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Effectiveness of Biologic Therapy in Inflammatory Bowel Disease in Duhok

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Abstract

Background: Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory bowel disorders (IBD). Biological therapy uses monoclonal antibodies against chronic inflammatory disease targets. Aim: To determine the primary response rate, the primary non-response rate (PNR) & the secondary loss of response rate (SLR) to biologic agents in patients with IBD. Also, to determine the side effect profile of biologic agents in patients with IBD. Patients and methods: This cross-sectional case series study was done in Azadi gastroenterology and hepatology center in Duhok, Iraq from March, 2022 to September, 2022. It included 40 IBD patients with diseased activity ranging from moderate to severe disease. The male: female ratio was 1.7 and the mean age was 27.2 years ranging between 9-60 years. Results: Of the study population, 7 (17.5%) had UC and 33 (82.5%) had Crohn's disease. The primary response rate was 62.5% (N=25) while the primary non response rate was 30% (N=12). The secondary loss of response rate was 7.5% (N=3) during the study period of 6 months. Mean CDAI was significantly reduced after second follow up of biological treatment (P=0.01) at 3 months of follow up. Patients on Remicade had the highest percentage of response and asymptomatic remission 83.3% compared to Remsima 59.3% and Adalimumab 0%. Biological therapy side effects were positive in 5% (N=2) is the form of skin rash. Conclusions: Biologic therapy have an acceptable effectiveness and safety profile for patients with moderate to severe disease activity. However, more studies are warranted to establish the cause of PNR and SLR to increase the effectiveness of these medications in future.

Keywords

Inflammatory bowel disease, Crohn's disease, ulcerative colitis, biologic therapy.

Irritable bowel disease (also known as IBD) is a collection of disorders that are defined by immunological activation and inflammation inside the gastrointestinal tract. This immune activation and inflammation can be chronic or it might relapse (1). Both Crohn's disease and ulcerative colitis are classified as inflammatory bowel diseases (IBD). Both CD and UC have a pattern called relapsing and remitting, and both have the potential to produce significant morbidity and adversely affect quality of life. Relapsing and remitting is a pattern that both CD and UC follow. Patients who have ulcerative colitis, also known as UC, have an inflammatory illness that impacts both the mucosa and the submucosa of the colon. Patients with UC often report having bloody stools and crampy lower abdominal pain, both of which are momentarily eased by bowel movements. This is one of the defining characteristics of UC. Because UC is marked by persistent inflammation, the condition

has the potential to worsen and eventually lead to colon cancer. Patients with Crohn's disease typically present with diarrhea, malabsorption, weight loss, and persistent abdominal pain. Up to one-third of patients present with complicated behavioral symptoms. Although Crohn's disease affects any part of the gastrointestinal tract from the mouth to the anus, most commonly the ileocolonic region, inflammation frequently is discontinuous along the longitudinal axis of the intestine and may involve all bowel layers from the mucosa to the serosa, patients with Crohn's disease most (1-3). Inflammatory bowel disease (IBD) is a condition for which its causes and its pathophysiology are not fully understood. It is generally accepted that an immunologic mechanism plays a part in the pathophysiology of the condition; however, the triggering variables are only partially understood (3). Intestinal flora, a number of different cytokines, including tumor necrosis factor (TNF), and a few of the interleukins, along with a number of other variables, are all thought to have a part in the continuous inflammatory process (4).

The use of biologic therapy brought about a complete paradigm shift in the management of patients with moderate to severe inflammatory bowel disease prior to its debut (4). The reference product is more expensive than the biosimilar, despite the fact that the two products are almost identical and share the same protein sequence. However, their patterns of glycosylation are distinct, which results in variances in the intricate quaternary structure of proteins (5). When a patient's clinical symptoms do not improve following the induction phase of treatment with an anti-TNF agent, this condition is referred to as "primary non-response," or PNR for short. As a result of this condition, the patient is required to discontinue use of the medicine. According to several reports, the incidence of PNR can range anywhere from 10 to 40 percent, depending on the ailment that is being researched and the methodology of the trial (6). Patients are said to have SLR if they respond to the medication following an induction regimen but subsequently stop responding while they are receiving maintenance treatment (3). The objective of the research was to determine the primary response rate, the primary non-response rate (PNR), and the secondary loss of response rate (SLR) to biologic medicines in patients who had been diagnosed with inflammatory bowel disease (IBD) (IBD). Additionally, to research the factors that contribute to SLR and to determine the side effect profile of biologic medicines in persons who have inflammatory bowel disease (IBD).

