No Response	7	36.8	3	23.1		

**Not significant.*

Table 6: Association between CRP and response to infliximab treatment in UC and CD patients.

Variable		**Response to Infliximab**						
		Good Response		**Partial Response**		**No Response**		**P value**
		No.	**%**	**No.**	**%**	**No.**	**%**	
Ulcerative colitis								0.19*
CRP	Positive	6	75.0	2	50.0	2	28.6	
	Negative	2	25.0	2	50.0	5	71.4	
Crohn's disease								0.58*
CRP	Positive	5	62.5	2	100.0	2	66.7	
	Negative	3	37.5	0	0.0	1	33.3	

**Not significant.*