Original Research Article

Evaluation of the relationship between fecal / serum levels of Infliximab and clinical response to treatment of IBD patients: a cross-sectional study

Abstract

Background: Inflammatory bowel disease (IBD) includes two major disorders: ulcerative colitis (UC) and Crohn's disease (CD). Infliximab is a monoclonal antibody that targets tumor necrosis factor (TNF) and is used to treat UC and CD**.** The aim of this study was to evaluate the fecal and blood levels of infliximab and the response to treatment of IBD patients after induction period.

Methods: This was a cross-sectional study conducted at the Imam Khomeini Hospital Complex (January to May 2021). All patients who were candidate for anti-TNF therapy received 5 mg/kg given as an IV induction regimen at 0, 2, and; 6 weeks, followed by a maintenance regimen of 5 mg/kg IV every 8 weeks. At the end of second week (day 14), Patient's response to treatment with either CDAI or Mayo score, fecal levels of infliximab, serum CRP and albumin level were measured. At the end of 14th week, fecal levels of Infliximab, serum levels of Infliximab serum albumin and CRP level were assessed again.

Results: A total of 28 patients (75% male and 25% female) were included into the study (14 patients with Ulcerative colitis and 14 patients with Crohn's disease). The mean age of the population was 34 ± 10. The distribution of Serum Infliximab after 14 weeks was not the same across clinical response ($P < 0.05$). Specifically, after adjusting for the Fecal Infliximab concentration day 14, UC patients had higher level of Serum Infliximab level at week 14 (3.853 ± 1.803) compared to the Crohn's disease patients.

Conclusion: Measurement of serum infliximab is widely recommended now and can be used for therapeutic monitoring of patients. The presence of higher serum infliximab is associated with a higher clinical response. In spite of early fecal loss of infliximab, which is an indicator of low serum infliximab level, late fecal infliximab is not a good marker for response since the inflammation is reduced.

Keywords: Inflammatory bowel disease, Crohn's disease, ulcerative colitis, Infliximab, Tumor Necrosis Factor-alpha

Introduction

Inflammatory bowel disease (IBD) includes two major disorders: ulcerative colitis (UC) and Crohn's disease (CD) [1]. Ulcerative colitis is an idiopathic chronic inflammatory condition characterized by repeated episodes of healing and recurrence of inflammation of the mucosal layer of the colon, frequently involving the rectal mucosa and may affect other parts of the colon continuously [2]. Crohn's disease is characterized by transmural inflammation and escaped lesions that can affect any part of the gastrointestinal tract, from the mouth to the perianal area. Transmural inflammation may lead to fibrosis, stenosis, or obstruction. Fistulas, sinus tracts, and micro perforations are also common [3].

Today management of IBD patient needs much more attention to patient severity, activity and target of treatment [4]. Early diagnosis and management of IBD patients in the opportunity window will prevent severe complication which may worsen the disease course. Goal of treatment should involve multiple aspect of patient disease and is best when lead to mucosal healing [5]. Anti-Tumor Necrosis Factor (TNF) drugs are widely used and have the ability to induce mucosal healing in both UC and CD [6][7]. In the case of ulcerative colitis, if the patient is resistant to corticosteroids and does not respond well to the immunomodulators (Azathioprine-6MP), the patient may be a candidate for initiation of anti TNF [8]. In contrast to UC, initiation of anti TNF in CD is depended on the severity of disease and will be treatment of choice in early course of the disease. [9]. Infliximab is a monoclonal antibody that targets TNF and is used to treat UC and CD [10]. This drug is one of the best drugs used to treat IBD patients for achieving mucosal healing [11]. Unfortunately, primary and secondary non-responders to this drug are increasing [12]. Multiple associated factors have been recognized to be responsible for increased clearance of this drug and, as a consequence, low serum levels of this drug. Low serum albumin level, high serum CRP, increased BMI, male sex have been studied [13][14][15]. Our knowledge is still limited about the factors influencing serum level of this drug. Recently an article had been published which had shown loss of infliximab in the stool have caused low serum infliximab level [16]. The aim of this study was to evaluate the fecal and blood levels of infliximab and the response to treatment of IBD patients after induction period.

