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SELENIUM SUPPLEMENTATION MAY DECREASE THE RATE OF INFLIXIMAB ADRS IN IBD PATIENTS

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ABSTRACT

Background: Crohn's disease (CD) and ulcerative colitis (UC) represent two distinct inflammatory bowel diseases (IBD), yet they share lots of similarities, both are idiopathic, progressive autoimmune diseases of unknown etiology, of a remitting and a reviving pattern with increasing incidence and prevalence all over the world. The introduction of infliximab in the treatment of both CD and UC patients had dramatically improves the disease activity and positively affects the quality of life. Selenium supplementation as antioxidant affect the inflamed bowel by changing the oxidative stress in the GIT environment and in this regard the combination of infliximab and selenium supplementation was studied to look for the effect of selenium supplementation on ADRs profile in IBD patients treated with infliximab. **Patients and methods:** A prospective interventional trial was conducted in the Gastroenterology and Hepatology specialized hospital, a tertiary center in Medical City Directorate in Baghdad, Iraq and patients were randomly assigned into 2 groups ,one received infliximab and the other group received infliximab plus selenium supplementation and patients were followed

up for 3 consecutive visits every 8 weeks for 24 weeks after the baseline visit. Data were collected at each visit regarding ADRs in both groups and assessments were made accordingly. **Results:** Forty six patients were enrolled in this study divided into two groups each with twenty three patients, one group of patients were treated with infliximab and the other with infliximab plus selenium supplementation. The reported ADRs were infection (28.3%), anemia (6.5%) and skin reactions (6.5%). There was a non significant difference in the ADRs profile between the infliximab and selenium group, in spite of that anemia was not reported in the selenium group and there was a decrease in the total reported ADRs in the selenium group by (13%) when compared to infliximab group. **Conclusion:** Selenium may have a role in decreasing the number of reported ADRs when supplemented to IBD patients receiving infliximab

KEYWORDS: (ADRs) adverse drug reactions, (CD) Crohn's disease, (IBD) inflammatory bowel disease, (IFX) infliximab, (TNF) tumor necrosis factor,(UC) ulcerative colitis.

OBJECTIVES OF THE STUDY

1. to investigate the ADRs profile in IBD patients treated with infliximab as compared to patients receiving selenium supplementation in addition to infliximab.
2. find out the effect of selenium supplementation on ADRs profile in those patients.

INTRODUCTION

Both Crohn's disease and ulcerative colitis as Inflammatory bowel disease affecting the GIT causing abdominal pain, diarrhea and bloody stool and may even lead to patient disability[1],therefore, the early introduction of anti-tumor necrosis factor(anti-TNF) agents such as infliximab is applied nowadays to control the progression of the disease.[2,3] Nevertheless, Infliximab(IFX) is a chimeric IgG1 monoclonal antibody to (TNF) that is composed of 75% human and 25% mouse sequences[4] and because of that there are major limitations associated with IFX; patients can develop tuberculosis soon after the initiation of treatment, which is often due to TNF-α neutralization.[5] Delayed hypersensitivity reactions are also frequently observed following administration of IFX. Its efficacy is frequently lost because of immunogenicity, and at 1 year, only 25% of patients were responding to infliximab and off corticosteroids.[5] Adverse side effects include infusion reactions, serum sickness-like reactions, deterioration of congestive heart failure, and central nervous system (CNS) demyelinating disease[6] and anemia. It can be responsible for emergence of serious

infections, including bacterial sepsis, and invasive fungal and other opportunistic infections.[7]

The use of selenium as an antioxidant in IBD has been tried previously without conclusive results. Selenium is an essential component of the catalytic part of glutathione peroxidase enzyme. Selenium deficiency is directly related with complete decrease of glutathione peroxidase activity in several tissues, which leads to an increase of oxidative stress. In conditions related with oxidative stress and inflammatory reactions, high selenium efficiency has been shown to have a positive effect as antioxidant factor.[8] A recent review regarding selenium and selenoprotien showed that selenium status affects gene expression, signaling pathways, and cellular functions in the small and large intestine as well as the gut microbiome composition. This data, specially from animal experiments, give hope that adequate dietary selenium supply may counteract chronic intestinal inflammation in humans.[9] In humans, selenium deficiency is commonly observed in patients with Crohn's disease; a study found that the low serum concentrations of zinc, copper and selenium in patients with CD are "probably a result of inadequate intake, reduced absorption, increased intestinal loss due to impairment of the absorption as a result of inflammatory process and may contribute to the continuation of inflammatory process of IBD".[10] Selenium toxicity in humans is not known to be a significant problem except in acute overdose cases. Selenium is not classified as a human teratogen.[11] Finally Recommended daily allowance for selenium is approximately 55 g/day and selenium can be incorporated into the body by ingesting foods such as carrots, cabbage, garlic, mushrooms, cheese, meats, and grains and selenium-containing supplements.[12]

