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OUTCOME OF ULCERATIVE COLITIS PATIENTS AFTER ONE YEAR OF BIOLOGICAL THERAPY IN SELECTED EGYPTIAN PATIENTS

By

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Abstract

The majority of inflammatory bowel disease (IBD) patients can live normal productive lives; but long-term ulcerative colitis is associated with a higher risk of dysplasia and colorectal cancer. Anti-TNF drugs remain the first-line therapy for moderate-to-severe IBD patients but these drugs have several drawbacks for the majority of patients. This study assessed one-year follow-up of ulcerative colitis patients receiving biological therapy. Selected twenty-eight patients with moderate to severe ulcerative colitis treated with biological therapy for at least one year were enrolled. Clinical and laboratory assessments were performed for patients before and after the biological treatment as well as assessments of clinical response and remission.

The results showed that after one year, patients (75%) clinical responded and clinical remission was in 46.4% of them. There was a significant improvement in Mayo Score and Mayo Endoscopic Sub-score.

Keywords: Patients, Inflammatory bowel disease, Mayo Score, Clinical response, Remission.

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are two subtypes of inflammatory bowel disease (IBD), which is chronic idiopathic autoimmune inflammatory diseases affecting gastrointestinal tract with remissions and relapses (Machado *et al,* 2013). The inflammatory process is driven by an excessive immune response to the antigenic stimulation by gut micro-biota in genetically susceptible subjects (Khor *et al,* 2011). Also, environmental factors and dysregulated immune response were IBD increased risk **(**Ananthakrishnan, 2015).

The majority of IBD patients can live normally, but in the long run up to 75% of them with Crohn's disease and 30% of UC patients required surgery (Esmat *et al,* 2014). Long-term UC was also a high risk of dysplasia and colorectal cancer due to uncontrolled inflammation (Colman and Rubin, 2016). IBD incidence and prevalence increased in African Countries specially Egypt (El-Bassyouni and El-Atrebi, 2017). These patients must be regularly monitored by medical professionals and a national registry was developed to encourage multicenter and molecular diagnostic studies (El-Atrebi *et al*, 2021).

The IBD therapeutic strategies were evolved over time from resolving disease symptoms to significant intestinal healing with minimal serious outcomes such as hospitalization and surgery (Neurath and Travis, 2012). The anti-TNF agents were the approved biological drugs for IBD (Meroni *et al*, 2016). Pagnini *et al.* (2017) reported that amongst the available therapies for moderate to severe Crohn's disease patients refractory to conventional therapy was the effective biological treatment option anti-TNF blockers. They added that many patients experience a primary or secondary non-response to anti-TNF therapy needed the alternative biological one targeting different mechanisms of action and inflammatory pathways. Thus, development and characterization of novel medicines with different modes of action from TNF inhibition were indicated for IBD, such as natalizumab®, vedolizumab®, and ustekinumab® already clinical treated (Pagnini *et al,* 2019).

Combined therapy increased the clinical response and remission rates in IBD patients

who have started biological treatments. This was accomplished with utilization of immunomodulator and anti-TNF medication, with high remission rates, higher anti-TNF drug levels, and lower loss of response (Sands *et al,* 2014). Even after successful initial treatment, those with UC or CD required longterm maintenance therapy (Loftus *et al,* 2020).

This study aimed to compare baseline and after one-year follow-up of biological therapy as to laboratory parameters, disease severity by Mayo Scoring System, blood transfusion number, colonoscopy, and hospitalization causing severe attacks in UC patients.

Subjects and Methods

This study was a descriptive, retrospective, cohort, single-center study. The 28IBD patients were selected from >180 patients attended the IBD clinic, Ain Shams University Hospitals between 2015 and 2020.

Patients were considered eligible if they fulfilled the following criteria: adults aged between 18-60 years, patients with moderate to severe UC according to European Crohn's & Colitis Organization (ECCO) guidelines, and patients received biological therapy for at least one year. Indications of starting biological therapy among those were either due to failure to respond to steroid therapy or the extra-intestinal manifestation.

