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Investigation of the effects of anti-TNF agents on hemoglobin levels in patients with inflammatory bowel disease

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Abstract

Inflammatory bowel disease (IBD) is characterized by many clinical features. Anemia is 1 of the most frequent complications and/or extraintestinal manifestations of IBD. There are conflicting data regarding the relationship between changes in hemoglobin levels and disease prevalence in IBD patients with and without antitumor necrosis factor (antiTNF) therapy. In our study, we aimed to investigate the long-term effect of antiTNF agents on anemia in IBD.

The records of IBD patients followed-up in our hospital between January 2011 and January 2021 were reviewed retrospectively. Demographic, clinical, endoscopic, radiological and medical treatment data of the patients were recorded. Complete blood count and laboratory markers of inflammation and disease activation, were recorded at the beginning and at the first year of treatment in all patients. The data of patients with and without antiTNF therapy were analyzed statistically. A total of 240 IBD patients who met the inclusion criteria were enrolled in the study. The number of patients with and without antiTNF therapy was 102 (42.5%) and 138 (57.5%), respectively. The change in all laboratory parameters between the beginning and the first year of treatment was statistically significant ($P < .001$) in all IBD patients with and without antiTNF therapy. The change in Hb level after 1 year of treatment was significantly different in patients with antiTNF therapy compared to those without therapy (3.00 ± 1.78 g/dL vs 1.19 ± 1.38 g/dL, $P < .001$). In the multiple regression analysis, male gender, antiTNF therapy, baseline Hb level and iron therapy were independent significant variables of hematopoietic response. This study showed that with appropriate treatment, hemoglobin levels of IBD patients with and without antiTNF therapy increased within 1 year, and the use of antiTNF agents in the treatment of IBD was an independent variable in correcting anemia.

Abbreviations: ADA = adalimumab, antiTNF = anti-tumor necrosis factor, CD = Crohn's disease, CER = certolizumab, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, HB = hemoglobin, HTC = hematocrit, IBD = inflammatory bowel disease, IFX = infliximab, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, MCV = mean corpuscular volume, RDW = red cell distribution width, UC = ulcerative colitis

Keywords: anemia, antiTNF, inflammatory bowel disease

1. Introduction

Anemia is a common complication and/or extraintestinal manifestation associated with inflammatory bowel disease (IBD).[1] Compared to other complications, it is frequently overlooked and negatively affects the quality of life.[2] The most common type of anemia in IBD is chronic iron deficiency due to chronic intestinal bleeding and intestinal iron absorption disorders. However, anemia of chronic disease, in which hepcidin plays an important role in its pathophysiology, is also common in IBD.[3] Anemia causes a significant increase in health care costs due to the increased need for medication and hospitalizations.[4]

IBD is a term for Crohn disease (CD) and ulcerative colitis (UC) that are characterized by chronic inflammation of the gastrointestinal tract of unknown etiology presenting with different clinical features.[5] antitumor necrosis factor (antiTNF) agents, which have an important place in the treatment of moderate and severe IBD, are monoclonal antibodies that show their effects by inhibiting the pro-inflammatory cytokine TNF-α. There are 3 antiTNF agents commonly used in remission induction, remission maintenance and treatment of extraintestinal findings in

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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IBD. These are infliximab (IFX), adalimumab (ADA) and certolizumab (CER).[6–8]

The aim of this study is to examine the change in hemoglobin levels in the follow-up of IBD patients with and without antiTNF therapy, and to investigate the relationship between this change and the antiTNF agent used and prevalence of the disease. Thus, we tried to evaluate the long-term effects of antiTNF agents on anemia in IBD.

2. Patients and Methods

2.1. Data collection and preparation

The records of the patients who were followed-up with the diagnosis of IBD in Ondokuz Mayıs University Faculty of Medicine between January 2011 and January 2021 were reviewed retrospectively. Age, gender, medical treatments, endoscopic and radiological extent of the disease were recorded. Among the laboratory parameters used in the follow-up, hemoglobin (Hb), hematocrit (Htc), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) values at diagnosis (year 0) and at the end of 1 year of treatment (year 1) were recorded. An increase of ≥ 2 g/dL in Hb levels was accepted as a hematopoietic response. The extent of the disease in patients with UC and CD was classified according to the Montreal classification system.[9]

Those who used antiTNF agents for any disease such as dermatological or rheumatological diseases, those younger than 18 years old, patients with hematological and oncological cancer, those who had bowel surgery, and those with a history of transplantation, immunodeficiency and hemoglobinopathy were excluded from the study (Fig. 1).

