Improvement of Work Productivity and Quality of Life with Anti-Tumor Necrosis Factor Treatment Used in Crohn's Disease in Routine Clinical Practice in Turkey

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Abstract

Background: *Patients with Crohn's disease experience major deterioration in work productivity and quality of life. We aimed to provide the long-term effects of anti-tumor necrosis factor agents on work productivity and activity impairment and quality of life in patients with Crohn's disease using the Inflammatory Bowel Disease Questionnaire and the Short-Form Health Survey-36.*

Methods: *Patients with Crohn's disease and initiated an anti-tumor necrosis factor treatment were included and followed up for 12 months in this observational study.*

Results: *A total of 106 patients were included in this study, and 64.2% of the patients were males. Mean [± standard deviation] age was 36.8 [± 10.9] years. At baseline, mostly perianal fistulas [65.7%] were observed [n = 23]. Intestinal stenosis was detected in 34.9% of the patients [n = 37], and most of the stenosis was located in the ileum [70.6%] followed by the colon [20.6%]. Extraintestinal symptoms were observed in 24 patients [22.6%]. Most frequent extraintestinal symptom was arthritis with 71.4% [n = 15]. Mean time from first symptom to initiation of anti-tumor necrosis factor treatment was 6.3 [± 5.0] years. Improvements in work productivity and activity impairment scores throughout 12 months were –24.1% [P = .003] for work time missed, –18.0% [P = .006] for impairment at work, –8.5% [P = .160] for overall work impairment, and –17.0% [P < .001] for daily activity impairment. Similarly, significant improvements [P < .001] were detected in all components of the Inflammatory Bowel Disease Questionnaire when compared to baseline. Statistically significant improvements [P < .05] were detected for all components of Short-Form Health Survey-36 except for mental health [P = .095].*

Conclusion: *Our study indicates the significant improvement in work productivity and activity impairment and quality of life of patients with Crohn's disease who receive long-term anti-tumor necrosis factor treatment.*

Keywords: *Anti-TNF, Crohn's disease, quality of life, work productivity*

INTRODUCTION

Crohn's disease (CD) is a relapsing inflammatory bowel disease manifested by focal asymmetric, transmural, and granulomatous inflammation, which affects any segment of the gastrointestinal tract.[1,2] Ethnic origin, the presence of susceptibility regions on chromosomes, environmental factors, and lifestyle are the main factors in the epidemiology of this disease.[3] Genome-wide studies determined 71 susceptibility loci on 17 chromosomes so far that can be triggered by environmental factors.[4] This situation has a negative effect on innate [i.e., disturbed intestinal barrier, defective unfolded protein response, autophagy] and

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adaptive immune response [i.e., imbalance of effector and regulatory T cells and cytokines, migration and retention of leukocytes].[2]

Treatment goals for CD generally consist of the rapid induction of a steroid-free remission and the prevention of CD complications as well as decreasing the severity of the disease.[3] Corticosteroids, azathioprine or methotrexate, are the conventional treatments that are prescribed initially for the induction of remission but not for maintenance of remission.[5] Therefore, most of the CD patients cannot be treated successfully using such conventional therapy. In addition, the quality of life (QoL) of patients still is low due to the long-term usage and adverse events of steroids and other drugs.[6] With the introduction of biological agents, such as anti-tumor necrosis factor (TNF)-α antibodies, the goals of therapy have advanced, including induction of remission with mucosal healing as well as reduction in the rate of complications, surgery, and mortality.[7,8] Therefore, current therapy for moderate to severe CD is based on "step-up" algorithms, which initiate treatment with corticosteroids followed by immunomodulatory agents and defer therapy with biological agents until patients become refractory to conventional medications.[9] However, accelerated step-up approach, comprising anti-TNF treatment with or without combined immunomodulators, may be necessary in cases with potential for complications or severe endoscopic activity. Despite biological treatment being associated with an improved health-related QoL,[10] patients still report significant impediment on lifestyle and daily activities during both flares and remissions.[11] As a result of this situation, indirect cost for CD is significantly high since employed CD patients generally rely on their sick leave. Therefore, current researches are based on CD-related questionnaires to assess the effect of biological therapy on work productivity.[12,13] The first analysis of the effect of biological therapies for CD on work productivity and activity impairment (WPAI) has been performed with certolizumab as a biological therapy.[13] Furthermore, adalimumab (ADA) treatment for CD patients has indicated the positive effect of the anti-TNF therapies on work productivity outcomes.[14,15] Study reports indicating positive effects of infliximab treatment on WPAI and health resource utilization are also available in the published literature.[16,17]

