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Predictors of Relapse among Inflammatory Bowel Disease Patients on Biological Treatment in Upper Egypt

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ABSTRACT

Background: Prevalence of inflammatory bowel disease (IBD) is increasing in Egypt. Multiple lines of biological treatment have been but still there is failure of treatment to these medications and because of high cost it is of great importance to personalize treatment options.

Aim of the study: This study aimed to assess the factors that can predict the response to biological treatment.

Subjects and methods: This study included 133 patients with IBD who were indicated to biological treatment (Anti-TNF), and followed up for 2 years. All demographic, clinical laboratory data and disease activity were recorded at 1st presentation. Patient were classified into 2 groups one group who showed nonresponse to treatment and the other one who responded well to treatment. All factors were analyzed as predictors of nonresponse using univariate and multiple regression.

Results: Out of 133 patients of IBD, 77 patient showed non-response. Younger age, family history of IBD, long duration of disease, previous surgical resection and presence of extraintestinal manifestation could be predictors of non-response. Increased levels of inflammatory markers of ESR, CRP and fecal calprotectin were associated with poor response to therapy (p value < 0.001, < 0.001 and 0.001 respectively). Moreover, increased activity and colonic extent in UC associated with nonresponse also marked activity and behavior of CD patients could be predictive factors of relapse. In multivariable analysis the factors independently associated with non-response were younger age, long duration of disease, presence of extraintestinal manifestations, elevated ESR and fecal calprotectin.

Conclusions: Multiple disease related factors can be associated and could predict the response to anti-TNF treatment.

Keywords: Inflammatory bowel disease, biological treatment, Anti-TNF, non-response to treatment.

INTRODUCTION

The chronic gastrointestinal illness known as inflammatory bowel disease (IBD) is typified by remission and exacerbations including ulcerative colitis (UC) and Crohn's disease (CD) manifested usually by bleeding per rectum abdominal pain, fecal urgency and chronic diarrhea and is associated with extraintestinal manifestation affecting joints, eye, skin and liver [(1)]. IBD has relapsing and progressive course affecting quality of life and contribute to high cost to the health care system, so there is a great need for a quick and consistent response from a safe and efficient treatment [(2)].

The new biological therapies act upon the molecular pathways included in the pathogenesis of IBD, as it act selectively to inhibit mediators in these inflammatory processes [(3)]. Anti tumour necrosis factor agents are usually the 1st line biological treatment in IBD include different agents as infliximab, which is chimeric monoclonal antibody, adalimumab as human monoclonal antibody and golimumab, which is fully human monoclonal antibody. It improves quality of life by enhancement of mucosal healing and decreases need for repeated courses of steroid and need for surgeries. However treatment failure for these agents is not uncommon. Among IBD patients on anti-TNF therapy, two thirds showed good first reaction to treatment and up to 50% of cases had secondary failure to treatment and may need switch to other class of biology [(4)]. Since these different agents of biologics do not have universal response and are expensive, so it seems to be important to study the various predictive factors of reaction to the subset of people with IBD who will also respond to several targeted medicines with the characterization of individual phenotype and genotype may affect the choice of treatment as old concept of "one drug suits all" should be replaced by the strategy of personalized medicine.

So, the aim of this research was to present the predictive factors of non-response to biological treatment as the current data suggest that there are multiple factors affecting this, which may be disease related or clinical and laboratory features. Moreover, microbiological, metabolic, and pharmacogenomics elements in addition to local mucosal features could have a great influence on response to different biological treatment.

PATIENTS AND METHODS

This was a prospective observational research carried out through the period from April 2021 to May 2023 in Assiut University Hospital (IBD Clinic and Pediatric Clinic). Data collected from 133 patients either UC or CD with confirmed diagnosis via histopathological analysis and colonoscopy, who were eligible to 1st line biological treatment by anti-TNF according the guidelines and local protocols (choice of the type of anti-TNF guided by nature of the disease, recent protocols, availability of the drug and preference of patients after counseling).

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All selected cases were asked about their health history, including their sociodemographic data (sex, age, residence, smoking status, prescribed medications, family history and surgical history).