2.2. Ethical approval

Ethics committee approval, numbered OMUKAEK 2021/488, was obtained from the local ethics committee for this study.

2.3. Statistical analysis

The Statistical Package for the Social Sciences for Windows 15.0 (SPSSInc., Chicago, Illinois, USA) was used for statistical analysis of the data. Descriptive statistics were given as the mean ± standard deviation, frequency, and percentage. Kolmogorov-Smirnov test was used to evaluate whether the continuous variables were normally distributed. Normal distribution was obtained by applying transformation to the data that did not show normal distribution. The independent samples t-test was used to compare the means between the 2 groups, and the chi-square test was used to compare the categorical data. Univariate and multivariate logistic regression analyzes were applied to test which variables could form a model in terms of hematopoietic response. Gender, IBD subtype (Crohn disease), age, antiTNF therapy, iron therapy, baseline hemoglobin, baseline ESR were used as potential confounders. Data were summarized by mean ± standard deviation. Values of $P < .05$ were considered statistically significant.

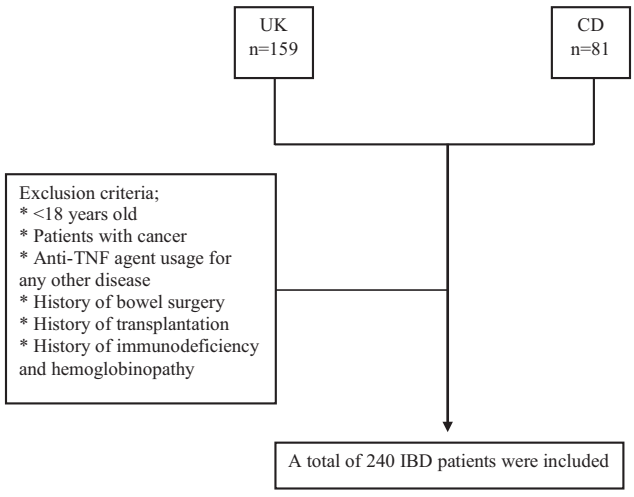

Figure 1. Patient flow diagram. CD = Crohn disease, IBD = Inflammatory bowel disease, UK = Ulcerative colitis.

3. Results

A total of 240 IBD patients, 159 (66.25%) UC and 81 (33.75%) CD, who met the criteria were included in the study. The mean age was 40.1 ± 14.3 years for UC patients and 33.3 ± 12.3 years for CD patients. The number of patients with and without antiTNF therapy was 102 (42.5%) and 138 (57.5%), respectively. Of the patients using antiTNF agents, 74 (72.5%) were using IFX, 22 (21.6%) were using ADA, and 6 (5.9%) were using CER. The rate of use of antiTNF agents was higher in patients with CD (66.7%, $P < .001$), and IFX was the most commonly used antiTNF agent in both CD and UC patients. Twenty-seven (26%) patients with antiTNF therapy and 36 (22%) patients without antiTNF received iron therapy. According to the Montreal classification, the most frequent involvement in UC patients was E1 (proctitis) and L3 (ileocolonic) in CD patients. The clinical and demographic characteristics of IBD patients are given in Table 1.

The changes in all laboratory parameters (Hb, Hct, MCV, MCH, MCHC, RDW, ESR, CRP) were statistically significant in all patients. There was a significant difference between baseline Hb levels of patients with antiTNF therapy (10.7 ± 1.9 g/dL) and those without (12.3 ± 2.1 g/dL) ($P < .001$). When the laboratory parameters of IBD patients at year 0 and at year 1 were categorized according to antiTNF use, the changes in Hb, Hct, MCV and MCH values were statistically significant. These changes are given in Table 2.

The Hb level was significantly higher in male patients ($P < .001$) at year 1 compared to year 0, while the change in Hb level was similar in both genders. Also, in antiTNF subgroups, the change in Hb levels at year 0 and at year 1 was similar.

Considering the subgroups in UC patients according to the Montreal classification, the change in Hb level was significantly different ($P < .001$). Especially, Hb change in E3 group was higher than both E2 group and E1 group. The Hb change was not different in the subgroup analysis according to the disease involvement site in CD patients. The Hb change in younger patients with CD (<40 years) was numerically higher than in older patients (≥40 years), but it was statistically similar.

The Hb change after 1 year of treatment was significantly different in patients who received antiTNF therapy compared to those who did not (3.00 ± 1.78 g/dL vs 1.19 ± 1.38 g/dL, $P < .001$) (Fig. 2).