Methods and Materials

This was a cross-sectional study conducted at the Imam Khomeini Hospital Complex (January to May 2021). This study was approved by the ethical committee of Tehran University Medical Sciences. Eligible patients were between 18 and 65 years, all contraindications of anti TNF drugs have been excluded. Exclusion criteria were active infection such as tuberculosis, hepatitis B and C, active malignancy, history of previous use of biologic drugs, cirrhosis or severe liver disease, multiple sclerosis, pancytopenia, history of lymphoma, history of autoimmune diseases and CHF with a history of recurrent decompensated heart failure. Not participating in other study, and the patient's willingness to participate in the study were considered. All CD patient had severe

disease or had CDAI more than 220 ,UC patient were non responsive to steroid or steroid dependent and had moderate to severe disease according to mayo score.

All patients who were eligible in our study and were candidate for anti-TNF therapy received 5 mg/kg given as an IV induction regimen at 0, 2, and; 6 weeks, followed by a maintenance regimen of 5 mg/kg IV every 8 weeks. At the end of second week (day 14), Patient's response to treatment with either CDAI or Mayo score, fecal levels of infliximab, serum CRP and albumin level were measured. At the end of 14th week, fecal levels of Infliximab, serum levels of Infliximab serum albumin and CRP level were assessed again.

The severity of the disease in Crohn's patients is determined by the Crohn's Disease Activity Index (CDAI) and in patients with ulcerative colitis by the Partial Mayo Score (before treatment and after 14 weeks). Response to treatment in Crohn's patients is CDAI 150. In patients with ulcerative colitis, the patient responds to treatment if they are asymptomatic or show a 3-point decrease according to the Partial Mayo Score.

SPSS version 26 was used to analyze all of the data. A Mann-Whitney U test was used to determine significance when the alpha level is less than 5% (P-value 0.05) compare the mean ranks (medians) of continuous parameters.

Result

A total of 28 patients (75% male and 25% female) were included into the study (14 patients with Ulcerative colitis and 14 patients with Crohn's disease). The mean age of the population was 34 ± 10. The descriptive statistics of the data are given in Table 1.

Table 1 - Descriptive Statistics

	Mean	Median	Percentile 25	Percentile 75
C-Reactive protein baseline	24.75	9.05	3.20	43.50
C-Reactive protein after 14 days	24	9	3	42
C-Reactive protein after 14 Weeks	19.47	13.30	4.20	30.55
Serum Infliximab After 14 weeks	3.90	1.56	.26	7.98
CDAI after 14 days	451.00	446.00	412.00	475.00
CDAI after 14 weeks	202.36	139.00	76.00	413.00
Partial MAYO score after 14 days	7.14	7.00	6.00	8.00
Partial MAYO score after 14 weeks	4.14	4.00	3.00	5.00
Fecal Infliximab After 14 days	15.72	1.69	.47	5.70
Fecal Infliximab After 14 weeks	7.16	.38	.10	5.70
Serum Albumin after 14 days	4.29	4.40	3.95	4.90
Serum Albumin after 14 weeks	4.07	4.10	3.70	4.60

The results of Mann-Whitney U test are provided in Table 2.

Table2 - The results of Mann-Whitney U test to compare variables according to clinical response				
	Clinical Response	N	Mean Rank	Sig
CDAI after 14 days	NOT response	5	5.50	P = 0.19
	Response	9	8.61	
CDAI after 14 weeks	NOT response	5	12.00	P = 0.001
	Response	9	5.00	
Partial MAYO score after 14 days	NOT response	4	7.88	P = 0.83
	Response	10	7.35	
Partial MAYO score after 14 weeks	NOT response	4	9.75	P = 0.24
	Response	10	6.60	
C-Reactive protein after 14 days	NOT response	9	18.61	P = 0.068
	Response	19	12.55	
C-Reactive protein after 14 weeks	NOT response	9	20.33	P = 0.009
	Response	19	11.74	
Serum Infliximab After 14 weeks	NOT response	9	8.72	P = 0.009
	Response	19	17.24	
Serum Albumin after 14 days	NOT response	9	14.39	P = 0.96
	Response	19	14.55	
Serum Albumin after 14 weeks	NOT response	9	11.39	P = 0.17
	Response	19	15.97	
Fecal Infliximab After 14 days	NOT response	9	12.61	P = 0.40
	Response	19	15.39	
Fecal Infliximab After 14 weeks	NOT response	9	14.56	P = 0.98
	Response	19	14.47	