Patients and methods

Between March 2022 and September 2022, this examination into a case series using a cross-sectional design was carried out at the Azadi gastroenterology and hepatology center in Duhok, Iraq. The center is located in Iraq. Forty patients with inflammatory bowel disease took part in the trial. The severity of their condition ranged from moderate to severe during the course of the study. Patients who were either pregnant at the time of the trial or who did not follow to their medication schedules were excluded from the research. Before the plan for the study could be implemented, it had to receive approval from both the research protocol ethics committee of the Kurdistan Board of Medical Specialties and the ethics committee of the Directorate of Health - Duhok Governorate. Both of these committees were necessary for the study to be carried out.

The patient was questioned by the biologic treatment committee prior to the beginning of the biologic therapy, and the committee confirmed that the patient absolutely required the biologic therapy. In addition, tests were performed on every patient to rule out the possibility that they were carriers of latent tuberculosis as well as hepatitis B and hepatitis C. The biologic therapy was delivered by medical staff that had obtained specialized training for the purpose of administering it, so that they could carry out the procedures in line with the protocols. In this clinical research, patients were given treatment with Infliximab (Remicade), a bio-similar variant of Infliximab called Remsima, and Adalimumab, which is commercialized under the brand name Humira. In addition, azathioprine or methotrexate was given to each patient in order to reduce the probability that the patients would acquire antibodies against the treatment. Patients who suffered from ulcerative colitis were given the Mayo score, whereas those who suffered from Crohn's disease were given the Crohn's disease activity index (CDAI). Following the completion of the follow-up with each patient, the severity of the disease was assessed using one of these scores. In addition, the amounts of fecal calprotectin were analyzed with each subsequent visit. At the beginning of the period of follow-up, documentation of the endoscopic and radiological tests that had been performed was done. Additional tests were only sought out when it was clinically required to do so. [For patients with UC] having a Mayo clinic score of less than two with no individual sub-scores of more than one and having a Crohn's disease activity index [CDAI] of less than one hundred fifty was what was considered to be clinical remission. [For patients with CD] having a

Mayo clinic score of less than two with no individual sub-scores of more than one was also considered to be clinical remission. Clinical reaction was used in place of clinical remission in cases when clinical remission was not recorded. A drop in the CDAI of 100 points was considered to indicate a clinical response (7). At each subsequent consultation, a profile of the adverse effects was recorded for documentation purposes.

In order to perform analysis on the data that was gathered, the Statistical Package for the Social Sciences (SPSS) tool, version 26.0 for windows, was used. For continuous variables, we determined the mean value as well as confidence intervals with a probability threshold of 95%. The qualitative variables, represented by the frequencies, and the interval variables, represented by the percentages, were derived. An inquiry into statistical methods was carried out in order to determine the P-value by making use of the formula 2.(or Fisher's exact test if an expected number in any cell was less than 5). The P-value needed to be equal to or less than 0.05 in order for the associations or differences to be considered statistically significant.

Results

This study included forty patients who were diagnosed with IBD. The patients' ages ranged from 9 to 60 years, with the mean age being 27.2 years, the standard deviation being 10.9 years, and the range being 9-60 years. Fifteen percent of the patients were less than 20 years old, sixty percent of the patients were between the ages of 20 and 29, and 12.5 percent of the patients were between the ages of 30 and 39. With a ratio of 1.7, there were significantly more male patients (N = 25, 62.5 percent) than there were female patients (N = 15, 37.5 percent). All of the patients in the study were of Kurdish descent. Patients' educational levels broke down as follows: illiterate (15 percent), school (65 percent), undergraduate (7.5 percent), and postgraduate (2.5 percent) (12.5 percent). The vast majority of patients were city dwellers, with only 12.5 percent coming from beyond the municipal limits. The patients were classified according to their occupations as follows: 45 percent were self-employed, 32.5 percent were students, 12.5 percent were homemakers, and 10 percent were public servants. as shown in table-1.