In the single regression analysis, a significant correlation was found between hematopoietic response and antiTNF therapy, iron therapy, baseline Hb and baseline ESR. However, in multiple regression analysis, male gender (OR = 0.360; 95% CI: 0.162–0.803; $P = .012$), antiTNF therapy (OR = 4.830; 95%CI: 2.237–10.430; $P < .001$), baseline Hb level (OR = 0.452; 95% CI: 0.341–0.600; $P < .001$) and iron therapy (OR = 2.686; 95% CI: 1.023–7.053; $P = .045$) were independent

Table 1

The clinical and demographic characteristics of IBD patients.

	Total IBD	UC	CD	*P*
Age, (Years ± SD)	37.0 ± 13.9	40.1 ± 14.3	33.3 ± 12.3	**<.001**
Gender, [Male (%)]	143 (59.6)	100 (62.9)	43 (53.1)	.143
antiTNF theraphy, n (%)	102 (42.5)	48 (30.2)	54 (66.7)	**<.001**
IFX, n (%)	74 (72.5)	41 (85.4)	33 (61.1)	**.006**
ADA, n (%)	22 (21.6)	6 (12.5)	16 (29.6)	**.036**
CER, n (%)	6 (5.9)	1 (2.1)	5 (9.3)	.124
Other drugs used for IBD treatment				
5- Aminosalicylic acid, n (%)	95 (39.6)	85 (53.5)	10 (12.3)	**<.001**
Azathioprine, n (%)	18 (7.5)	0	18 (22.2)	**<.001**
5-Aminosalicylic acid + Azathioprine, n (%)	127 (52.9)	74 (46.5)	53 (65.4)	**<.001**
Montreal classification for UC				
Proctitis [E1, n (%)]		67 (42.1)		
Left sided colitis [E2, n (%)]		46 (28.9)		
Extensive colitis [E3, n (%)]		46 (28.9)		
Montreal classification for CD				
Ileum [L1, n (%)]			35 (43.2)	
Colon[L2, n (%)]			4 (4.9)	
Ileocolon [L3, n (%)]			42 (51.9)	
Upper GI [L4, n (%)]			0	
Inflammatory [B1, n (%)]			38 (46.9)	
Stricturing [B2, n (%)]			22 (27.2)	
Penetrating [B3, n (%)]			21 (25.9)	
Perianal [p, n (%)]			11 (13.6)	
Iron theraphy, n (%)	63 (26.3)	49 (30.8)	14 (17.3)	**.024**
Oral, n (%)	32 (13.3)	26 (16.4)	6 (7.4)	.054
IV, n (%)	31 (12.9)	23 (14.5)	8 (9.9)	.316

The significance of bold values is $P < .05$.

Table 2

Changes in laboratory parameters of IBD patients.