The distribution of Serum Infliximab after 14 weeks was not the same across clinical response ($P < 0.05$). Also, the distributions of CDAI after 14 weeks and C-Reactive protein after 14 weeks were not same across clinical response ($P < 0.05$). Patients who response to the treatment with infliximab had significantly higher Serum Infliximab after 14 weeks and lower CRP after 14 weeks. All other parameters did not show statistically significant differences.

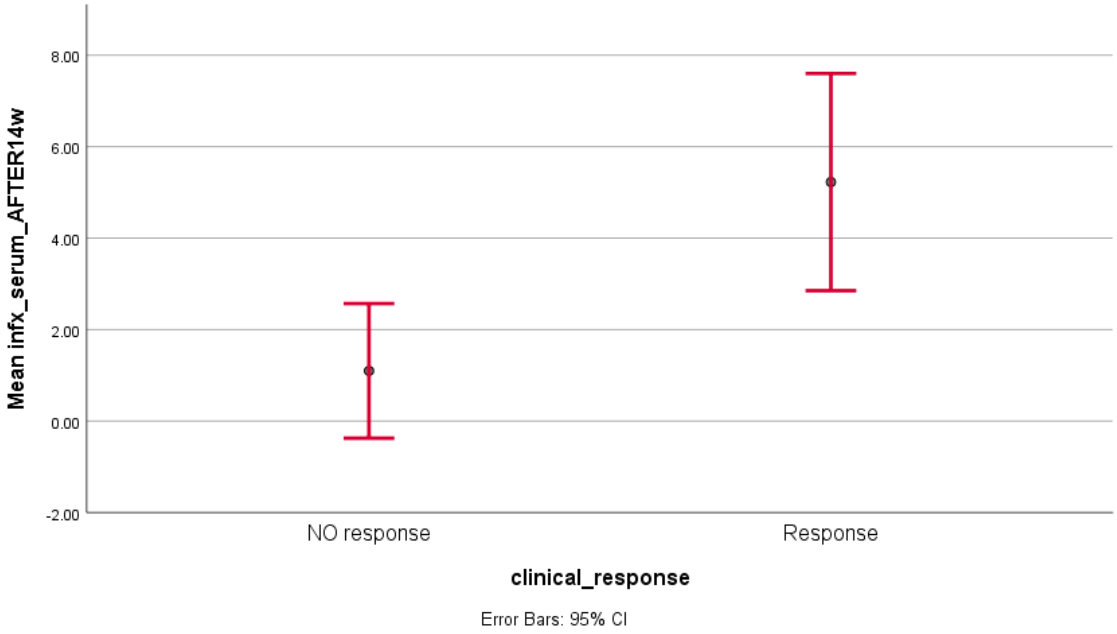

Figure 1 – Serum infliximab concentration in No response and Response groups.