PATIENTS AND METHODS

This was an interventional clinical trial conducted in the Gastroenterology and Hepatology specialized hospital, a tertiary center in Medical City Directorate in Baghdad. Collection of data was started in April 2014 and ended in February 2015. Patients were randomly assigned into two groups; the first group received infliximab (Remicade, Janseen biotech) at a dose of 5 mg per kilogram of body weight, this group consist of both CD and UC patients. The second group received selenium supplementation 200 mcg per day(Jamieson) plus intravenous infusions of infliximab (Remicade, Janseen biotech) at a dose of 5 mg per kilogram of body weight, at the same dosing schedule and also consisting of both diseases

patients. A bottle of 100 tables was supplied to each patient in the selenium group at 8 weeks intervals.

Patients were enrolled in this study if : age between 18-60 years, previously diagnosed UC or CD out patients (using endoscopic, histological and clinical criteria), scheduled to receive at least 3 doses of infliximab infusion and had received at least 3 doses of infliximab, with or without concomitant treatment (prednisolone and/or azathioprine or mesalamine), on stable medication for more than 4 weeks, had no reported ADRs that may be attributed to IFX at the time of enrollment and have the willingness to participate in the study. Patients were excluded if : age below 18 years, with the short bowel syndrome, an ostomy (fecal diversion), a recent history of abdominal surgery (within the previous 6 months), a positive chest radiograph or tuberculin skin test, active infection with hepatitis B or C. On no supplementations containing selenium or vitamin A, or other antioxidants.-with a known hepatic dysfunction and /or renal insufficiency, unwillingness to participate at any time point.

Patients were followed up for four visits for 24 weeks every 8 weeks and the first visit was considered as the baseline visit before any intervention was made. Data on disease extent and duration were extracted from hospital records, Co morbidities, duration of symptoms, medication history, previous operation history, previous infliximab therapy and number of infliximab exposures was also recorded. Patients were hospitalized for at least 8 hours at each visit in order to receive infliximab treatment and the following were assessed for all the patients at each visit; Measurement of body weight in kilogram (Kg). Diseases activity for both CD and UC. Laboratory tests measurements of total blood count, was made before each dose as part of their routine investigation. Questioning about nocturnal symptoms, features of extraintestinal manifestations involving the mouth, skin, eye, or joints, episodes of perianal abscess, or anal fissure was made. General examination includes general wellbeing, pulse rate, blood pressure, temperature, abdominal tenderness or distension, palpable masses, perianal and oral inspection was also made. Adverse events and concomitant medications were recorded at each study visit.

STATISTICAL ANALYSIS

Analysis of data was carried out using the available statistical package of SPSS-17. The data obtained are expressed as means ± SD. A significant P- value was considered when it is less than 0.05 and it was considered highly significant when P-value less than or equal to 0.01

Descriptive statistics were used to summarize differences in demographic and baseline characteristics among study groups. Differences between the two groups assessed using unpaired t- test.

ETHICAL APPROVAL

Ethical approval for the study was obtained from the ethical committee in ministry of health and college of pharmacy, Baghdad university ethical committee. written consent preceded data collection from each patient after clarifying the purpose of the study and assuring confidentiality and anonymity.

RESULTS

The study started with fifty – four (54) IBD patients but only forty –six(46) completed the follow up for 24 weeks, eight (8) patients went out of the study for different reasons; 2 patients had serious ADRs (fatty liver and seizure),1 patients had to go through coloctomy,2 patients quit the study after the 1st and 2ed visit and 3 patients quite selenium supplementation at any points of the study.

Fourteen(14) ulcerative colitis patient and nine (9) Crohn's disease patients with a total of twenty –three (23) patients received selenium supplementation plus infliximab during the study period and this group will be referred to as the selenium group, while in the infliximab group twelve(12) ulcerative colitis and eleven (11) Crohn's disease patients with a total of twenty three (23) patients were included.