Table-1: General characteristics of IBD patients (N=40)

Variable	No.	%
Age		
<20 years	6	15.0
20-29 years	24	60.0
30-39 years	5	12.5
≥40 years	5	12.5
Sex		
Male	25	62.5
Female	15	37.5
Ethnicity		
Kurdish	40	100.0
Educational level		
Illiterate	6	15.0
School	26	65.0
Undergraduate	3	7.5
Postgraduate	5	12.5
Residence		
Outside city	5	12.5
Inside city	35	87.5
Occupation		
Self employed	18	45.0
Student	13	32.5
Homemaker	5	12.5
Public servant	4	10.0
Total	40	100.0

Patients were diagnosed with CD in 82.5 percent of cases, while only 17.5 percent of patients were identified with UC. UC was most extensive in the pancolitis stage (71,4 percent), next in the extensive colitis stage (14,3 percent), and finally in the left sided colitis stage (14.3 percent). Ileocolonic illness accounted for 54.5 percent of cases, ileal disease for 36.5 percent, and colonic disease was the third most common site (9 percent). The average length of the disease was 2.9 years, with a standard deviation of 2.2 years; 10% of patients had a disease that lasted less than one year, 42.5 % of them had IBD that lasted between 1-2 years, and 47.5 % of them had IBD that lasted more than two years.as shown in table-2.

Table-2: Clinical characteristics of IBD patients (N=40)

Variable	No.	%
Diagnosis		
Ulcerative colitis	7	17.5
Crohn's disease	33	82.5
Ulcerative colitis extent		
Left sided colitis	1	14.3
Extensive colitis	1	14.3
Pancolitis	5	71.4
Crohn's disease location		
Ileal	12	36.5
Colonic	4	9.0
Ileocolonic	17	54.5
Duration of disease		
<1 year	4	10.0
1-2 years	17	42.5
>2 years	19	47.5
Total	40	100.0

IBD patients had a positive previous pharmacological history in 95 percent of cases, which included the usage of azathioprine,

methotrexate, steroids, and mesalamine. The prior medical history of one patient was positive, while 25 percent of IBD patients had a positive past surgery history. The patient's past medical history was only positive in one instance. About two thirds of patients who were diagnosed with inflammatory bowel disease (IBD) did not smoke (N = 26, or 65 percent). On the other hand, 17.5 percent of patients were current smokers and 17.5 percent were previous smokers. The mean body mass index (BMI) of patients with inflammatory bowel illness was 21.4 kg/m2, with a standard deviation of 3.2 kg/m2; 17.5 percent of patients had a BMI that was below normal, 67.5 percent of patients had normal BMIs, and 15 percent of patients were overweight. as may be seen in table three.

Table-3: Clinical history and BMI of IBD patients (N=40)

Variable	No.	%
Past medical history		
Positive	1	2.5
Negative	39	97.5
Past surgical history		
Positive	10	25.0
Negative	30	75.0
Drug history		
Positive	38	95.0
Negative	2	5.0
Smoking history		
Smoker	7	17.5
Ex-smoker	7	17.5
Non-smoker	26	65.0
Body mass index		
Underweight	7	17.5
Normal	27	67.5
Overweight	6	15.0
Total	40	100.0

In patients with inflammatory bowel disease who were part of the study, the biological medicines infliximab (Remsima) (N=32, 80 percent), infliximab (Remicade) (N=7, 17.5 percent), and adalimumab (Humira) (N=1, 2.5 percent) were administered. Two of the five percent of IBD patients who had side effects from biological therapy did so in the form of a skin rash.

At three months of follow up, the mean CDAI of patients with CD showed a substantial reduction after the second follow up of biological treatment (P = 0.01) As shown in table-4, the means of hemoglobin increased after the second follow up, while the means of Mayo score, fecal calprotectin (FC), ESR, and c-reactive protein (CRP) decreased after the second follow up. However, there were no significant differences in the means of these variables after the second follow up.

Table-4: Distribution of outcome measures in follow up periods (N=40)

Variable	Outcome measures		P-value
	1st follow up	2nd follow up	
	Mean ± SD	Mean ± SD	
CDAI	182.1±94.5	130.8±85.8	0.01 S
Mayo score	4.00±4.04	2.86±2.41	0.29 NS
Hb	11.9±1.7	12.1±1.6	0.66 NS
ESR	17.4±17.3	8.4±9.7	0.16 NS
CRP	27±27.7	14±10.7	0.3 NS
FC	328.8±379.6	279.6±257	0.79 NS

S=Significant, NS=Not significant.

25 patients out of the total population of the study were considered to be in asymptomatic remission, 12 patients out of the total population did not meet the remission criteria within 3 months and were considered to be primary non-responders, and 3 patients out of the total population lost response to treatment after 3 months of follow up during the course of the study and were considered to be secondary loss of response (SLR). In those patients with SLR, the development of antibodies to anti-TNF was evaluated, and the results were negative (2.5 ng/l). At the same time, the medication level was assessed, and it was found to be below the therapeutic level (3, 0.5, and 0.2 mg/l).

