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ORIGINAL ARTICLE

Immunomodulatory Effects of Treatment on Inflammatory Markers and Outcomes in Crohn's Disease

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ABSTRACT

Background: *Crohn's disease is a long-term inflammatory condition affecting the bowel. Monitoring inflammation with markers like C-reactive protein and white blood cell counts is essential for guiding clinical decisions and managing disease progression.* ***Objectives:*** *to examine, from an immunological point of view, how different treatment strategies influence systemic inflammatory markers and key clinical complications such as anemia and rectal bleeding in patients with Crohn's disease.* ***Methodology:*** *A cross-sectional study was conducted at the Gastroenterology Unit of Al-Hakeem Hospital in Najaf, Iraq. 108 confirmed Crohn's disease patients were enrolled in this study. Patients were classified according to their primary treatment regimen at the time of assessment: immunosuppressants, biological therapies, corticosteroids, or amino-salicylates. All participants had been on their respective treatments for at least three months before data collection. Serum C-reactive protein and white blood cell counts were measured using standard laboratory techniques. Statistical comparisons among groups were performed using one-way ANOVA.* ***Results:*** *The results showed that 46(42.6%) of patients presented with rectal bleeding, while the remaining 62(57.3%) did not. Also, 44(40.7%) were anemic, and half of them, 22 (50%), suffered from rectal bleeding. The mean CRP level was 44.50±16.220, and the mean of WBC was 17500±5561.8. The distribution of patients according to various regimes of treatment was 52 patients (48.1%) treated with immunosuppressant drugs, 22(20.4%) with biological medications, 20(18.5%) with steroids, and 14(13%) with Amino-salicylates.* ***Conclusion:*** *Monitoring inflammatory markers helps assess treatment response. Amino-salicylates may not be adequate for moderate to severe cases, highlighting the need for tailored treatment approaches.*

INTRODUCTION

Crohn's disease (CD) is a chronic, relapsing inflammatory bowel disease (IBD) that can affect any part of the gastrointestinal tract, most commonly the terminal ileum and colon. It typically begins in early adulthood and is characterized by periods of remission and relapse, with symptoms that include abdominal pain, chronic diarrhea, fatigue, anemia, and weight loss. Although the etiology of Crohn's disease is complex and multifactorial, the most widely accepted hypothesis supports CD as an immune-mediated condition in genetically susceptible individuals, three main factors (genetics, gut immune response, and the microbiota) are influenced by the individual's environmental exposures or triggers to engage different sub-mechanisms giving rise to Crohn's disease [1-3].

Crohn's disease management targets are to lower inflammation, achieve and maintain remission, minimize complications, and improve patient quality. Therapeutic options include immunosuppressants like methotrexate and azathioprine, corticosteroids, 5-aminosalicylic acid (5-ASA) compounds, and the target for biologic agents is the interleukin or tumor necrosis factor-alpha (TNF-α) pathways [4-6]. Still, no single form of therapy has been effective, and every case of a patient differs in how much they respond to the treatment.

In clinical practice, tracking inflammatory markers is critical in evaluating disease activity and aiding in treatment selection. One such indicator is C-reactive protein (CRP), which is widely accepted as a laboratory measure of inflammation for patients suffering from inflammatory bowel disease (IBD). As a part of an acute phase response, CRP is synthesized in the liver as a result of interleukin-6 and thus provides an indicator of inflammatory activity within the body [7]. CRP levels correlate well with the degree of disease actively observed during endoscopy, including the clinical activity of Crohn's disease and its evaluation. Similarly, white blood cell (WBC) count is also essential as it

indicates the level of immune system activation and inflammation occurring within the body [8].

Despite the understanding of these markers, methodologies studied in practice have not deeply investigated their response to various treatment approaches. This research aims to identify the impact of different treatment plans on patients with Crohn's disease, scrutinizing particularly CRP and WBC values, and correlating these inflammatory markers with the clinical manifestations of anemia and rectal bleeding.

METHODOLOGY

This cross-sectional study was carried out between January and November 2024. Peripheral blood samples were collected from 108 patients with Crohn's disease who were attending the Gastroenterology Unit at Al-Hakeem Hospital in Najaf, Iraq. The study included both male and female patients, aged 18 to 59 years, all of whom had a confirmed diagnosis of Crohn's disease based on endoscopic, histological, and radiological findings.

Written informed consent was obtained from all patients before blood sample collection. At the time of sample collection, patients were grouped according to their primary treatment type: immunosuppressants, biological therapies, corticosteroids, or amino-salicylates. Importantly, all participants had been receiving their respective treatments for at least three months before data collection.