Criteria of each disease were collected including colonic extent in UC, and Montreal classification in CD cases including behavior and location of disease. Activity of UC was calculated using Mayo score (UC: 0-2 normal, 3-5 mild, 6-10 moderate and 11-12 sever). Crohn's disease activity index was calculated (CD < 150 normal, 150-219 mild, 220-440 moderate and > 450 sever). These were recorded at baseline presentation. Laboratory investigations recorded at baseline presentation included CBC, ESR, CRP, fecal calprotectin and albumin.

Patients were followed up for 2 years. If patient showed no signs of clinical, laboratory and endoscopic improvement at 14 weeks of biologic treatment so primary non-response was diagnosed. If patient showed improvement and after that worsening of symptoms occurred then secondary non-response was established (guided by laboratory, endoscopic evaluation and relevant imaging).

Our patients after this follow up period were categorized into 2 groups, group which showed failure or non-response to 1st biological treatment, another group that showed good response till the end of follow up. ‘

Exclusion criteria:

Patients who had a history of lymphoma or cancer, severe infections, heart failure, multiple sclerosis, demyelinating disorders, immunodeficiency, abnormal chest radiography, positive tuberculin test, history of tuberculosis, positive HBsAg or anti-hepatitis C virus, pregnancy, lactation, and other conditions that may have contributed to their illness exacerbation as Clostridium difficile or CMV infection.

Ethical considerations: All participants provided written informed consents, and the study was approved by The Research Ethics Committee of Faculty of Medicine, Assiut University (IRB#300168). The study was conducted in accordance with the Declaration of Helsinki, the World Medical Association's code of ethics involving human subjects.

Definitions:

Primary non-response (PNR): Since definitions differ throughout research, there is no agreement on what constitutes primary nonresponse (PNR) in individuals with IBD. PNR was defined by **Papamichael *et al.*** [(5)] as the inability to objectively measure an improvement in baseline inflammatory symptoms following induction of treatment when the medication was present at appropriate quantities and antidrug antibodies (ADAs) were absent. PNR often denotes the failure to enhance objective measures or clinical symptoms during the induction period. According to reports, the prevalence of PNR varies between 13% and 40% [(6)].

Secondary non-response (SNR):

The clinical phenomena of patients who initially respond to biologics but later lose this response is described by SNR, also known as LOR. The two main characteristics of the SNR are that the patient's symptoms became better after the first course of treatment and that the return of symptoms can only be attributed to the inflammatory response of IBD and not to an infection and fibrous stenosis, or other concomitant conditions. Eventually, 20%–50% of patients experience SNR [(7)].

Statistical analysis

The statistical package for the social sciences (IBM-SPSS) version 26.0 program was used to analyze the data. The frequencies and percentages were used to represent the categorical data. The data normality of all numerical variables was assessed using the Shapiro-Wilk test. Means ± SD was used to express quantitative data. To compare the proportions between the groups, Chi square test was employed. T test on independent samples was employed to compare mean difference between two independent groups. We used univariate logistic regression analysis to find potential predictors for relapse among IBD patients and significant variables entered in a multivariate LR adjusted odds ratios (AORs) were computed using logistic regression analysis. A P value ≤ 0.05 was considered significant.

RESULTS

Demographic data and medical history at index date:

The current study included 133 patients with IBD treated by Anti-TNF as 1st line therapy. Most of the patients were men (53.4%) and the mean age of studied patients was 33.46 ± 12.88. The mean duration of disease was 4 ± 2.31 years and current smoking was positive in 21.8% of cases. Moreover, 21.1% of patients had positive history of IBD in 1st degree relatives, previous surgical resection was found in 11.3% and appendicectomy in 7.5%. The presence of extraintestinal manifestations either peripheral arthritis, bilateral sacroiliitis, ocular diseases and skin manifestations were present in 24.8%. UC patients were 52.6% and CD was 47.4% of cases. At the end of our follow up period we had 77 patients with failure or nonresponse to treatment and 56 patients were doing well during the follow up period. As regards treatment, there were 47 patients on azathioprine, 45 patients on 5 aminosalicylic acid (5ASA), 20 patients on steroid with 5ASA and 21 patients on steroid with azathioprine in 21 patients. Regarding Anti-TNF treatment, 40.6% of patients were on adalimumab,16.5% on golimumab and 42.9% on infliximab (Table 1).