The mean age of the total studied group was 33.54 ± 9.56 years. and there were a non significant difference between the two study groups (IFX and selenium group) regarding, sex, age, disease duration and previous abdominal operation.

Significant difference was observed regarding the different sites of ulcerative colitis between the two studied groups, Proctitis seemed to have a significant p- value (P-Value = 0.05), while left sided colitis show a non significant results as was the pancolitis as shown in **(table 1)**.

Crohn's disease location L1 results were not significant when statistically tested, L2 was also not significant and L3 was the same. Regarding the behavior of Crohn's disease, the test results show that B1 had significant difference (p value = 0.05) , however, B2 shows a non significant results **(table 1)**.

Disease activity moderate sub scoring represent the most predominant one in the infliximab group (43.5%), while the mild sub scores was the predominant in the selenium group (56.2%).There was a non significant differences among the studied disease sub scores between the two groups **(table 1)**.

The presence of other medications besides IFX and selenium was also tested statistically for both study groups and all show a non significant results as shown in **(table 1)**.

Mean duration treatment for both group was 20.4 months in the infliximab group and 21.6 months in the selenium group, show a non significant differences in both groups **(table 1).**

Table 1: Baseline clinical and lab. parameters of IBD patients included in the study

	Infliximab group	**selenium group**	**Total**	**P value**
Number of patients	23	23	46	NS†
Male % (no)	47.8 % (11)	52.2% (12)	50% (23)	NS
Age year, mean± SD	30.65 ± 6.09	36.43 ±11.52	33.54 ± 9.56	NS
Disease duration years, mean ± SD	5.826 ± 3.78	5.522 ± 3.95	5.67 ± 3.8	NS
Previous abdominal surgery (%), no	8.7% (2)	13% (3)	10.8 % (5)	NS
Disease location UC % , no. *				
E1 Proctitis	33.4% (4/12)	71.4% (10/14)	54% (14)	0.05
E2 Left sided	41.6% (5/12)	7.2 % (1/14)	23% (6)	NS
E3 pancolitis	25% (3/12)	21.4% (3/14)	23% (6)	NS
Disease location CD %, no.*				
L1 ileum	45.4% (5/11)	33.3% (3/9)	40 % (8)	NS
L2 large bowel	45.4% (5/11)	55.5% (5/9)	50% (10)	NS
L3 ileum and colon	9.2% (1/11)	11.2 %(1/9)	10% (2)	NS
Disease behavior CD %, no. *				
B1 no stricture	81.8 % (9)	66.7 % (6)	75 % (15)	0.05
B2 causing stricture	18.2 % (2)	33.3 % (3)	25 % (5)	NS
B3 causing perforation	0	0	0	NS
Disease activity score IBD % , no.				
Remission (inactive)	8.3 % (1)	8.7% (2)	6.5 % (3)	NS
Mild	39.1 % (9)	56.2% (13)	47.8 % (22)	NS
Moderate	43.5 % (10)	30.4 % (7)	36.9 % (17)	NS
Severe	8.3 % (3)	8.3 % (1)	8.8 % (4)	NS
Concomitant medication % ,no. ₸				
AZA alone	52.2 % (12)	34.8 % (8)	43.5 % (20)	NS
Prednisolone alone	None	4.3 % (1)	2.2 % (1)	NS
Mesalazine alone	8.7 % (2)	4.3 % (1)	6.5 % (3)	NS
AZA plus Prednisolone	13 % (3)	13% (3)	13% (6)	NS
AZA plus Mesalazine	21. 8 % (5)	26 % (6)	23.9 % (11)	NS

AZA, Mesalazine and prednisolone	None	13% (3)	6.5 % (3)	NS
Multivitamins	43.5 % (10)	26 % (6)	34.8 % (16)	NS
No medication	4.3% (1)	0	2.2 % (1)	NS
Duration of IFX treatment mean	20.4 months	21.6 months	21 months	NS

** the number of ulcerative colitis and Crohn's disease patients were calculated as per 26 ,20 patient respectively.† NS = non significant, ‡ Total may not equal to 100 since patients might receive multivitamins besides other medication.*

There was a non significant difference between the 2 study groups regarding the presence of ADRs that was attributed to infliximab treatment, where ADR occurs in 47.8% (11/23) of the IFX group and in 34.8% (8/23) of the selenium group. ADR types felt into three categories infection, anemia and skin reactions .In addition to that, anemia was detected in the infliximab group only as shown in **(table 2)**. The total IFX group ADRs was 47.8% compared to 34.8% in the selenium group. As a consequence of ADRs, a temporary delaying of infliximab dose due to ADRs was required in 30.5% (7/23) of IFX group compared to 26% (6/23) of selenium group. There was no detected ADRs that could be related to selenium supplementation.