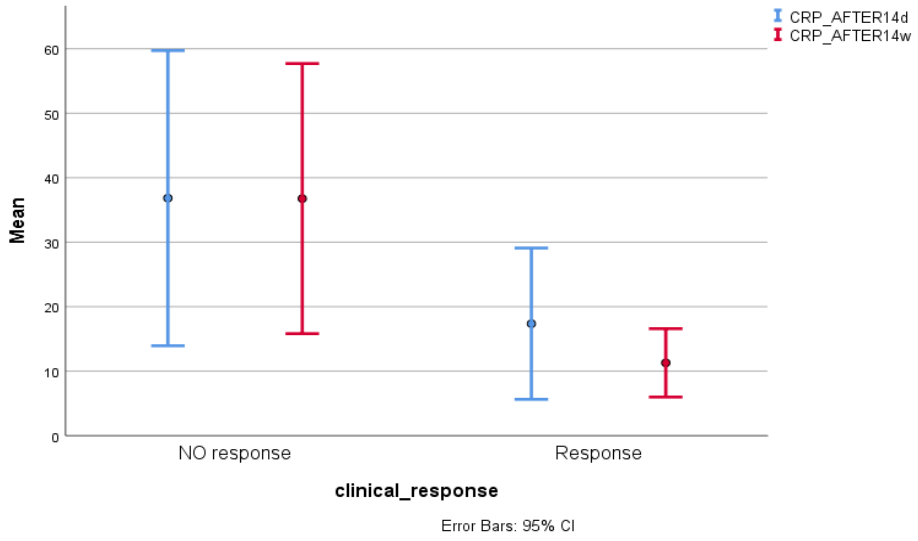

Figure 2 – CRP concentration at day 14 and week 14 in No response and Response groups.

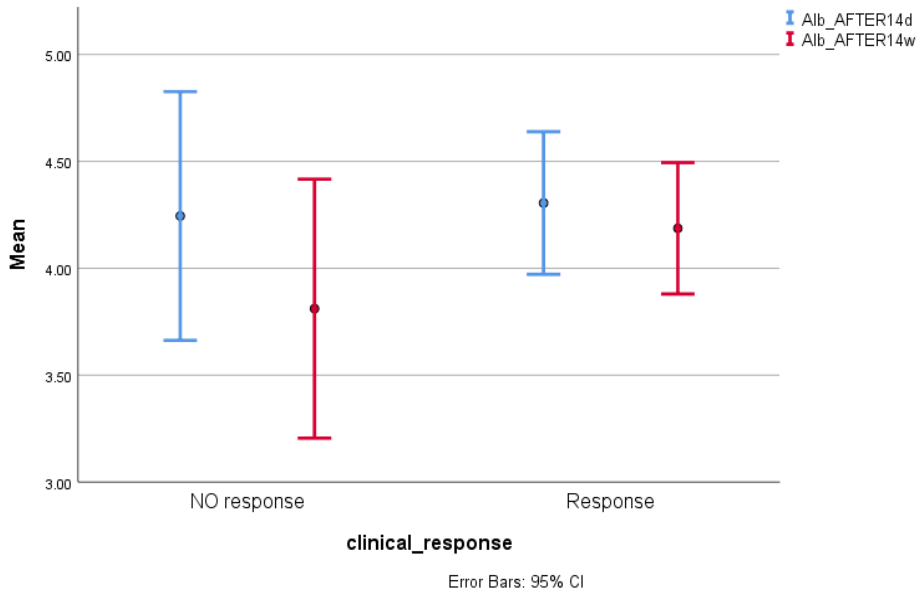

Figure 3 – Serum albumin concentration at day 14 and week 14 in No response and Response groups.