Table (1): Demographic and clinical characteristics of patients with IBD

Variables	Total (n=133)	%
Age (years): Mean ± SD	33.46±12.88 (8-62)	
Gender		
▪ Male	71	53.4%
▪ Female	62	46.6%
Residence		
▪ Urban	90	67.7%
▪ Rural	43	32.3%
Smoking		
▪ Yes	29	21.8%
▪ No	104	78.2%
Presence of family history of IBD	28	21.1%
Duration of disease (years)	4±2.31 (1-17)	
Type of disease		
▪ Ulcerative colitis	70	52.6%
▪ Chron's disease	63	47.4%
Previous surgical resection	15	11.3%
Appendicectomy	10	7.5%
Presence of extraintestinal manifestation	33	24.8%
▪ Peripheral arthritis	16	12.0%
▪ Bilateral sacroiliitis	8	6.0%
▪ Erythema nodosum	5	3.8%
▪ Ocular disease	4	3.0%
Relapse		
▪ Relapsed	77	57.9%
▪ Non-Relapsed	56	42.1%
Types of non-response (n=77)		
▪ Primary non-response	7	9.1%
▪ Secondary non-response	70	90.9%
First line of biological treatment		
▪ Infliximab	57	42.9%
▪ Adalimumab	54	40.6%
▪ Golimumab	22	16.5%
Concurrent medication		
▪ Azathioprine	47	35.4%
▪ 5ASA	45	33.8%
▪ Steroid + azathioprine	21	15.8%
▪ Steroid+5ASA	20	15.0%

Data were expressed as frequency (%) or mean ± SD

Indicators of suboptimal response: The results demonstrated the existence of statistically significant lower mean age among relapsed patients compared to non-relapsed (30.82 ± 12.59 vs 37.13 ± 12.61 years respectively), and statistically significant higher duration of disease among relapsed patients compared to non-relapsed (4.70 ± 2.73 vs 3.04 ± 0.94 years respectively). Moreover, individuals with an IBD family history had higher percent in nonresponse patients compared to responded patients (28.6% vs 10.7% respectively). Also, patients with history of previous surgical resection had higher percent in non-response patients compared to responded (16.9% vs 3.6% respectively) and patients with extraintestinal manifestation had higher percent in relapsed patients compared to non-relapsed (32.5% vs 14.3% respectively). There was no discernible statistical difference between relapsed and non-relapsed regarding gender, residence, smoking, disease type, appendectomy, and types of first line biological treatment (Table 2).

Table (2): Association between relapse and non-relapse IBD according to their demographic and clinical characteristics

Variables	Relapsed (n=77)	Non-relapsed (n=56)	P-Value
Age (years): Mean ± SD	**30.82±12.59**	**37.13±12.61**	**0.005 ***
Gender			
▪ Male	40 (51.9%)	31 (55.4%)	0.697 **
▪ Female	37 (48.1%)	25 (44.6%)	
Residence			
▪ Urban	48 (62.3%)	42 (75.0%)	0.123 **
▪ Rural	29 (37.7%)	14 (25.0%)	
Smoking			
▪ Yes	19 (24.7%)	10 (17.9%)	0.347 **
▪ No	58 (75.3%)	46 (82.1%)	
Presence of family history of IBD	**22 (28.6%)**	**6 (10.7%)**	**0.013 ** **
Duration of disease (years)	**4.70±2.73**	**3.04±0.94**	**<0.001 ***
Type of disease			
▪ Ulcerative colitis	38 (49.4%)	32 (57.1%)	0.374 **
▪ Crohn's disease	39 (50.6%)	24 (42.9%)	
Previous surgical resection	**13 (16.9%)**	**2 (3.6%)**	**0.017 ** **
Appendicectomy	6 (7.8%)	4 (7.1%)	0.888 **
Presence of extraintestinal manifestation	**25 (32.5%)**	**8 (14.3%)**	**0.017 ** **
First line of biological treatment			
▪ Infliximab	34 (44.2%)	23 (41.1%)	0.915 **
▪ Adalimumab	31 (40.3%)	23 (41.1%)	
▪ Golimumab	12 (15.6%)	10 (17.9%)	