In Turkey, there is no study to indicate the effects of anti-TNF agents on WPAI in CD patients and these types of analyses. Therefore, the primary objective of this study was to demonstrate the long-term [12 months] effects of anti-TNF agents on WPAI scales in patients with CD under routine clinical care.

Main Points

- *Patients with Crohn's disease (CD) experience major deterioration in work productivity and quality of life (QoL).*
- *Long-term anti-tumor necrosis factor (TNF) treatment may provide significant improvement in work productivity and QoL of patients with CD.*
- *Anti-TNF treatments may help to reduce the health, social, and economic burden of CD.*

MATERIALS AND METHODS

Study Design

This study was designed as a multicenter, prospective, post-marketing, observational study to be conducted in Turkey. Anti-TNF treatments were administered according to the treating physician's decision and applicable product label in Turkey. No interventions were made to the treatment, patient discontinuance, or to the follow-up decisions of the treating physician.

Ethical Considerations

All the procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Clinical Research Ethics Committee of Ibni Sina University on September 9, 2012, with an approval number 14-493-12. All patients provided written informed consent prior to participation.

Inclusion and Exclusion Criteria

All eligible patients signed a written informed consent form and consequently were enrolled in the study. Patient treatments were left to discretion of the treating physician, who was regularly seeing patients with CD. Male or female patients between 18 and 65 years of age with moderate to severe CD for whom the treating physician had recently initiated an anti-TNF treatment were included in this study. Subjects with a history of any kind of biological therapy and/or anti-TNF treatments for CD or other indications and who were participating in any other clinical trial of an experimental drug 30 days prior to the baseline visit were excluded from this study. Additionally, subjects who had septic complications [active infection and/or active tuberculosis (TB), undrained abscess],

bowel obstructions [intestinal stenosis were not classified as bowel obstructions], and fibrotic strictures were excluded from the study.

Outcome Measures and Assessments

Demographic data [age, gender, height, weight, race, and smoking behavior], TB diagnostics/result [including purified protein derivative test and chest x-ray, consultation with pulmonologist], medical history [history of CD, CD-related surgery and hospitalization records, concomitant diseases, concomitant medication use and change of dose/interval, CD-related medication history, patient-reported outcomes (WPAI, IBDQ, and short-form survey-36 [SF-36]), laboratory values (ANA [antinuclear antibodies], ANCA [anti-neutrophil cytoplasm antibodies], ASCA [Anti-Saccaromyces cerevisiae antibodies], anti-double-stranded DNA, whole blood count, sedimentation, leukocyte and thrombocytes count, hematocrit, C-reactive protein)], current manifestation of CD, extraintestinal manifestation [EIM; skeletal, dermatological, hepatobiliary, ocular, and oral manifestations according to physician's assessment], colonoscopy [endoscopic imaging for mucosal healing will be recorded], anti-TNF treatment, serious adverse events (SAEs), and isoniazid prophylaxis treatment were collected during the conduct of the study.

The WPAI-General Health (GH) questionnaire is an instrument to measure impairments in both paid work and unpaid work. Work productivity and activity impairment outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity. Absenteeism (work time missed) is defined as the percentage of time absent from work due to the health of the last week. Presenteeism (impairment at work) is defined as reduced productivity while at work due to health-related problems, and it is determined by measuring the quality of the work performed during the last 7 days on a rating scale ranging from 0 to 10, with 0 indicating that health problems had no effect on the patient's work and 10 indicating that health problems completely prevented the patient from working. The outcome is expressed as a percentage score representing the impairment due to health reasons while working, with higher numbers indicating greater impairment and less productivity. Work productivity loss is the combined absenteeism and presenteeism for employed patients. In other words, it is the percentage of overall work productivity lost due to health problems. Activity impairment is the percent impairment of nonwork-related activities due to health.