Study design: Data were obtained from medical records before taken biological therapy, and after one-year treatment follow-up. They were subjected to complete history taken with stress on hospitalizations number, motions number, extra-intestinal complications, and any biological therapy adverse effect. Then, they were subjected to laboratory examinations to evaluate changes in the blood tests, CBC, and liver profile at baseline and at follow-up.

Assessing disease severity before starting biologics and after 1-year of biological therapy was done using the Mayo Scoring system (Rutgeerts *et al,* 2005), and Mayo Endoscopic Sub-score (D'Haens *et al,* 2007). Col onoscopy with terminal ileoscopy was done before starting biologics and after one-year according to the ECCO guidelines (Campbell and Vaughn, 2016).

Assessing clinical response and clinical remission after one year biological therapy was done reporting any adverse side effects or reasons to stop therapy. Clinical response was a decrease of ≥3 points in total Mayo Score from baseline, and at least 30%, a decrease in rectal bleeding sub-score of ≥1 point or an absolute sub-score of 0 or 1 (Turner *et al,* 2009). Clinical remission was a total Mayo score of ≤2, without individual sub-score >1 (Peyrin-Biroulet *et al,* 2015).

Ethical consideration: The study was done following regulations of the ethical guidelines of the 1975 Declaration of Helsinki (6^{th} revision, 2008), with an ethical approval number: FMASU 122/2021 (14/3/2021). Written informed consent for study participation was collected from all patients.

Statistical analysis: Data were revised, coded, tabulated, and introduced to Pc using statistical package of social sciences (SPSS 25). Continuous variables were expressed as mean or median and binary variables were expressed as numbers and percentages. Paired samples were compared by either paired t-test or Wilcoxon signed-rank test. Fisher's exact test was used to examine relationship between two qualitative variables. The McNemar test was used to assess the statistical significance of the difference between qualitative variables measured twice for the same study group. A P-value less than 0.05 was considered significant.

Results

Twenty-eight IBD patients were enrolled in this study with severe ulcerative colitis. Mean age was 30.14±7.65, 64.3% were female (n=18), and 7.1 % of them were smokers (n=2). The illness duration ranged from 1 to 10 years with a median (range) of 3 (2-5.5) years.

Baseline CBC, liver functions, liver enzymes, kidney functions, and serum electrolytes were normal except for serum albumin and hemoglobin levels were lower than normal levels. Baseline viral and bacterial mar-

kers showed one positive patient (3.6%) for CMV-IgM and one positive patient (3.6%) for Quantiferon test, but all were negative for HCV Ab, HBs Ag, and HIV Ab.

Previous biological therapy experience, 67.9% (n=19) of patients were biologic naïve, but 32.1% (n=9) were biologic experienced. Among those 9 patients, seven were given infliximab (77.8 %) and two were given adalimumab (22.2%).

At a year follow-up, 16 patients (57.1%) received adalimumab, 11 patients (39.3%) received infliximab, 1 (3.6%) patient received ustekinumab and 71.4% of patients received combined azathioprine and biologics.

Two patients (7.1%) developed complications with biological therapy; one developed a severe hypersensitivity reaction, and one developed a severe pneumonic chest infection. Patients (n=17) 60.7% discontinued the biologics after a year. Patients 15 (88.2%) stopped due to failure in clinical remission, and two patients (11.8%) stopped due to complications. Patients stopped biologics shifted to another biologic or underwent surgical intervention. Recruited patients (75%) achieved clinical response at one year and number of hospitalizations and blood transfusion needed decreased to 46.4% (n=13) achieved clinical remission. Mayo Scoring system showed a significant improvement, with the median decrease from 11.5 points at baseline to 8 points after one year of biological therapy. None of the laboratory parameters had shown any significant changes between baseline and after one-year follow-up.

Details were given in tables (1, 2, 3, 4 & 5) and Figure (1).

Table 1: Baseline laboratory investigations among cases.