		Antitnf (+)			Antitnf (–)		
	IBD Total	Total	UC	CD	Total	UC	CD
Hb year 0 (g/dL) (mean ± SD)	11.6 ± 2.2	10.7 ± 1.9	10.4 ± 1.9	10.9 ± 1.9	12.3 ± 2.1	12.3 ± 2.2	11.8 ± 1.6
Hb year 1 (g/dL) (mean ± SD)	13.6 ± 1.4	13.7 ± 1.5	13.9 ± 1.5	13.5 ± 1.6	13.5 ± 1.4	13.5 ± 1.4	13.1 ± 1.0
P	**<.001**	**<.001**	**.009**	**<.001**	**<.001**	**<.001**	**<.001**
Hct year 0 (%) (mean ± SD)	36.1 ± 5.6	33.8 ± 5.3	33.3 ± 5.6	34.3 ± 5.0	37.7 ± 5.2	37.9 ± 5.5	36.8 ± 3.9
Hct year 1 (%)(mean ± SD)	41.0 ± 3.7	41.2 ± 3.8	41.6 ± 3.4	40.9 ± 44.1	40.8 ± 3.6	41.0 ± 3.7	39.6 ± 2.8
P	**<.001**	**<.001**	**.017**	**<.001**	**<.001**	**<.001**	**.003**
MCV year 0 (fL) (mean ± SD)	82.0 ± 8.3	81.4 ± 8.9	81.2 ± 10.0	81.6 ± 8.0	82.4 ± 7.9	83.1 ± 7.7	79.0 ± 7.7
MCV year 1 (fL) (mean ± SD)	85.4 ± 6.7	85.5 ± 6.4	85.2 ± 6.3	85.8 ± 6.4	85.3 ± 6.9	85 ± 6.4	86.2 ± 8.8
P	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	**.009**
MCH year 0 (pg) (mean ± SD)	26.3 ± 3.8	25.8 ± 3.9	25.5 ± 4.2	26.0 ± 3.6	26.7 ± 3.7	26.9 ± 3.6	25.4 ± 3.2
MCH year 1 (pg) (mean ± SD)	28.3 ± 3.0	28.4 ± 3.0	28.4 ± 3.0	28.4 ± 3.1	28.1 ± 3.0	28.0 ± 2.9	28.5 ± 3.2
P	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**	**.018**
MCHC year 0 (g/dL)(mean ± SD)	32.0 ± 2.0	31.5 ± 1.9	31.2 ± 1.9	31.8 ± 1.8	32.4 ± 2.0	32.5 ± 2.0	32.0 ± 1.4
MCHC year 1 (g/dL) (mean ± SD)	33.1 ± 1.5	33.1 ± 1.6	33.3 ± 1.6	33.0 ± 1.6	33.0 ± 1.5	32.9 ± 1.5	33.0 ± 1.2
P	**<.001**	**.003**	.238	**.001**	**<.001**	**<.001**	**<.001**
RDW year 0 (%)(mean ± SD)	15.1 ± 2.6	16.0 ± 2.8	16.5 ± 3.1	15.6 ± 2.1	14.4 ± 2.1	14.2 ± 2.1	15.1 ± 2.1
RDW year 1 (%)(mean ± SD)	14.5 ± 2.6	14.4 ± 2.4	14.5 ± 2.7	14.3 ± 2.1	14.6 ± 2.8	14.5 ± 2.8	14.8 ± 2.7
P	**.005**	**<.001**	**.038**	**<.001**	**<.001**	**.003**	.068
ESR year 0 (mm/h) (mean ± SD)	41.5 ± 26.6	46.5 ± 26.1	43.8 ± 22.2	49.0 ± 29.0	37.7 ± 26.5	34.6 ± 25.6	50.3 ± 26.4
ESR year 1 (mm/h) (mean ± SD)	22.8 ± 16.6	22.7 ± 16.3	22.1 ± 13.8	23.1 ± 18.3	23.0 ± 16.8	21.6 ± 16.4	28.6 ± 17.4
P	**<.001**	**.004**	**.006**	.106	**<.001**	**<.001**	.241
CRP year 0 (mg/L) (mean ± SD)	26.0 ± 36.9	29.1 ± 36.6	21.3 ± 27.3	36.0 ± 42.3	23.6 ± 37.0	21.5 ± 35.2	32.0 ± 43.0
CRP year 1 (mg/L) (mean ± SD)	6.2 ± 8.8	6.9 ± 11.6	5.4 ± 5.8	8.2 ± 14.8	5.7 ± 5.9	5.5 ± 6	6.4 ± 5.5
P	**<.001**	.079	.891	.155	.065	.1	.496

The significance of bold values is $P < .05$.

significant variables in terms of hematopoietic response (Table 3).

4. Discussion

Although there are many data showing the efficacy of antiTNF agents in the treatment of IBD, data are limited regarding the effectiveness of antiTNF agents on anemia which is the most common systemic complication of IBD.[10] Anemia in IBD may develop due to many factors such as blood loss due to mucosal damage, dietary factors and inflammatory changes during active disease. As is known, inflammatory cytokines (especially TNF-α) adversely affect duodenal iron absorption via hepcidin and inhibit erythropoiesis with their systemic effects on bone

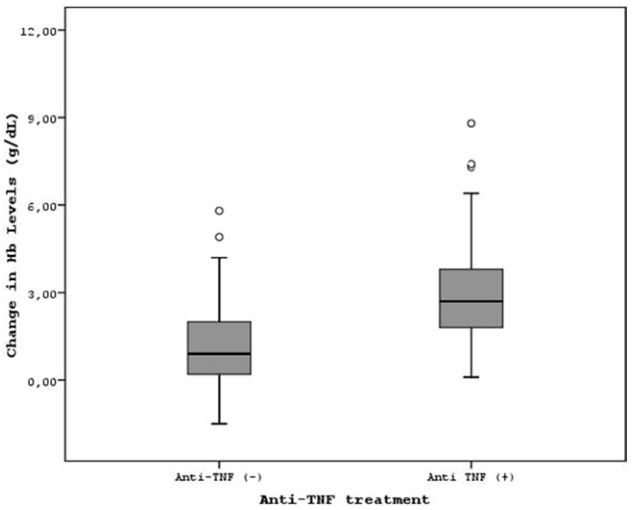

Figure 2. The change in Hb level at year 1 in patients with and without antiTNF treatment.