Inflammatory Bowel Disease Questionnaire (IBDQ) is a validated and self-administered questionnaire to measure the health-related quality of life in adult patients with CD. It contains 32 items, which are grouped into 4 subscales, including bowel symptoms [10 items], systemic symptoms [5 items], emotional function [12 items], and social function [5 items]. Each item is scored on a 7-point Likert-type scale ranging from 1 [worst] to 7 [best].

The SF-36 is an indicator of overall health status and has 8 scaled scores [vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health]. Scores range from 0 to 100 [lower scores = more disability, higher scores = less disability].

Study Size

The sample size calculation was based on provided prevalence and incidence values. The possibility of occurrence for the disease was calculated as 0.065. It had been determined that to demonstrate an improvement of at least 3% in WPAI, on 0.05 significance level and 0.95 CI, 93 patients would be enough to evaluate the study objectives when the power of the test was set to 80%. When adjusting the sample size with the addition of 10% dropout rate, it was determined that 102 patients would be necessary.

Statistical Analysis

Descriptive statistics were provided for demographics data and baseline characteristics including mean, median and standard deviation, minimum and maximum values. All statistical tests were 2-tailed on 0.05 alpha level with 95% CI.

Long-term effects of anti-TNF agents on WPAI scales after 12 months of anti-TNF therapy have to be analyzed using paired-sample *t*-test. However, the data were not normally distributed; therefore, nonparametric tests such as Friedman test and the Wilcoxon signed-ranked test were used instead. Responsiveness was assessed by comparing the changes in WPAI scores from baseline to month 12 using the Friedman test and the Wilcoxon signed-ranked test. Standardized response means were calculated to evaluate the influence of the changes.

Same comparisons and statistical methods [Friedman and the Wilcoxon signed-ranked tests] were used for the determination of improvements in patients, IBDQ and SF-36 scores on a .05 significance level. The null hypothesis was set as no difference, and to seek a meaningful difference, the scores were compared. Laboratory values

were compared for the determination of any difference between visits with paired-sample *t*-test on .05 significance level.

Serious adverse events were tabulated and summarized with descriptive statistics. Serious adverse events were tabulated by system-organ class and preferred term by means of the most current Medical Dictionary for Regulatory Activities. Statistical analyses were performed using Statistical Package for the Social Sciences 19.0 software (IBM Corp.; Armonk, NY, USA).

RESULTS

A total of 106 patients were enrolled in the study and were intended to be followed up for 12 months. However, at the 12th-month visit, data were available for 73 patients who continued to the study visits and an anti-TNF treatment. The remaining 33 patients did not complete the study and were considered as lost to follow-up.

Male patients formed 64.2% of the total population, and the mean [± SD] age of the total population at enrolment was 36.8 [± 10.9] years. Most of the patients belonged to the age group of 31-45 years [44.3%]. Mean weight was 64.7 [± 12.5] kg and mean body mass index was 22.3 [± 3.6] kg/m^2. Among all, 67.9% of the patients were nonsmokers. Mean time since the first symptoms and time since diagnosis were 74.8 [± 60.7] and 18.3 [± 31.5] days, respectively.

At baseline, fistula formation was present in 35.8% of the patients and 65.7% of these fistulas were perianal, whereas 34.3% were ileocutaneous. Intestinal stenosis was detected in 34.9% of the patients. Most of the stenosis was located in ileum [70.6%] followed by colon [20.6%] and other locations [8.8%]. Extraintestinal manifestations were observed in 24 patients [22.6%], and they were mostly arthritis [n = 15, 71.4%] followed by sacroiliitis [n = 6, 28.6%].