Serum C-reactive protein (CRP) levels and white blood cell (WBC) counts were measured using standard laboratory methods. In addition, clinical data, including the presence of anemia and rectal bleeding, were assessed.

Serum C-reactive protein (CRP) levels were measured at the hospital laboratory using a C-Reactive Protein IV (Cobas c311 analyzer, Roche, Germany), while white blood cell (WBC) counts were determined with standard automated hematology analyzers. Clinical data were also collected, including whether the patient had anemia or rectal bleeding. Anemia was defined using World Health Organization (WHO) criteria as hemoglobin levels below 13 g/dL in men and below 12 g/dL in women. Rectal bleeding was recorded based on the patient's report and the physician's assessment during clinic visits.

Statistical analysis

Statistical analysis was performed using SPSS version 25.0. Descriptive statistics (means, standard deviations, frequencies) were calculated for all variables. Comparative analysis of CRP and WBC levels across treatment groups was conducted using one-way ANOVA, with a p-value <0.05 considered statistically significant.

RESULTS

The current study consists of 108 patients with Crohn's disease (CD); 68 (63%) females and 40 (37%) males, the mean age is 34.56 ±10.35 with a minimum of 18 years and a maximum age of 59 years. Regarding clinical features, rectal bleeding was reported in 42.6% of cases, while anemia was observed in 40.7% of patients. The most commonly used treatment modality was immunosuppressants (48.1%), followed by biological agents (20.4%), corticosteroids (18.5%), and amino-salicylates (13%); these results are illustrated in table (1).

Table 1: Demographic, Clinical, and Treatment Characteristics of Crohn's Disease Patients (N = 108)

Characters	Patients no (%)
Age (years)	
Mean ±SD	34.56 ±10.35
Range	18-59
Sex	
Male	40 (37%)
Female	68 (63%)
Rectal bleeding	
present	46(42.6%)
Absent	62(57.3%)
Anemia	
present	44(40.7%)
Absent	64(59%)
Treatment regimens	
Immuno-suppressants	52(48.1%)
Biological treatment	22(20.4%)
Steroid	20(18.5%)
Amino-salicylates	14(13%)

As shown in Table 2, the mean overall white blood cell (WBC) count among the 108 Crohn's disease patients under analysis was 17,500 ± 5,535.78 cells/µL. Steroid-treated patients had the lowest mean WBC count (15,800 ± 4,420.05), while amino-salicylate-treated patients had the highest mean WBC count (21,000 ± 4,076.20). WBC levels in patients receiving biological treatments and immunosuppressants were moderate (17,384.62±5,559.50 and 17,090.91 ± 6,480.07, respectively). The results fell short of the traditional criterion ($p = 0.052$) even though the variations in WBC count across treatment groups were close to statistical significance.

Table 2: White Blood Cell Count (WBC) Levels in Crohn's Disease Patients According to Treatment Type

Treatment	WBC			
	N (%)	Mean	Std. Deviation	P value
Immuno-suppressants	52 (48.1%)	17384.62	5559.496	0.052
Biological treatment	22 (20.4%)	17090.91	6480.073	
Steroid	20 (18.5%)	15800.00	4420.050	
Amino-salicylates	14 (13%)	21000.00	4076.197	
Total	108 (100%)	17500.00	5535.780	

Table 3:C-Reactive Protein (CRP) Levels Among Patients with Crohn's Disease According to Treatment Types

Treatment	CRP			
	N (%)	Mean	Std. Deviation	P value
Immuno-suppressants	52 (48.1%)	41.27	17.288	0.003
Biological treatment	22 (20.4%)	45.73	14.974	
Steroid	20 (18.5%)	41.80	4.830	
Amino-salicylates	14 (13%)	58.43	17.662	
Total	108 (100%)	44.50	16.144	

C-reactive protein (CRP) levels among Crohn's disease patients across different treatment modalities were assessed in Table 3. The mean CRP level in the study population of 108 Crohn's disease patients was 44.50 ± 16.14 mg/L. The greatest mean CRP values were seen in patients treated with amino-salicylates (58.43 ± 17.66 mg/L), followed by those treated with immunosuppressants (41.27 ± 17.29 mg/L), steroids (41.80 ± 4.83 mg/L), and biological agents (45.73 ± 14.97 mg/L). The statistically significant difference in CRP readings between treatment groups (P = 0.003) indicates that the therapy used can affect how well inflammation is controlled.