According to table-5, patients taking Remicade saw the highest primary response rates and asymptomatic remission compared to those on Remsima (57.7 percent for CD and 66.6 percent for UC) and Adalimumab (0%), respectively.

Table-5: Response rates among biologic agents (N=40)

		Remicade		Remsima		Adalimumab	
CD	Primary response rate	5	83.3%	15	57.7%	0	0%
	Primary non response rate	1	16.7%	9	34.7%	1	100%
	Secondary loss of response	0	0	2	7.6%	0	0%
UC	Primary response rate	0	0	4	66.6%	0	0
	Primary non response rate	1	100%	1	16.7%	0	0
	Secondary loss of response	0	0	1	16.7%	0	0

Discussion

Inflammatory bowel diseases (IBD) are chronic diseases that cause significant morbidity and largely afflict the working class. Research into inflammatory bowel disease (IBD) is required to determine the full extent of the disease's impact on public health and shape decisions about how funds and services should be distributed to those who suffer from the condition (8-9).

Forty patients with IBD were enrolled in this study with a mean age of (27.2) years; 60% of the patients were between the ages of 20 and 39, and 13% were between the ages of 30 and 40. Diagnosis of Crohn's disease or ulcerative colitis can be made at any age from 0 to over 90 years old (10,11); however, the majority of patients are identified in their 20s and 30s (12,13). Patients with Crohn's disease tend to be five to ten years younger than those with ulcerative colitis (UC) when comparing mean and median ages (14,15). However, some studies have not found evidence for a second, smaller peak in incidence, often in the sixth or seventh decade, especially among UC patients (16,17). (18,19). It is still unknown whether these variations in age distribution are real or the result of other factors like changes in diagnostic methods, a decline in the number of cases of ischemic colitis and microscopic colitis that were incorrectly diagnosed as IBD, and/or an excess of a young-age-debut phenotype of the diseases (20). It is alarming that the onset of these diseases at a younger age is becoming more common.

Patients with inflammatory bowel illness were diagnosed with UC in 17.5% of cases, and CD in 82.5% of cases. As the most common extent of UC at diagnosis is left sided colitis, which will usually respond to topical and oral 5-aminoslaicylates and less likely to need biologic therapy, the higher prevalence of CD in this study may reflect the increasing prevalence of IBD over time (especially CD). Furthermore, there is a higher likelihood of requiring biologic therapy for people with Crohn's disease than for those with UC (21-25). A little over two-thirds of people with IBD weren't smokers, while 17.5 percent were either current smokers or had been smokers in the past. According to Hamasur, most UC patients did not smoke, and there was no discernible difference between UC and CD patients with regard to smoking (26). A further finding reached by Bastida and Beltrбn was that smoking offers some protection against UC. In other words, current smokers have a lower risk of developing UC. This is because nicotine has been shown to have immunosuppressive properties, to decrease inflammation associated with UC, and to stimulate the production of mucus in the colon, which serves as a protective barrier. Nitric oxide, which is produced by nicotine, may also help reduce intestinal spasms, the primary reason of the need to defecate, by decreasing colonic muscular activity. They went on to say that keeping up with smoking after a diagnosis of UC improves outcomes and lessens the need for a colectomy (27).

Patients with inflammatory bowel disease (IBD) were most often treated with infliximab (Remsima) (80%), infliximab (Remicade) (17.5%), and adalimumab (Humira) (2.5 percent). Positive adverse effects of the biological treatment included a skin rash in almost 20% of patients with inflammatory bowel disease. It wasn't until anti-tumor necrosis factor (TNF) medications became widely available that the therapy of inflammatory bowel disease (IBD) was allowed to undergo a radical transformation. Subcutaneous administration of the anti-TNF medication adalimumab is an effective therapy option for patients with moderate-to-severe CD or UC. Reduced need for surgery, hospitalization, and other health-related consequences is one of the many benefits of anti-TNF treatment for these diseases. However, about 30−40% of patients may not respond to anti−tumor necrosis factor drugs (primary non−response; PNR); about 30−40% of patients may experience a loss of response over time (secondary loss of response; SLR); and people may be intolerant to anti−TNFs (28). While the study's PNR rate of 30% is comparable to worldwide data, the SLR rate of 7.5% is significantly lower than international data due to the study's very short follow-up duration of 6 months. This is due to the fact that the follow-up duration was shorter domestically than it was internationally. According to previous studies, the response to a second anti-TNF drug following the discontinuation of treatment with the index anti-TNF agent can vary depending on the reason for discontinuing treatment with the index anti-TNF agent. Those who stopped taking their first anti-TNF due to intolerance had a 61% clinical remission rate with their second anti-TNF, while those with SLR had a 46% clinical remission rate. Gisbert et al. found this out. Lowest likelihood of a good response to a second anti-TNF treatment is shown in patients who had an initial negative reaction to the index anti-TNF (29).