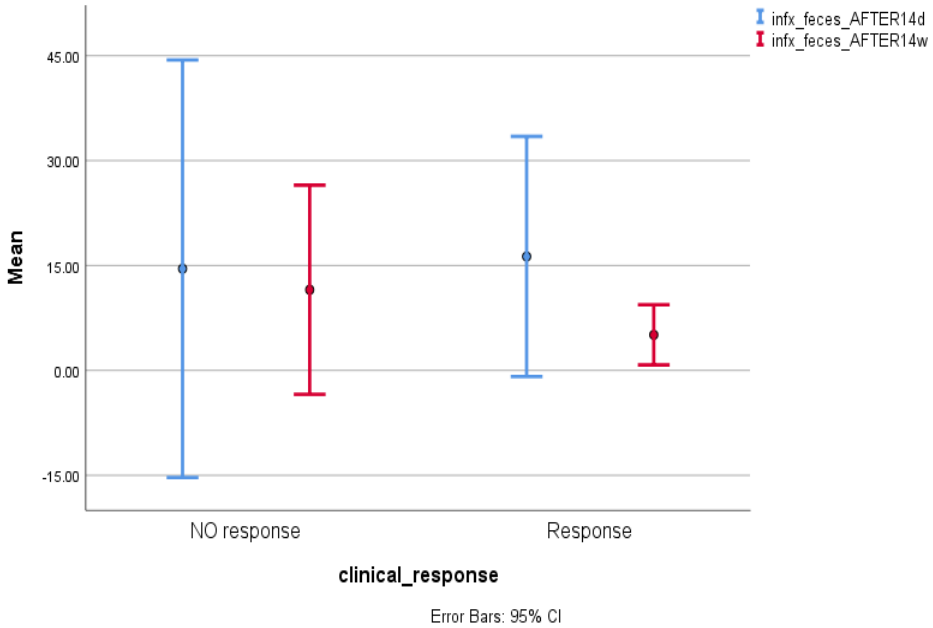

Figure 4 – Fecal infliximab concentration at day 14 and week 14 in No response and Response groups.

A Wilcoxon matched-pairs test was performed to evaluate the baseline CRP level with CRP day 14 and CRP week 14. The results showed that baseline CRP and CRP week 14 did not elicit a statistically significant change in the patients (Z = -1.093, p = 0.274). However, the difference between baseline CRP and CRP day 14 was statistically significant (Z = -3.425, p = 0.001).

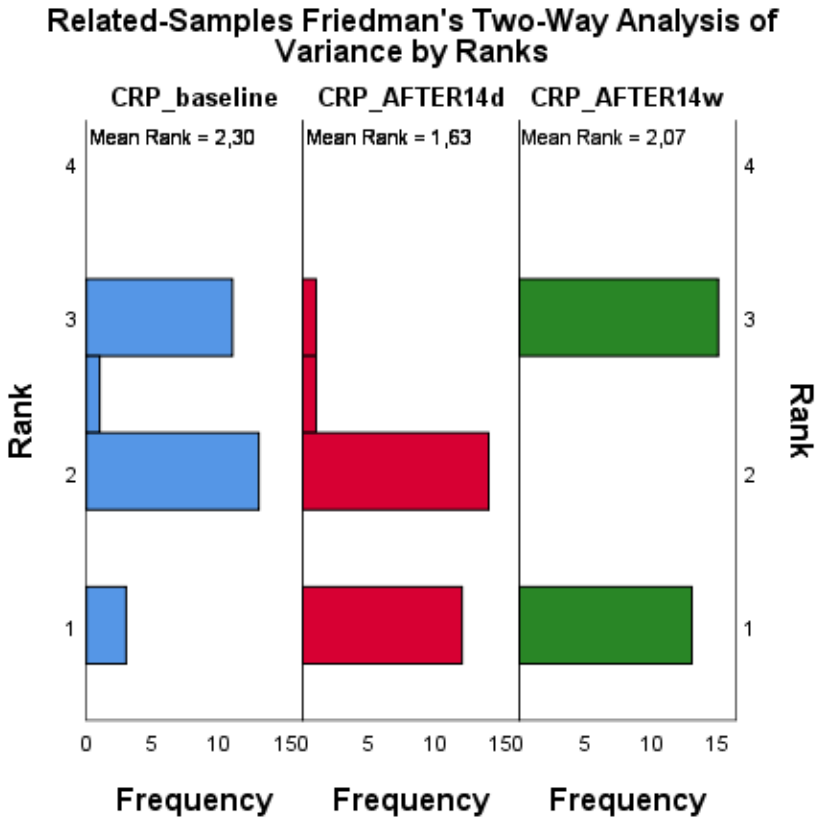

Figure 5 – Comparison of baseline CRP with CRP day 14 and CRP week14.