A cross-tabulation analysis was conducted to explore the association between treatment type and the presence of rectal bleeding in 108 Crohn's disease patients, as shown in Table 4. Among those with rectal bleeding (n = 46), the majority (65.2%) were receiving immunosuppressants, followed by steroids (26.1%), while biological treatments (4.3%) and amino-salicylates (4.3%) were infrequently used in this subgroup. The distribution of treatment type differed significantly between patients with and without rectal bleeding (P = 0.001), suggesting a potential relationship between therapeutic class and control of mucosal symptoms.

Table 4: Association Between Treatment Type and Rectal Bleeding in Crohn's Disease Patients

			Rectal bleeding		Total	P value
			PRESENT	ABSCENT		
Treatment	Immuno-suppressants	Count	30	22	52	0.001
		% within rectal bleeding	65.2%	35.5%	48.1%	
	Biological treatment	Count	2	20	22	
		% within rectal bleeding	4.3%	32.3%	20.4%	
	Steroid	Count	12	8	20	
		% within rectal bleeding	26.1%	12.9%	18.5%	
	Amino-salicylates	Count	2	12	14	
		% within rectal bleeding	4.3%	19.4%	13.0%	
Total		Count	46	62	108	
		% within rectal bleeding	100.0%	100.0%	100.0%	

The association between strategies for treatment and anemia in individuals with Crohn's disease (CD) was evaluated using a cross-tabulation analysis. As shown in Table 5, Immunosuppressants were administered to the majority of anemia patients (n = 44) (68.2%), followed by steroids (18.2%) and amino-salicylates (13.6%). Interestingly, none of the patients with anemia were receiving biologic therapy. The percentage of patients without anemia (n = 64) on biologics was 34.4%, immunosuppressants were 34.4%, steroids were 18.8%, and amino-salicylates were 12.5%. Treatment type and anemia status were statistically significantly correlated (P = 0.001).

Table 5: Relationship between Anemia and Treatment Approaches in Patients with Crohn's Disease

			Anemia		Total	P value
			Yes	No		
Treatment	**Immuno-suppressants**	Count	30	22	52	0.001
		% within anemia	68.2%	34.4%	48.1%	
	Biological treatment	Count	0	22	22	
		% within anemia	0.0%	34.4%	20.4%	
	Steroid	Count	8	12	20	
		% within anemia	18.2%	18.8%	18.5%	
	Amino-salicylates	Count	6	8	14	
		% within anemia	13.6%	12.5%	13.0%	
Total		Count	44	64	108	
		% within anemia	100.0%	100.0%	100.0%	

DISCUSSION

According to the findings of this study, Crohn's disease patients are aged between 18 and 59 years, which aligns with the known epidemiological trend of Crohn's disease affecting young adults, particularly those in their second to fourth decades of life. This finding is consistent with other studies, such as a study by Burisch etal[9], which documented a peak incidence of Crohn's disease between 20–40 years of age. Female predominance (63%) deviates from several worldwide studies that indicate either an equal distribution between the sexes or a male predominance. For example, a population-based study conducted in Canada revealed a virtually equal male-to-female ratio [10]. Possible explanations for the variation include geographical variations in the clinical signs of diseases or how Iraqi patients seek medical care, both of which may increase the likelihood of a diagnosis.

More than two-thirds (42.6%) of participants reported rectal bleeding. This corroborates a report that stated roughly 30% of patients with Crohn's disease suffer from rectal bleeding [11]. Perhaps the more advanced colonic involvement in our patients, or greater delay in diagnosis, accounts for the more severe mucosal damage. Moreover, 40.7% of our patients with Crohn's disease had anemia, which corresponds with other studies from developing countries where there is inadequate nutrition and delayed medical attention. As Gasche et al[12] pointed out, anemia associated with inflammatory bowel disease (IBD) tends to have an abundant origin, most frequently from chronic inflammation, iron deficit, or other drug complications. Our findings also support Bergamaschi et al[13], who posited that 30 to 45% of patients suffering from Crohn's disease are anemic.

The study group used immunosuppressive therapy the most, utilizing it in 48.1% of cases. This follows international recommendations, including the ECCO Guidelines[14], which also recommend immunomodulators like azathioprine or methotrexate as primary therapies for CD (Crohn's disease) of moderate to severe levels. On the other hand, biological therapies in this study were only used in 20.4% of cases, which is lower than some Western countries would expect.

This difference likely reflects the challenges of limited access and economic barriers faced in many low- and middle-income countries. For comparison, a U.S. study by Targownik et al[15] reported that nearly half of moderate-to-severe CD patients received biologic therapy. This contrast probably indicates the difficulties posed by access and financial constraints prevalent in many low and middle-income economies.