Table 2: ADRs profile during the study period

ADR type	IFX group	Selenium group	Total	P –value
Infection	26% (6/23)	30.4% (7/23)	28.3% (13/46)	NS
Anemia	13% (3/23)	0	6.5 % (3/46)	NS
Skin reactions	8.8% (2/23)	4.4% (1/23)	6.5% (3/46)	NS
Total	47.8% (11/23)	34.8% (8/23)	41.3% (19/46)	

DISCUSSION

The mean age of the total studied group was 33.54 ± 9.56 years ,the age range between 18 and 54 years. Both sexes were equally distributed in the two groups (IFX and selenium), this may reflect the wide picture that had been seen generally in many studies.[13, 14]

Regarding UC disease location in this study, proctitis shows 54% while left sided colitis 23% and pancolitis 23% and it seems to be in the same order that had been found in other studies.[15,16]

In the current studied CD patients, disease located in the large bowel (L2) was 50%, disease isolated to ileum (L1) 40% and 10% for disease affecting ileum and colon compared to the disease location that was reported in European studies where all sites were equally affected[17], and in Asian were the ileum and colon was the most affected segments.[18] The

behavior of CD in our studied CD patients, was as follows; 75% (B1) as inflammatory,25% (B2) causing strictures and no perforation was reported compared to other studies where the same order of behaviour was noticed.[19, 20]

It is well known that TNF- antagonists have improved the care of CD and UC patients but may lead to primary and secondary therapy failure and increased risk of serious infection.[1, 21] This study showed a total percentage of 41.3% of ADRs detected during the study period. ADRs are routinely detected in patients receiving IFX infusion.[22] Comparing the result of ADRs of this study with a recent study in 2014 that followed the ADRs profile of IFX patients for 2 years, skin rash and eruption were seen in (6%) of patients, infection and anemia were not reported, with a total adverse events of 28% (6) compared to (28.3% , 6.5%, 6,5%) for infection, anemia and skin reaction in the current study.

All ADRs cases have been reported in patients on concomitant therapy with immunosuppressive agents and the same notion was found in other previous study (7). Thus there is increasing interest in attempting to withdraw immunosuppressive agents at a year in order to reduce the risk of developing some of these serious complications of treatment.[23] On the other hand, the development of antibodies against infliximab is frequently found and is associated with reduced efficacy and increased numbers of infusion reactions. The concomitant use of immunosuppressants has been shown to reduce the incidence of antibody formation[23] therefore continuous patient monitoring is crucial. Finally, the mortality rates and serious infections in IBD patients treated with IFX was studied and found to be similar to non – IFX treated patients, but there was an increased risk for serious infections that partly due to disease severity and prednisolone concomitant use[22] and in this study the increased number of ADRs was found in the IFX treated group which show a more severe disease activity when compared to the selenium group.

In this study although ADRs were statistically not significant when comparing IFX and selenium groups, there was a total difference of 13% less ADRs in the selenium group, and this could be attributed to the fact that selenium act to decrease the oxidative stress in IBD patients[8,24] and this may affect the rate of ADRs. Additionally, one study found that there is an impaired erythrocyte antioxidant defenses in active IBD and a down regulation of glutathione peroxidase 1(GPX1) caused by anemia[25] thus addition of selenium may have contributed to an increase in the activity of GPX1 and affect the rate of anemia detection and that can explain why anemia was not detected in the selenium group compared to 6.5% in

the IFX group. Infection is one of the most reported ADRs during IFX therapy[26], and in this study, the incidence of infection in both groups were very close to each other (table 2). Finally up to our knowledge, this trial is the first to study the effect of selenium supplementation on ADRs profile of IFX in IBD patients and hope to be a base for further reproductive studies.

CONCLUSION

The reported ADRs in this study were infection (28.3%) anemia(6.5%) and skin reactions(6.5%). Selenium supplemented group showed a non significant decrease in the number of reported ADRs by 13% when added to infliximab treated IBD patients. Furthermore, no anemia was reported in this group.

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