Adalimumab (ADA, AbbVie) and infliximab [IFX, Merck Sharp & Dohme] were 2 types of anti-TNF treatments that were observed during the study. Numbers and percentages of used anti-TNF treatments are presented in Table 1. Throughout the study, ADA was the most used anti-TNF treatment in CD. At baseline, ADA was administered to 77.2%, and IFX was administered to 22.8% of the patients. These ratios were similar in the following visits.

Baseline and the 12th-month scores were compared, and statistically significant improvements were observed

Table 1. Anti-TNF Treatments

	ADA		IFX	
	n	%	n	%
Baseline	78	77.2	23	22.8
Month 1	77	79.4	20	20.6
Month 2	66	77.6	19	22.4
Month 4	56	69.1	25	30.9
Month 6	68	79.1	18	20.9
Month 12	59	80.8	14	19.2

ADA, adalimumab; IFX, infliximab; TNF, tumor necrosis factor.

in patients under treatment of anti-TNF for all types of WPAI scores. Mean WPAI score for absenteeism was 38.3 at baseline and dropped significantly [P = .004] to 14.2 at the 12th-month visit (Table 2). Similarly, a significant reduction was detected for WPAI score of presenteeism at the 12th-month visit compared to baseline [39.8 vs 21.8, P = .022, Table 2]. Mean work productivity loss score was also reduced significantly at the 12th month [24.2 vs. 15.7, P = .006, Table 2]. The most pronounced improvement was observed in activity impairment scores. Mean activity impairment score at baseline was 47.0 and reduced by 17.0 points to 30.0 at the 12th-month visit (P < .001, Table 2).

Patients with CD who received anti-TNF treatment experienced significant improvements in their QoL in terms of IBDQ evaluation. Baseline and the 12th-month visit scores were compared, and significant improvements were observed for all 4 measures of IBDQ including bowel-related symptoms, systematic symptoms, emotional function, and social function (P < .001, Table 3).

Results revealed that patients with CD who are receiving anti-TNF treatment experienced significant improvements in their QoL in terms of the SF-36 health survey. Baseline and the 12th-month visit scores were compared, and significant improvements were observed for all 8 measures of SF-36 including physical functioning, role-physical, role-emotional, vitality, mental health, social functioning, bodily pain, and general health (P < .05, Table 3).

Additionally, patients with and without fistula, extraintestinal symptoms, or stenosis were categorized into subgroups and their QoL was compared. There was no statistical difference between the patient groups with and without fistula or extraintestinal symptoms in terms

Table 2. WPAI Scores

Outcome		Baseline	Month 1	Month 2	Month 4	Month 6	Month 12	*P**	*P***
WPAI									
Work time missed [absenteeism %]	n	67	52	42	43	43	33	**.003**	**.004**
	Mean ± SD	38.3 ± 39.0	26.8 ± 37.4	24.6 ± 34.1	18.4 ± 29.3	15.4 ± 26.8	14.2 ± 27.0		
Impairment at work [presenteesism %]	n	58	54	50	49	57	40	**.006**	**.022**
	Mean ± SD	39.8 ± 31.7	31.9 ± 30.4	31.2 ± 29.7	26.7 ± 29.0	23.5 ± 25.6	21.8 ± 19.3		
Work productivity loss [%]	n	57	46	42	41	41	33	**.160**	**.006**
	Mean ± SD	24.2 ± 21.2	22.7 ± 22.2	18.2 ± 19.0	17.4 ± 18.5	19.5 ± 17.2	15.7 ± 16.4		
Activity impairment [%]	n	105	94	80	81	82	62	**<.001**	**<.001**
	Mean ± SD	47.0 ± 32.0	33.8 ± 29.1	35.9 ± 31.9	31.2 ± 31.4	28.4 ± 29.7	30.0 ± 27.0		

*Friedman test.
**Post hoc test results comparing baseline and the 12th-month visits with Wilcoxon test.
SD, standard deviation; WPAI, work productivity and activity impairment.

of IBDQ or SF-36 scores ($P > .05$). Similarly, there was no significant difference between IBDQ and SF-36 scores of patients with and without stenosis, except for systematic symptom scores of IBDQ questionnaire. When the 12th-month systematic symptom scores were compared to baseline, the increase in the mean scores of patients without stenosis was greater than that of patients with stenosis ($P = .014$).