marrow stem cells.[11–13] Anemia is also associated with the extent and activity of the disease in IBD. Effective treatment of the disease provides mucosal healing, reduces inflammatory cytokines and makes anemia less common.[14] Our study showed that Hb levels significantly improved with appropriate treatment in all IBD patients and the mean Hb levels of patients who additionally used antiTNF agents increased significantly after 1 year of treatment compared to those who did not. It was thought that the effect of iron therapy in the emergence of this result was very low, since the patients with and without antiTNF therapy in this study used iron therapy at a similar rate.

AntiTNF agents not only abolish the cytokine effect on erythroid gene expression and increase erythropoietin production leading to erythropoiesis, but also inhibit hepcidin production by reducing proinflammatory cytokines. Moreover, they increase intestinal iron absorption by providing mucosal healing and reduce intestinal blood loss.[3] In a study including 362 IBD patients in which the effects of antiTNF agents on Hb levels were examined, it was shown that inhibition of TNF-α was effective for the treatment of anemia in both UC and CD patients.[15] In a case report by Domenech et al, in a CD patient with anemia resistant to medical treatment, anemia improved after IFX treatment.[16] Also, in a cross-sectional study conducted by Bergamaschi et al, it was observed that anemia improved in 12 of 18 patients who continued IFX treatment.[17] On the other hand, a multicenter study in 410 IBD patients, of whom 114 (27.8%) used antiTNF agents, revealed that anemia was associated with disease severity and frequency of hospital admission, but the effect of antiTNF agent use on anemia was limited.[18] In another study by the same group, including 430 patients using antiTNF, it was demonstrated that anemia continued to be an important problem after 1 year of treatment, but the use of antiTNF provided a significant improvement in Hb levels, and this improvement was more pronounced in those with severe anemia. It was suggested that this improvement might be due to both antiTNF therapy and iron replacement therapy.[19] In our study, age, type of antiTNF, route of administration of iron therapy (oral & parenteral), immunomodulatory therapy, type, extent, location and pattern of the disease were not effective on hematopoietic response according to multiple logistic regression analysis. However, antiTNF therapy, Hb level at the beginning of treatment, gender and iron theraphy were found as independent significant variables in terms of hematopoietic response. These findings suggest that oral or parenteral iron therapy may be prescribed to IBD patients with severe anemia at the time of admission. The severity of anemia at the beginning of treatment and the improvement in anemia in the first year of treatment are also important parameters for determining IBD activity and severity.[19] The significant increase in Hb levels in those using antiTNF agents in our study confirms the knowledge that inflammatory processes play an important role in the anemia among IBD patients.

Our study has some important limitations. First, the study population consisted of moderate and severe IBD patients because the study was conducted in a tertiary healthcare institution. Second, the type of anemia and possible changes in the parameters could not be investigated due to the lack of iron parameters in the follow-up of IBD patients. Third, the IBD activity was evaluated with ESR and CRP. Fourth, the results were limited in the ability to represent patients with pediatric-onset IBD as the study included patients older than 18 years. Finally, although using an antiTNF agent, regardless of the type, was interpreted as a significant improvement in Hb levels, the small number of patients treated with CER was not sufficient to evaluate the effectiveness of this drug.

5. Conclusion

In conclusion, this study shows that Hb levels of IBD patients with and without antiTNF therapy increase significantly within 1 year with appropriate treatment, and the use of antiTNF agents in the treatment of IBD is an independent variable in correcting anemia.

Author contributions

Conceptualization: Muhammed Okuyucu
Data curation: Tuğba Şenel
Formal analysis: Ufuk Avcıoğlu
Investigation: Müge Ustaoğlu
Methodology: Muhammed Okuyucu, Ufuk Avcıoğlu
Project administration: Ufuk Avcıoğlu
Resources: Tuğba Şenel
Software: Müge Ustaoğlu

Table 3

Single and multiple regression analysis of IBD patients.