In this particular study, 18.5% of the patients were prescribed corticosteroids. This relatively low number indicates that there is an ongoing effort to decrease the use of steroids in chronic illness treatment due to long-term side effects. Also notable is the fact that the most infrequently prescribed treatment was amino-salicylates, which were prescribed in 13% of cases, which is sensible considering their limited utility in controlling Crohn's disease. Recent meta-analytic studies support these findings, including the one conducted by Chande et al [16] and AL-Huchaimi et al[17]. While the results still corroborate other studies, some discrepancies real-main striking, such as the greater percentage of women and the increased prevalence of immunosuppressants. These differences might be a result of the local healthcare system's available resources and the availability of specialized care services.

An indicator that is often used as a marker for a more general inflammatory process in diseases of Inflammatory Bowel disease, including Crohn's disease, is the leukocyte or WBC count. The findings of this study suggest that WBC counts were high in all treatment arms. Despite treatment, the inflammation is still active.

The greatest number of white blood cells was noted in people on an amino-salicylate therapy, on average, 21,000. It might be because this class of medications does not manage inflammation in Crohn's disease very well. This is in conjunction with a study[18], which underscored the limited effectiveness of amino-salicylate in inducing or sustaining remission in patients

with Crohn's disease. The increase of white blood cells in this group signals that the disease is likely poorly controlled, which raises the question of whether amino-salicylate mono-therapy is truly sufficient for moderate to severe disease.

Patients who received steroid therapy had the lowest mean white blood cell count of 15,800. However, as noted previously, corticosteroids are well known to exert a potent anti-inflammatory effect, which may unexpectedly elevate white blood cell count [19]. Thus, the lower WBC counts in this subgroup may indicate that inflammation was controlled, or they may suggest that patients were moderately advanced in treatment. These patients might also be offered less severe inflammation and subsequently denominated for steroid over biologic or immunosuppressive therapy.

Regarding our current results, the study group that received immunosuppressants and biologic agents had moderately elevated white blood cell counts (17,384 and 17,090, respectively), and their disease was partially controlled [20]. These findings nearly align with another study that reported that patients who received biologic therapy, especially anti-TNF agents, mostly show gradual improvements in inflammatory markers over time [21]. While the continuous elevation in WBC counts for those patients may reflect ongoing disease activity, a response to treatment, or it may be a stress response or an underlying infection unrelated to IBD. Thus, these observations highlight that the treatment's effectiveness in patients with Crohn's disease can vary, and changes in inflammatory lab markers like WBC counts may offer insight into this variability. Additionally, lower white blood cell counts in patients on steroids might indicate that they are either in the early stages of treatment or that the medication is successfully controlling inflammation. Conversely, patients treated with amino-salicylates who have higher white blood cell counts could be showing that their condition isn't being managed as effectively. These findings underscore the importance of personalizing treatment plans based on both the clinical signs and lab results for each patient.

C-reactive protein (CRP) serves as a key marker of inflammation in the body, especially in conditions such as inflammatory bowel disease (IBD), where it is particularly significant for Crohn's disease (CD). It plays a critical role in monitoring treatment efficacy and is closely related to disease activity. In this study, patients taking amino-salicylates exhibited the highest average CRP levels (58.43 mg/L), indicating that inflammation remains present or is not well-controlled. This finding aligns with results from Vermeire et al[22] and Muresan et al [23], which emphasize the limited effectiveness of 5-ASA drugs in managing Crohn's disease compared to other treatment options. These findings reinforce the growing consensus that amino-salicylates are generally insufficient as a sole treatment for moderate-to-severe CD and that their continued use may delay transitioning to more effective therapies.

Although biologics are generally more effective than traditional medications, not all patients achieve full biochemical remission. This is reflected in the relatively higher CRP levels (mean = 45.73 mg/L) observed in patients on biologic therapy, despite being on a more advanced treatment regimen. According to research by Na et al [24], a subset of patients using anti-TNF medications or other biologics may show primary non-response or partial response, require therapy adjustment, or switch to more successful regimens. This finding is in line with their findings.

Interestingly, CRP levels were lower in individuals on immunosuppressants and steroids (41.80 mg/L and 41.27 mg/L, respectively), which may indicate improved short-term inflammation suppression. Despite their quick anti-inflammatory benefits, corticosteroids are not recommended for long-term usage because of their serious adverse effects and inability to sustain remission. Similar to this, immunosuppressants such as azathioprine take weeks to achieve therapeutic activity, but they may eventually help reduce inflammation [25]. Significant therapeutic variations in reducing systemic inflammation are highlighted by the statistically significant difference in CRP levels between treatment groups (P 0.003). The consistently high CRP levels in the amino-salicylate group underscore the need to reassess treatment strategies for patients who aren't showing an adequate response, even though steroids and immunosuppressants are effectively controlling inflammation.