Data were expressed as frequency (%) or mean ± SD.
* Independent Sample T test compares meaning between groups. ** Chi square test compare proportions between groups.

Laboratory indices as predictors of suboptimal response at 1st presentation: Laboratory markers are of great importance in evaluating IBD patients. In this study results showed that hematological changes occurred could be related to response to treatment. It was noticed that increased platelets and decreased hemoglobin occurred in non-response group (P value 0.015 and 0.003 respectively) and decreased serum level of albumin occurred significantly in non-response patients (P value 0.006). Moreover, levels of CRP, ESR and fecal calprotectin were raised significantly in non-response group compared to responded group (P value <0.001, <0.001 and 0.001 respectively) (Table 3).

Table (3): Comparison between relapser and non-relapser IBD according to laboratory investigation

Variables	Relapsed (n=77)	Non-relapsed (n=56)	P-Value*
WBCs	6.08±1.28	6.042±1.23	0.903
Platelets	337.23±19.19	291.6±9.78	**0.015**
HB(g/dL)	10.01±1.40	10.72±1.17	**0.003**
Albumin	3.71±0.43	3.92±0.40	**0.006**
Total proteins	7.12±0.33	7.21±0.35	0.130
CRP (mg/L)	14.45±3.33	9.56±2.52	**<0.001**
ESR (mm/H)	52.42±3.35	29.56±4.70	**<0.001**
Fecal calprotectin	479.25± 27.62	337.02± 11.57	**0.001**

Data were expressed as frequency (%) or mean ± SD *
Independent Sample T test compares meaning between groups.

Activity of disease, extent and behavior as predictors of nonresponse:

Regarding UC patients, extensive colonic affection was associated with less response to treatment (P value 0.022). This was noticed to occur much more in patients with pancolitis. Also, patients with moderate and severe disease, according to Mayo score, had statistically significant higher percent of non-response compared to responded group. Moreover, there was a higher statistically significant mean Mayo score among non-response patients compared to responded patients (8.60 ± 1.78 vs 6.71 ± 1.07 respectively) (Table 4).

Table (4): Association between relapse and non-relapse UC according to their site and Mayo score

Variables	Relapsed (n=38)	Non-relapsed (n=32)	P-Value
Site of disease in UC			
▪ Proctitis	11 (28.9%)	19 (59.4%)	**0.022***
▪ left sided colitis	16 (42.1%)	10 (31.3%)	
▪ Pancolitis	11 (28.9%)	3 (9.4%)	
Mayo score: Mean ± SD (range)	8.60±1.78 (3-12)	6.71±1.07 (5-9)	**<0.001****
▪ Remission	0 (0.0%)	12 (37.5%)	**0.003***
▪ Mild disease	2 (5.3%)	4 (12.5%)	
▪ Moderate disease	13 (34.2%)	6 (18.8%)	
▪ Severe disease	23 (60.5%)	10 (31.3%)	

Data were expressed as frequency (%) or mean ± SD, * The Chi square test compares proportions between groups
**Independent Sample T test compares meaning between groups.

In patients with Crohn's disease, patients with penetrating, structuring and perianal disease have statistically significantly higher percent of non-response to treatment (P value 0.043). Moreover, there was a higher statistically significant mean Crohn's disease activity index (CADI) score among non-response patients (P value 0.001). Location of CD had no significant difference (Table 5).