	Univariate logistic regression			Multivarite logistic regression analysis		
Predict	**Odds ratio**	**95% CI**	***P* value**	**Odds ratio**	**95% CI**	***P* value**
Gender (male)	1.010	0.602–1.693	.971	0.360	0.162–0.803	**.012**
Crohn disease	1.303	0.762–2.228	.333			
Age (yr)	0.987	0.969–1.005	.152			
AntiTNF treatment	6.624	3.747–11-710	**<.001**	4.830	2.237–10.430	**<.001**
Use of iron treatment	6.492	3.324–12.680	**<.001**	2.686	1.023–7.053	**.045**
Hb year 0 (g/dL)	0.428	0.344–0.531	**<.001**	0.452	0.341–0.600	**<.001**
ESR year 0 (mm/h)	1.021	1.010–1.032	**<.001**			

The significance of bold values is $P < .05$.

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References

[1] Stein J, Dignass AU. Management of iron deficiency anemia in inflammatory bowel disease–a practical approach. Ann Gastroenterol. 2013;26:104–13.
[2] Wells CW, Lewis S, Barton RJ, et al. Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. Inflamm Bowel Dis. 2006;12:123–30.
[3] Murawska N, Fabisiak A, Fichna J. Anemia of chronic disease and iron deficiency anemia in inflammatory bowel diseases: pathophysiology, diagnosis, and treatment. Inflamm Bowel Dis. 2016;22:1198–208.
[4] Gajendran M, Umapathy C, Loganathan P, et al. Analysis of hospital-based emergency department visits for inflammatory bowel disease in the USA. Dig Dis Sci. 2016;61:389–99.
[5] Mak WY, Zhao M, Ng SC, et al. The epidemiology of inflammatory bowel disease: east meets west. J Gastroenterol Hepatol. 2020;35:380–9.
[6] Peyrin-Biroulet L, Van Assche G, Gómez-Ulloa D, et al. Systematic review of tumor necrosis factor antagonists in extraintestinal manifestations in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2017;15:25–36.e27.
[7] Shivaji UN, Sharratt CL, Thomas T, et al. Managing the adverse events caused by anti-TNF therapy in inflammatory bowel disease. Aliment Pharmacol Ther. 2019;49:664–80.
[8] Billiet T, Rutgeerts P, Ferrante M, et al. Targeting TNF-α for the treatment of inflammatory bowel disease. Expert Opin Biol Ther. 2014;14:75–101.
[9] Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a working party of the 2005 montreal world congress of gastroenterology. Can J Gastroenterol. 2005;19:5A–36A.
[10] Núñez-Gómez L, Mesonero-Gismero F, Albillos-Martínez A, et al. Anti-tumour necrosis factor agents in Crohn's disease and ulcerative colitis: beyond luminal disease. Gastroenterol Hepatol. 2018;41:576–82.
[11] Vagianos K, Clara I, Carr R, et al. What are adults with inflammatory bowel disease (IBD) eating? A closer look at the dietary habits of a population-based Canadian IBD cohort. J Parenter Enteral Nutr. 2016;40:405–11.
[12] Shu W, Pang Z, Xu C, et al. Anti-TNF-α monoclonal antibody therapy improves anemia through downregulating hepatocyte hepcidin expression in inflammatory bowel disease. Mediators Inflamm. 2019;2019:1–13.
[13] Nielsen OH, Soendergaard C, Vikner ME, et al. Rational management of iron-deficiency anaemia in inflammatory bowel disease. Nutrients. 2018;10:82.
[14] Gasche C, Berstad A, Befrits R, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases#. Inflamm Bowel Dis. 2007;13:1545–53.
[15] Lucendo AJ, Roncero O, Serrano-Duenas MT, et al. Effects of anti–TNF-alpha therapy on hemoglobin levels and anemia in patients with inflammatory bowel disease. Dig Liver Dis. 2020;52:400–7.
[16] Domenech E, Mañosa M, Masnou H, et al. Infliximab for the treatment of chronic anemia in Crohn's disease. Am J Gastroenterol. 2005;100:496.
[17] Bergamaschi G, Di Sabatino A, Albertini R, et al. Prevalence and pathogenesis of anemia in inflammatory bowel disease. Influence of anti-tumor necrosis factor-α treatment. Haematologica. 2010;95:199–205.
[18] Koutroubakis IE, Ramos-Rivers C, Regueiro M, et al. Persistent or recurrent anemia is associated with severe and disabling inflammatory bowel disease. Clin Gastroenterol Hepatol. 2015;13:1760–6.
[19] Koutroubakis IE, Ramos-Rivers C, Regueiro M, et al. The influence of anti-tumor necrosis factor agents on hemoglobin levels of patients with inflammatory bowel disease. Inflamm Bowel Dis. 2015;21:1587–93.