Of the patients with CD, 21 had reached asymptomatic remission (63.5%), while of the patients with UC, just 4 had done so (57.2 percent). A lower UC response rate may have resulted from the very small sample size of participants with UC included in this analysis.

Although there was a difference in the total number of patients treated, those who were given Remicade had a significantly higher response and asymptomatic remission rate than those who were given Remsima or Adalimumab. The clinical remission rate at week 8 was lower in patients who had an induction dosage of 160 mg followed by 80 mg for moderate to severe UC (9.6 percent vs. 24.0 percent, respectively) compared to patients who weighed less than 82 kg (28.8 pounds) (30). Findings similar to these have been shown for infliximab-treated obese patients. Drug clearance was also found to be higher in this patient population, with a shorter time to loss of response (31). Post hoc analyses of data from large clinical trials showed that the response rate to certolizumab pegol and adalimumab was higher in patients with a disease history of less than 2 years compared to individuals whose condition had been present for a longer amount of time in the case of CD (32,33). Anti-TNF medications have been shown to be effective in treating CD, although the degree to which an individual patient responds to treatment depends on a number of factors, one of which being the disease's location. The response to infliximab appears to be greater in patients with isolated colonic CD (34), while those with isolated small bowel or upper gastrointestinal involvement may have an increased risk of PNR. The prognosis for patients with isolated colonic CD appears to be more favorable (35). When a patient in remission throughout treatment begins to exhibit symptoms that can be definitively linked to active IBD, this is an example of the clinical presentation of SLR. The annual risk for SLR was found to be 20,3 percent for adalimumab patients in a meta-analysis of 39 research (36) and to be 13,0 percent for infliximab patients in a systemic assessment of 16 studies (37). In order for medical practitioners to diagnose SLR, they must first objectively demonstrate increased disease activity owing to inflammatory bowel disease (IBD) utilizing biomarkers (such as fecal calprotectin or C-reactive protein), endoscopy, and/or imaging (38). (38).

Recently, researchers have focused on developing plans to ensure that these untreated individuals have the best possible access to these innovative biologic medicines and small compounds. In a network meta-analysis of patients with moderate to severe CD who had not previously been treated with biologics, infliximab and adalimumab were found to be the most effective therapies for producing and maintaining remission, respectively. Infliximab and vedolizumab scored highest in a network meta-analysis of the capacity to elicit clinical remission in patients with UC who had not been treated with biologics previously (39). This theory seems to reflect observations made in patients with a greater inflammatory burden, as measured by a higher CDAI/Mayo score (40). Larger levels of C-reactive protein (a higher inflammatory load) correspond with lower medication concentrations and worse outcomes, according to studies on infliximab (41,42). Loss of medicine through an ulcerated GIT is another probable explanation for low anti-TNF drug concentrations in patients with severe illness. Ulcers are more common in patients with advanced illness. Sixty-six percent of stool samples at 2 weeks revealed quantifiable amounts of infliximab in a small prospective study including 30 biologic-naive individuals with moderate to severe UC treated with infliximab. The fecal concentration of infliximab was also significantly higher in patients who did not have a clinical response (5.01 g/mL vs 0.54 g/mL, respectively; P=.0047) compared to patients who did (42). There is also the possibility that low circulating medicine concentrations are the result of immune-related clearance, which occurs when anti-drug antibodies are generated. By immobilizing the medication in circulation, these antibodies boost elimination rates by blocking its effects. The development of anti-drug antibodies can have a significant effect on treatment outcomes as early as the induction phase (43).

In conclusion, the efficacy and safety profile of biologic therapy are advantageous for patients with inflammatory bowel disease (IBD) who have moderate to severe disease activity. Future improvements in the efficacy of these medications will depend on the results of more studies investigating the causes of PNR and SLR. These studies should have larger sample sizes and longer follow-up periods. As quickly as possible, we need to do these analyses.

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