Table (5): association between relapse and non-relapse CD according to their behavior, location, and CADI score

Variables	Relapsed (n=39	Non-relapsed (n=24)	P-Value
Behavior of CD			
▪ Non-stricturing non-penetrating	21 (53.8%)	21 (87.5%)	**0.043***
▪ Penetrating	2 (5.1%)	0 (0.0%)	
▪ Stricturing	13 (33.3%)	3 (12.5%)	
▪ Perianal disease	3 (7.7%)	0 (0.0%)	
Location of CD			
▪ Ileal	25 (64.1%)	18 (75.0%)	0.367*
▪ ileocolonic	14 (35.9%)	6 (25.0%)	
CADI score: Mean ± SD (range)	**429.13±150.83 (220-850)**	**337.22±85.32 (210-468)**	**0.010***
▪ Mild to moderate active CD	1 (2.6%)	1 (4.2%)	0.344*
▪ Moderate to severe active CD	25 (64.1%)	19 (79.2%)	
▪ Severe active to fulminant disease	13 (33.3%)	4 (16.7%)	

Data were expressed as frequency (%) or mean ± SD.
* Chi square test compares proportions between groups.
**Independent Sample T test.compares meaning between groups.

The study revealed that, by univariate logistic regression analysis, the significant predictors associated with occurrence of non-response among IBD patients were decrease age of patients, increase duration of illness, presence of family history of IBD, previous history of surgical resection, presence of extraintestinal manifestation, decrease of Hb and albumin level, increase platelets, CRP, ESR and fecal calprotectin. Significant predictors in univariate logistic regression were entered in a multivariate logistic regression and the remaining significant predictors were decrease age of

patients (OR=0.94, P value=0.003), increase duration of illness (OR=2.54, P value = < 0.001), presence of extraintestinal manifestation (OR=5.60, P value =0.010), increase ESR (OR=1.10, P value <0.001) and increase fecal calprotectin (OR=1.10, P value <0.001) (table 6).

Table (6): predictors/factors associated with relapse among patients with IBD

Predictors	Univariate		Multivariate	
	OR (95% CI)	P-value	AOR (95% CI)	P-value
Age	0.96 (0.93-0.98)	0.006	0.94 (0.90-0.97)	**0.003**
Duration of disease	2.10 (1.47-2.90)	**<0.001**	2.54 (1.60-4.04)	**<0.001**
Presence of family history	3.33 (1.25-8.88)	**0.016**		
Previous surgical resection	5.48 (1.18-25.38)	**0.029**		
Presence of EIM	2.88 (1.18-7.00)	**0.019**	5.60 (1.49-20.94)	**0.010**
HB(g/dL)	0.66 (0.50-0.88)	**0.004**		
Platelets	1.10 (1.01-1.20)	**0.014**		
Albumin	0.32 (0.13-0.74)	**0.008**		
CRP (mg/L)	1.13 (1.10-1.21)	**<0.001**		
ESR (mm/H)	1.10 (1.04-1.20)	**<0.001**	1.10 (1.04-1.12)	**<0.001**
Fecal calprotectin	1.10 (1.01-1.30)	**0.002**	1.10 (1.01-1.11)	**<0.001**

Logistic regression analysis, OR: Odds ratio, AOR (adjusted odds ratio), 95% CI: 95% confidence interval.

DISCUSSION

Anti-tumour necrosis therapy is the first line of management for either ulcerative colitis (UC) or Crohn's disease (CD) patients after failure of conventional treatment. Moreover, in the current study biological therapy was indicated in patients with UC who were steroid dependent despite use of immunosuppressive drugs, steroid refractory and in cases of acute sever colitis who need hospitalization. On the other hand, in CD patients were indicated in fistulizing illness, active luminal disease intolerant to steroids, and steroid-dependent cases and steroid refractory patients [8].

Our results showed that young age at presentation of disease may be significant indicator of relapse or failure of biologic treatment. On the other hand, gender, residence either urban or rural and smoking status has not been shown to be risk factors of non-response to treatment. There are conflicting previous results as regards age, 3 study stated that the response in CD patients was decreased with aging [9]. Also, **Arias *et al.*** [10] reported that young patients with UC have greater benefit of treatment [10]. GEMINI 2 study showed better response in younger patients [11]. As regards, gender most of studies including anti-TNF demonstrated no change in response between males and females [12]. However, one study revealed better response favorably in male CD patients and other benefit in female UC patients [13].