A Spearman's rank-order correlation was run to determine the relationship between 28 patients' serum infliximab level (at week 14) and C-reactive protein (on day 14 and also week 14). There was a strong, negative correlation between serum infliximab level (at week 14) and C-reactive protein level (at day 14), which was statistically significant [r = -0.549, p = 0.002]. Also, a strong and significant negative correlation between serum infliximab level (at week 14) and C-reactive protein level (at week 14) was found [r = -0.724, p = 0.0005]. Furthermore, fecal infliximab level

(at week 14) and C-reactive protein level (day 14) were negatively correlated significantly [r = -0.486, p = 0.009]. Serum albumin on day 14 was negatively correlated with CRP on day 14 [r = -0.618, p 0.0005]. Also, serum albumin week 14 and CRP week 14 were negatively correlated [r = -0.0485, p = 0.003]. Finally, serum albumin day 14 and week 14 were positively correlated [r = 0.763, p 0.0005], while CRP day 14 and CRP week 14 were positively correlated [r = 0.553, p = 0.002].

An ANCOVA was performed to examine the mean differences in Serum Infliximab level week 14 among two groups (UC and Crohn's) after adjusting for the Fecal Infliximab level day 14. The results indicated that the Serum Infliximab level week 14 did significantly differ among the two groups after controlling for the Fecal Infliximab concentration day 14, F (1, 25) = 4.566, p < 0.005. The model explained about 16.44% (93.775/570.389) variance in Serum Infliximab level week 14. Specifically, after adjusting for the Fecal Infliximab concentration day 14, UC patients had higher level of Serum Infliximab level at week 14 (3.853 ± 1.803) compared to the Crohn's disease patients.

A logistic regression (Table 3) was performed to ascertain the effects of age, CRP week 14, Fecal Infliximab level, and Serum Infliximab level on the likelihood that patient's response to the treatment. The logistic regression model was statistically significant, $\chi 2(4) = 19.38$, $p < 0.0005$. The model explained 69.8% (Nagelkerke R^2) of the variance in treatment response and correctly classified 78.6% of cases.

Table 3 – logistic model for predicting patients' response to treatments			
Variable	Odds ratio	CI 95%	P – value
CRP week 14	0.828	[0.708 – 0.968]	0.018
Fecal Infliximab level week 14	0.853	[0.738 – 0.989]	0.036
Overall model	35	-	0.010

The odds of patient's response to the treatment were same in males and females. Increased CRP (week 14) and Fecal Infliximab level (week 14) was associated with a reduction in the odds of treatment response.

A multiple regression was run to predict Serum Infliximab level (at week 14) from C-reactive protein day 14 and C-reactive protein week 14. These variables statistically significantly predicted Serum Infliximab level (at week 14), F (2, 25) = 7.456, p < .005, R^2 = 0.374. All two variables added statistically significantly to the prediction, p < 0.05.

Serum infliximab level at week 14 = 6.734 – 0.04 (CRP day 14) – 0.098 (CRP week 14)

Discussion

The introduction of anti-TNF drugs has revolutionized the treatment of autoimmune diseases, including IBD [17]. These medications are used for the treatment of moderate-to-severe diseases. Agents such as Infliximab, Adalimumab, Certolizumab pegol, and Golimumab are in this group [18]. Regarding the high expense of these drugs, patients' selection has become a matter of great importance for clinicians [19]. Recent studies suggest that there is a correlation between serum

drug concentration and clinical outcome [20][21][22]. Based on previous studies, multiple factors have been suggested to affect the serum trough level of these drugs, including the patient's sex, age, weight, serum albumin level, and serum CRP level. Our hypothesis was that patients with higher serum Infliximab levels and lower fecal Infliximab levels at the end of induction doses would have a higher response.