Items	Mean	SD*	Median (IQR)**	Range
TLC	6.17	2.02	6.45 (4.5 – 7)	(2 – 10)
HGB (gm/dl) N (11.6- 16.6)	9.28	1.72	10 (8 – 10.5)	(6 – 12)
PLT	296.57	102.44	300 (209 – 359)	(150 – 527)
AST(U/L) up to 39 IU/L	22.25	9.63	20 (18 - 24.5)	(12 - 61)
ALT(U/L) up to 52 IU/L	19.36	7.46	18 (16 - 21.5)	(6 - 44)
T. BILIRUBIN (mg/dl) up to 1 mg/dl	0.76	0.21	0.8 (0.65 - 0.95)	(0.2 - 1)
S ALBUMIN(gm/dl) N (3.5-5.7)	2.64	1.48	3.2 (1.1 - 3.75)	(0.1 - 4.2)
INR	1.04	0.09	1 (1 - 1)	(0.9 - 1.3)
CREATININE(mg/dl) N up to 1.2 mg/dl	0.78	0.15	0.8 (0.7 - 0.9)	(0.4 - 1)
Na (mg/dl) N (135-145)	136.39	4.45	135 (135 - 139.5)	(120 - 144)
K (mg/dl) N (3.5-5.5)	3.79	0.52	3.8 (3.25 - 4)	(3.2 - 5)

*Standard deviation (SD); ** Interquartile range (IQR).

Table 2: Baseline data as to disease, response to steroids, and extra-intestinal manifestations (n=28).

Items	Parameter	No.	Percentages
Location of disease by colonoscopy	Left	7	25.0%
	Pan colitis	21	75.0%
Response to steroids before starting biological therapy	Resistant	7	25.0%
	Dependent	21	75.0%
Extra-intestinal manifestations	No	19	67.9%
	Yes	9	32.1%
Type of extra-intestinal manifestations	Sacroiliac	4	14.3%
	Arthritis	3	10.7%
	Sacroiliac and uveitis	1	3.6%
	Uveitis and arthritis	1	3.6%

Table 3: Causes of biologics discontinuation after one year.

Items	Parameter	No.	Percentages
Stoppage of the current Biologics after one year	No	11	39.3%
	Yes	17	60.7%
Causes of stopping biologics after 1 year (n=17)	No remission	15	88.2%
	Complication	2	11.8%
If no remission/ complications (n=17)	Shift to other biologics	14	80.0%
	Surgical intervention	3	20.0%
Type of biologics shifted to (n=14)	Ustekinumab	12	85.7%
	Vedolizumab	2	14.3%

Table 4: Blood transfusion, number of hospitalizations/year, and disease severity in UC patients before & after biologics.

Patients (n=29)		Pre	After one Year	Mc-Nemar test		
		N (%)	N (%)	P-value*	Significant	
Blood transfusion	No	13 (46.43%)	19 (67.86%)	0.109	NS	
	Yes	15 (53.57%)	9 (32.14%)			
		Pre	After one Year	Wilcoxon signed test		
		Median (IQR)**	Median (IQR)	*Z***	P-value	Significant
Number of hospitalization		3 (2 - 4.5)	1 (0 - 3)	-3.667	<0.001	S
Disease severity by Mayo scoring		11.5 (11 – 12)	8 (2 – 9)	-4.638	<0.001	S

*P< 0.05 significant, **Interquartile range (IQR), ***Wilcoxon signed test of significance (z= Wilcoxon signed test).

Table 5: Comparing before & after one year of biologics among cases (UC =28) as to Mayo Endoscopic Sub-score.

variables		Pre	After one Year	Marginal homogeneity test	
		N (%)	N (%)	P-value*	Significant
Mayo Endoscopic Sub-score	Mild	0 (0.0%)	9 (32.14%)	<0.001	S
	Moderate	0 (100%)	7 (25%)		
	Severe	28 (0.0%)	12 (42.86%)		

*P< 0.05= significant.

Discussion

The present study, confirmed significant improvement in the Mayo Endoscopic Sub-score, all patients had a severe Mayo Endoscopic Sub-score at baseline, and only 42.9% of them remained with a severe Mayo Endoscopic Sub-score at one-year follow-up.