The recent study showed a significant correlation between the type of medication and the occurrence of rectal bleeding in Crohn's disease (CD) patients. Remarkably, 65.2% of patients with rectal bleeding were receiving immunosuppressant drugs. Although those drugs are broadly used to manage CD, some patients may continue to experience chronic mucosal symptoms like bleeding due to the overdue onset of action and varying individual responses[26]. In disparity, patients without rectal bleeding were more likely to be treated with biologics, mainly anti-TNF agents (32.3%), suggesting these treatments are more effective in promoting mucosal healing. This finding aligns with recent findings from the work of Fine[27], and clinical studies such as the CALM study, which confirmed that biologics are more effective than traditional immuno-modulators in reducing complications of disease, such as rectal bleeding. As well as, 26.1% of patients with rectal bleeding were on steroids, which agrees with the well-known capability of steroids to rapidly improve symptoms. However, despite their short-term benefits, their use is concerning in the long run due to side effects and lack of mucosal repair[28,29]. The high usage of steroids in this group may reflect inadequate disease control, indicating the need for treatment escalation or

steroid-refractory disease. Finally, although amino-salicylates are less effective in treating Crohn's disease, they were more commonly prescribed to patients without bleeding (19.4%) compared to those with bleeding (4.3%). Their preferred use in milder instances or colonic illness presentations may be the reason for this observation. Their function in CD is still unclear [30].

Our study shows a strong correlation between the type of treatment and anemia in people with Crohn's disease. The most common treatment for anemia was immunosuppressants (68.2%), which may be due to the medications are often used in patients with more aggressive disease phenotypes, where anemia is also more common because of gastrointestinal bleeding, chronic inflammation, and malabsorption[31,32].

Notably, nearly one-third (34.4%) of patients without anemia were on biologic therapy, whereas none of the anemia patients were. This result strongly implies that by encouraging mucosal healing and lowering systemic inflammation, biologic treatments, in particular, anti-TNF agents, may have protective effects against inflammation-associated anemia [33]. This is in line with new research showing that patients on biologics frequently exhibit notable improvements in hemoglobin levels and a decreased incidence of anemia as a result of improved disease activity management[34,35]. Steroid use was moderately common in both anemic (18.2%) and non-anemic (18.8%) patients with CD. While corticosteroids can rapidly decrease inflammation and may even improve anemia, their long-term effectiveness is restricted because they don't encourage mucosal healing or maintain remission[36]. Moreover, according to Al-Sharefi et al[37] and Saad et al[38], steroids are concomitant with side effects that can exacerbate nutritional deficiencies, actually contributing to anemia. On the other hand, the nonappearance of anemia in patients on biologic treatments suggests that early and targeted biologic therapy may help fewer complications like anemia in Crohn's disease. Therefore, these findings support the idea of earlier use of biologic therapy in patients with high-risk factors and moderate to severe CD disease, perhaps improving lasting outcomes.

CONCLUSION

According to the main findings in the present study, different types of treatments for Crohn's disease impact the immune system. Biologic therapies were found to better control systemic inflammation, leading to significantly lower counts of WBC and CRP levels, along with fewer complications such as anemia and rectal bleeding. In contrast, patients on immuno-suppressants and amino-salicylates showed high levels of these inflammatory markers and more clinical symptoms. So, the use of biologic therapy early in treatment is a more effective immunomodulatory choice and highlights the importance of tailoring treatment based on measures of inflammatory activity and how patients respond clinically.

Recommendations

Further prospective studies with longitudinal follow-up and additional biomarkers are recommended. Integrating patient-reported outcomes and quality of life assessments would provide a more comprehensive evaluation of treatment impact.

Assignment

All the participants provided informed consents for inclusion in the study and were assured that all the information provided would be used solely for this study and would be treated confidentially.

Ethical Approval Declaration

All procedures conducted in this study complied with the regulations of the relevant clinical research ethics committee and adhered to the ethical principles outlined in the World Medical Association's Declaration of Helsinki. Ethical approval was obtained from the Faculty of Medicine, University of Kufa Ethics Committee (Approval No. 112, dated 28 December 2023). Written informed consent was obtained from all patients.

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Competing interests

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