Smoking is known poor indicator of response in CD patients, however still studies have no definite conclusion regarding smoking and its relation to response to biologics [14]. PANTS study found that smoking has poorer outcome in response to infliximab at week 14 (primary non-response). Moreover, studies observed that smoking increases the immunogenicity to infliximab explaining less response to anti-TNF [15]. Studies of UC have conflicting findings, an Italian study discovered that ex-smokers responded less well although some people did not get this finding [16].

The current study revealed that the presence of positive IBD in first-degree relatives' family history may be poorer indicator of response to biologics. In previous study in agreement with our findings showed that positive family history was associated with more aggressive phenotype and revealed association with steroid refractory cases of UC that may lead to colectomy [17].

In our study, the duration of disease was a weak indicator of biological therapeutic response. In agreement with our results the Kopylov et al study revealed more remission rates in CD patients diagnosed for up to 2 years compared to patients with longer duration [18]. However, in UC the studies cannot find the same finding. On the contrary, some studies found better response to Anti-TNF with longer duration of disease [19]. Other studies reported that UC patients who had their disease for a shorter period of time respond better to anti-TNF medications, however the recent studies cannot purely explain the association of poor response to longer duration. This can be attributed to development of intestinal fibrosis requiring early intervention more beneficial to these cases [20].

In the current study, previous surgical resection has been shown to be predictive factor of non-response to treatment in CD patients. Moreover, **Macaluso *et al.*** [21] revealed that previous surgery is independent risk factor for primary non-response. Another study with 201 CD patients showed that prior surgery was a predictor of unsatisfactory response**.** Patients who had surgery may have a more severe illness and be more likely to respond poorly to medication [22].

Our results revealed that appendectomy showed no difference between groups and cannot be considered as risk factor of relapse or increase of the severity of disease, meanwhile there are conflicting data regarding appendicectomy. Some studies concluded that it is not risk factor of CD, while other studies revealed that it is

associated with increased severity of the disease and a poor prognostic factor [23].

It is noteworthy stated that the relevant study showed that the presence of extra intestinal manifestations (EIM) either rheumatologic and ocular or dermatological might be considered a predictive factor for non-response of biological treatment in IBD patients. A study from Germany stated that patients with EIM has more risk of colectomy and poorer response [24]. Also, in Swiss IBD cohort, the requirement for therapeutic escalation was linked to the existence of EIM. **Duricova *et al.*** revealed that EIM at time of diagnosis is a predictive factor of more sever disease outcome and unsatisfactory response in both pediatric and early onset UC [25].

Disease-related factors and clinical presentation are of great importance in predicting the progression of the illness and how it reacts to therapy specially the first presentation. Our results showed in patients with UC that colonic extent might be correlated with a poor response as pancolitis patients have more relapse and failure to anti-TNF therapy. However, other studies in UC patients pattern of colonic extension could not be correlated with the severity of disease or its reaction to medical intervention [26]. **Haritunians *et al.*** stated that extensive colonic disease could be associated with steroid refractory cases and a poor prognostic indicator to biological treatment that may lead to colectomy [27].

In the current study, the results showed that, behavior of CD according to Montreal classification, non-stricturing non-penetrating phenotype was associated with better response to Anti-TNF in comparison with stricturing, penetrating and perianal disease. In agreement with these results, **Atreya *et al.*** [3] confirmed that inflammatory phenotype associated with better outcome than stenosing or fistulizing disease. Another study showed that non-stricturing non-penetrating phenotype was associated with better response to treatment and long remission. However the location of CD showed no difference in outcome of disease in these results. On the other hand, **Vermeire *et al.*** [28] showed that terminal ileitis was correlated with poor response to treatment in comparison with isolated colitis.