Inflammatory bowel disease (IBD) is a chronic intestinal inflammation with a clinical relapsing and remitting pattern with hospitalization admission, low productivity and high morbidity (Yeshi *et al*, 2020). IBD is progressive, with damage accumulation and treatment failure over time as systemic disease, with extra-intestinal manifestations affecting joints, skin, eyes, and less frequently liver, pancreas, or lungs leading to impaired quality of life and morbidity (Tejeda Taveras *et al*, 2021). However, the incidence and prevalence of IBD being increasing in the general population was age (Coward *et al,* 2019). Hazel and O'Connor (2020) Ireland reported that there is specific treatment. They added that therapeutic advances, such as gut-specific anti-integrins, gave patients an alternative option to systemic immunosuppression, as anti-interleukin 12 (anti-IL-12)/IL-23 agents and effective treatment options for CD, but oral small molecules offered an oral alternative for treatment of moderate-to-severe disease, previously requiring subcutaneous injection or intravenous infusion. They concluded that pharmacological treatment such as stem-cell transplant and fecal macrobiotic transplant that showed some promise in treatment.

The present study dealt with 28 patients with severe UC and on biological therapy selected from 180 over five years (January 2015 to March 2020. This went with El-Bassyouni and El-Atrebi (2017) in Egypt who declared that IBD was a rare disease, but added that there must be awareness of its presence in the East Mediterranean countries

In the current study, the patients mean age was 30.13 years, and the majority (64.3%) was females. On the contrary, Satoshi *et al,* (2014) in Japan recruited 33 UC patients of whom 39.39% were females with a mean ages of 43.2 years, which might be due to ethnic differences between the UC patients. Tozun *et al.* (2019) in Turkish Multicenter studies found that the diagnosed UC patients aged between 20 and 40 years, the great majority was females

In the present study, smokers were 7.1% of the UC patients. But, Jin *et al.* (2013) in China reported that the smokers were 17.6% of 153 UC patients. This controversy may be due to the difference in the UC patients' number, behaviors variability and the environmental factors between both countries as to female smoking.

In the present study, the patients' baseline of mean hemoglobin level was 9.28gm/dl. This agreed with Sabah *et al.* (2015) in Egypt reported that the epigastric pain and heart burn were represented about 90% of symptoms in positive *Helicobacter pylori* antigenic patients, and that the incidence was about

70% in the Nile Delta Also, Mansour *et al.* (2018) in Egypt reporting that the mean hemoglobin level was 9.52gm/dl in the *Helicobacter pylori* initiated IBD patients.

In the present study, an UC patient (3.6%) was IgM positive for CMV. This disagreed with Cottone *et al.* (2001) in Italy who reported that in seven (ulcerative colitis five and Crohn's disease two) out of 19 patients with refractory disease, cytomegalovirus was the cause. Five patients went into remission after antiviral treatment, one did not respond and was operated on and one patient, cytomegalovirus was found in the surgical specimen. They concluded that cytomegalovirus infection was a frequent cause of severe refractory colitis.

In the present study, a patient 3.6% (28/180) was Quantiferon positive. But, Lai *et al.* (2019) in Taiwan found that that 8% (10/130) of the IBD patients were quantiferon positive. This difference may be due to the fact that TB was more reported in male Taiwan patients.

In the present study, the IBD according to Montreal classification showed pan-colitis in 75%, and left-sided UC in 25% of patients, but without proctitis diagnosed in any one. Satoshi *et al.* (2014) in Japan reported that out of 33 IBD patients on biological therapy, 60.6% of them had extensive colitis and 39.4% had left-sided colitis. Esmat *et al.* (2014) in Egypt found that the patients had left-sided UC, proctitis and pan-colitis (65%, 18.5%, & 16.2%, respectively)

In the present study, as to the steroid response before biological therapy, 75% of the patients were corticosteroid dependent and 25% were corticosteroid resistant. This disagreed with Khan *et al.* (2013) in USA found that about half of newly-diagnosed patients with UC requir- ed corticosteroid (CS). One third of them had a sustained response after the initial CS course and two-thirds required further CS therapy. They concluded that a trend towards higher than previously reported thiopurine use accompanied by marked reduction in colectomy rates.

In the present study, patients (32.1%) had extra-intestinal manifestations (sacroiliac, arthritis, sacroiliac and uveitis, or uveitis and arthritis). Rawal *et al.* (2021) in India retrospective cohort study found 7.92% of UC patients, which may be due to different ethnicity of patients.