In our study 28 IBD patients, including 14 cases of CD and 14 cases of UC, with moderate to severe form of disease were treated with Infliximab. In order to evaluate the factors associated with patients' response we measured serum CRP level, as an acute phase reactant, and serum Albumin level, as a negative phase reactant. We also measured the serum infliximab level on day 14th and week 14th and the fecal infliximab level on week 14th. Disease activity was assessed by CDAI in CD patients and partial mayo score in UC patients. Crohn's disease patients have shown a significant decrease in CDAI in the response group. Moreover, patients in the response group had a higher serum infliximab level and lower serum CRP at week 14th. The presence of a high serum infliximab level at week 14 in the response group is strongly supportive of our hypothesis. In a study conducted by Elana A. Maser et al., there was an association between trough serum infliximab and clinical outcome after maintenance treatment for Crohn's disease [23]. Patients with a detectable trough of serum infliximab had higher clinical remission in comparison with patients in whom serum infliximab was undetectable. A detectable trough of serum infliximab was also associated with a lower CRP and a higher rate of endoscopic improvement. The results of the study of Ruben J Colman et al. also found similar results in children with Crohn's disease. They found that higher end of induction infliximab trough concentration is associated with lower fecal calprotectin [24]. In another study Xavier Roblin et al. tried to find the best noninvasive method to predict clinical relapse in infliximab treated patients with Crohn's disease. They suggested that a combination of trough level of infliximab>2µg/ml and fecal calprotectin>250µg/g of stool is a good model to predict loss of response in these patients [25]. A recent study conducted by Erwin Dreesen et al. shows that the combination of fecal concentration of calprotectin and trough concentration of infliximab can be a useful guide for dose adjustment and increase the chances for endoscopic response and remission [26]. These findings, aligned with our results, may suggest that higher levels of serum infliximab are associated with better clinical response.

However, we didn't find a significant decrease in fecal infliximab level at week 14th. Also, this latest finding is in contrast with our hypothesis, multiple factors may affect it, including errors in feces collection by the patients, one-sample feces collection, false positive results, and the limited numbers of patients in our study. The results of the study by Johnnan F. Brandse et al. are supportive of our hypothesis [16]. They found that patients who didn't have a good response had a higher fecal infliximab at week 2. As per pharmacokinetic facts, infliximab has a 92% bioavailability (intravenous). Its metabolism is done by the reticuloendothelial system. It is predicted that it will be nonspecifically metabolized into peptides and amino acids, which can then be re-used in the body for de novo protein synthesis or excreted by the renal system.

Because our sample size was small, the fecal concentration findings did not follow normal distribution.

Serum CRP levels have also demonstrated a significant correlation with other factors. After 14 weeks, there was a significant decrease in serum CRP levels in the response group. Patients who had a higher level of serum CRP at day 14th also had a lower serum albumin level at day 14th and a higher serum CRP level at week 14th. Considering CRP as an acute phase reactant, this data suggests that patients who were in a higher inflammatory state at the beginning of treatment couldn't achieve a proper response after the treatment. Another result that supports this conclusion is that patients with a higher level of serum CRP at day 14 had a lower level of serum infliximab at week 14 as well. In contrast, patients with higher serum CRP levels on day 14 had lower fecal infliximab levels on week 14. As a fact, patients with higher serum CRP levels at the beginning of the treatment have higher inflammation in their bowel mucosa. It could be suggested as more bowel inflammation, more infliximab is secreted in the feces of these patients in the first days of treatment. But after resolving inflammation in first few weeks of treatment the fecal infliximab secretion become steady and does not influence treatment response.

Since we don't have a fecal infliximab level on first days of treatment, we may suggest that measuring this factor could help us better understand this correlation.

The result of ANCOVA may suggest that when Fecal Infliximab concentration on Day 14 is constant, UC patients have higher Infliximab serum concentration in comparison to the CD group. As previously mentioned, higher Infliximab serum concentration is associated with better clinical response. It seems that UC patients may respond more properly to the treatment. However, it is a primary finding and more clinical research is needed to confirm it. Finally, we conducted multiple regression to calculate the serum infliximab level at week 14 by CRP. This formula may come in handy when infliximab measurement is impossible. This formula is also an early finding and more trials are needed to confirm it.

Conclusion

In order to personalize the treatment of IBD patients with infliximab, we need to first select those who will benefit most from this drug and then monitor them during treatment. Measurement of serum infliximab is widely recommended now and can be used for therapeutic monitoring of patients. The presence of higher serum infliximab is associated with a higher clinical response. In spite of early fecal loss of infliximab, which is an indicator of low serum infliximab level, late fecal infliximab is not a good marker for response since the inflammation is reduced. We also found out that UC patients had a better response in comparison to CD patients. This recent finding may be due to differences in inflammatory states between these diseases, but surely it needs to be evaluated in future studies.

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