Our results revealed that in UC cases activity of the disease detected by Mayo score correlated with failure to anti-TNF as increased Mayo score increases risk of relapse on biological therapy. Moreover, in CD patients marked activity of the disease mainly at 1st presentation had much more badly clinical outcome and less response to biological treatment and this was recorded according to Crohn's disease activity index (CDAI). On the other hand, another study showed that disease activity is not a predictor of response to biological treatment in UC and CD [29]. Meanwhile in GEMINI 1 and 2 trials showed that less degree of activity was associated with better response to treatment compared to placebo [30]. A French cohort of **Amiot *et al.*** [31] included among individuals with CD and UC, those with a baseline Harvey-Bradshaw index (HBI) score greater than 10 or a baseline Mayo score greater than 9 and reported that they had more aggressive course and less long term remission.

It has been hypothesized that IBD has inflammatory burden characterized by elevated markers as C-reactive protein (CRP) and fecal calprotectin (FC), which could influence prognosis and response to biologics. The current results revealed that elevated CRP level could be prognostic factor of severity of disease and poor response to treatment. The study of **Magro *et al.*** [32] showed that higher baseline level of CRP in CD more than 15 mg/l is associated with primary non-response with 67% sensitivity and 65% specificity. Another study showed that in UC patients with high CRP associated with high rate of drug failure and need for colectomy, however increased effectiveness of anti-TNF induction and maintenance was more in patients with low CRP [10].

The relevant study revealed that fecal calprotectin (FC) was higher in patients with non-response to treatment and elevated baseline level might be correlated with aggressive course of disease and poor response to anti-TNF. **Beltran *et al.*** [33] in agreement with our results showed that high baseline FC at week 0 is associated with primary non-response [33].

Our results showed that higher level of baseline ESR was associated with non-response to anti-TNF. On the other hand, **Gomes *et al.*** [34] revealed that there was no correlation between activity of the disease and ESR and CRP [34]. There are conflicting data regarding ESR as inflammatory marker of activity or as predictor of poor response to therapy.

Baseline albumin in our results showed much more decreased level in patients with poor response to anti-TNF so low level could be indicator of worse outcome of the disease. **Fasanmade *et al.*** [35] demonstrated that high serum albumin maintain higher serum infliximab concentrations, less clearance and longer half-life so better response. In a recent study, during the induction phase, infliximab levels were considerably lower in patients with acute severe UC compared to those with mild UC, and this was connected with albumin levels [18].

Regarding hematological changes that may occur in IBD patients, it is noticed in our study that increased platelets could be poor predictor of response. This is in agreement with Høivik et al study, which showed that UC patients had significantly elevated levels of platelets compared to control. On the hand, our results showed that decreased hemoglobin level was associated with patient non-response. Moreover, **Høivik *et al.*** [36] study showed that anemia was correlated with activity of the disease and might be indicator of more aggressive outcome.

In the current study, different types of anti-TNF were used but the results showed no difference regarding the response and outcome of the disease. This point may need further studies and assessment. Moreover, different ethnic population may results in different treatment responses as study in South Korea

stated that no difference in treatment outcome observed between adalimumab (ADA) and infliximab (INF) among 113 biologic naïve UC patients. However, in a different nationwide registry-based study comparing the all-causes of hospitalization among Danish biologic-naïve UC patients treated with INF and ADA. Patients treated with ADA had an almost two-fold increased risk of hospitalization compared to those treated with INF. So, from these studies it is concluded that different nationalities respond differently to Anti-TNF [37].

Limitation: Limited number of patients, unavailability of therapeutic drug monitoring including trough level and drug antibody to detect immunogenicity, more lines of biological treatment are needed to be investigated and more comparison between different phenotypes of IBD.

CONCLUSION

This study confirmed that patients' related factors as young age, family history of IBD, history of surgical resection, presence of extraintestinal manifestations, disease-related factors including marked activity of disease at 1st presentation, extent and behavior of disease and also inflammatory markers as elevated fecal calprotectin, ESR, CRP and decreased level of albumin could be risk factors of nonresponse to anti-TNF treatment. Moreover, the study emphasizes the importance to predict treatment failure to revise management decisions and improve long-term outcome in IBD patients.

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