In the present study, 16 patients (57.1%) received adalimumab, 11 patients (39.3%) recei-ved infliximab and one patient (3.6%) received ustekinumab. Most of the cases (71.4%) were receiving azathioprine in conjunction with biological therapy. Besides, two (7.2%) experienced complications, and one (3.6%) had significant hypersensitivity reactions. The other had a serious pneumonic chest infection that led to a cessation of biological therapy. This more or less agreed with Satoshi *et al.* (2014) who reported that among 2/33 (6.1%) who experienced adverse events drug eruption in one patient and the second anaphylactic shock.

In the present study, 3/28 (10%) patients required total colectomy with ileo-pouchal anastomosis. But, Satoshi *et al.* (2014) reported that 6/33(18.2%) refractory IBD patients underwent colectomy during follow-up. This controversy may be due to the differences in the patients' criteria.

In the present study, the overall clinical response to biologics (infliximab, Adalimumab, and Ustekinumab) at 1-year follow-up was 75%. This agreed with Reinisch *et al.* (2013) in Austria concluded that in an open-label study, adalimumab was effective for maintaining clinical remission in anti-tumor necrosis factor-naive patients with moderately to severely active ulcerative colitis who did not adequately respond to conventional therapy. Also, Barberio *et al.* (2021) in Italy who concluded that among the different anti-TNF treatments, moderate-to-severe UC responded better to infliximab (IFX) and adalimumab (ADA), whereas golimumab (GOL) was less effective, despite a similar good safety profile.

In the present study, clinical remission at one-year follow-up was 46.4%. Panaccione

et al. (2014) compared efficacy and safety of infliximab and azathioprine therapy alone or in combination for ulcerative colitis in concordance with the active ulcerative colitis trial 1 & 2 (ACT1 & ACT2) clinical trials for infliximab, they concluded that anti-TNF factor-a–naive patients with moderate to severe UC treated with infliximab plus azathioprine were more likely to achieve corticosteroid-free remission at 16 weeks than who received either monotherapy. Reinisch *et al.* (2020) reported that clinical remission was 30 % at week 30 in ACT1 with a very similar remission rate at week 54 in ACT2 Besides, ulcerative colitis long-term remission and maintenance with adalimumab (ULTRA 2) clinical trial had shown that 22 % of cases had achieved remission at week 52.

In the present study, the anemia persisted even after anti-TNF treatment. This agreed with Koutroubakis *et al.* (2015) who reported that followed up 430 Pennsylvanian IBD patients received anti-TNF drugs for one year, but the anemia remained the same after one year treatment

In the present study, number of IBD patients who required blood transfusion decreased significantly after one year of biological therapy, which indicated the effective role of biologics in decreasing intestinal hemorrhage and bleeding in UC patients.

In the present study, IBD activity represented in Mayo Scoring Index and Mayo Endoscopic Sub-score had decreased significantly after treatment with the biologics. This agreed with Fernández-Blanco *et al.* (2018) in Spain reported a significant lowing in both scores after adalimumab administration in moderate to severe IBD patients.

In the present study, the hospitalization frequency decreased from 95 UC-related admissions in a year to 45 UC-related admissions with the significant decrease ($p<0.001$). This agreed with Sandborn *et al.* (2009) who in 54-week placebo-controlled trial found a significant reduction in the UC-related hospitalizations number among the infliximab-treated group compared to the placebo ones.

Conclusion

Generally speaking, the inflammatory bowel disease (IBD) consists of chronic intestinal inflammation caused by the interaction of genetics, environmental factors, and the microbiome that affect both sexes at all ages

There are a variety of available IBD treatment from conventional to biological or small molecules. Biological therapies improved the Mayo Scoring system and Mayo Endoscopic Sub-score in patients with severe UC. Clinical response was (75%) after one-year, but clinical remission was 46.4%.

Consequently, biologics reduced the hospitalizations, blood transfusions and severe attacks in patients with IBD.

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Explanation of figure

Fig. 1: Bar chart illustrating a comparison between before and after one year of biologics among cases as to Mayo Endoscopic Sub-score.