Extraintestinal symptoms and comorbidities were evaluated for skeletal system, skin, hepatobiliary system, ocular, and oral systems according to the physician's assessment. Skeletal symptoms were detected in 18.9% of the patients at baseline, and this percentage was reduced to 11.0% at the 12th-month visit. Due to the limited amount of data, only descriptive statistics were presented, and no further statistical analysis was performed (Table 4).

A total of 2 SAEs [1.9%] were observed during this study in 2 patients [abdominal abscess and an anal abscess].

DISCUSSION

Crohn's disease is a chronic, relapsing, and remitting disease that can affect the entire gastrointestinal tract of the patient and can have a debilitating effect on a patient's social, professional, and familial activities. This disease has negative impacts on patients' social and emotional well-being. Therefore, CD patients usually experience poor health-related QoL, work productivity, physical, and social exertion. There are many studies evaluating the effect of anti-TNF agents on health-related QoL and WPAI scales in CD patients.[10,13-17] However, there have been no local data published on either work productivity or daily activity impairment in CD patients. Besides, the impact of anti-TNF drugs on work productivity, in general, was not evaluated in CD patients in Turkey. Therefore, this study has great importance to demonstrate the long-term effects of anti-TNF agents on WPAI scales and related analyses in patients with CD under routine conditions. Our results revealed that CD patients experienced significant improvements in their QoL after long-term treatment with anti-TNF agents compared to baseline.

A recently published study revealed that only disease activity factors affect work-related performance rather than demographic or socioeconomic factors.[18] Therefore, WPAI questionnaire is an important tool to assess work impairment in CD patients.[19] The baseline WPAI characteristics of our CD patients were similar with the published randomized clinical trial of certolizumab pegol versus placebo study, and in this study, clinically meaningful change was established in all WPAI scores.[13] Also, the meta-analysis study of ADA on WPAI for CD patients included 4 clinical trial studies [ACCESS, CARE, CHOICE, and EXTEND]. All of these studies revealed that ADA therapy was related to significant and clinically meaningful improvements in WPAI scores for patients with moderate to severe CD.[20] In line with these studies, our study results indicated significant improvements in all types of WPAI scores in CD patients who were treated with either ADA or IFX.

Additionally, in this study, patient's QoL was measured with 2 questionnaires [IBDQ and SF-36]. We observed that CD patients under long-term treatment of anti-TNF

Table 3. IBDQ and SF-36 Scores

Outcome		Baseline	Month 1	Month 2	Month 4	Month 6	Month 12	*P**	*P***
IBDQ	n	105	94	82	82	84	64		
Systematic symptoms	Mean ± SD	3.8 ± 1.4	4.4 ± 1.r4	4.5 ± 1.5	4.8 ± 1.5	4.9 ± 1.3	4.9 ± 1.1	**<.001**	**<.001**
Bowel-related symptoms	Mean ± SD	4.5 ± 1.1	5.0 ± 1.1	4.9 ± 1.3	5.0 ± 1.2	5.1 ± 1.2	5.2 ± 1.1	**.001**	**<.001**
Social function	Mean ± SD	4.3 ± 1.5	5.0 ± 1.5	5.1 ± 1.6	5.2 ± 1.6	5.4 ± 1.5	5.3 ± 1.5	**<.001**	**<.001**
Emotional function	Mean ± SD	4.0 ± 1.1	4.4 ± 1.1	4.4 ± 1.2	4.6 ± 1.2	4.7 ± 1.2	4.7 ± 1.0	**<.001**	**<.001**
SF-36 Health Survey	n	105	94	82	81	83	61		
Physical functioning scores	Mean ± SD	62.8 ± 30.1	73.7 ± 26.1	72.7 ± 27.3	77.5 ± 21.6	76.9 ± 25.8	81.2 ± 21.4	**<.001**	**<.001**
Role-physical scores	Mean ± SD	29.3 ± 39.1	52.9 ± 44.9	52.4 ± 45.7	58.0 ± 44.0	59.0 ± 44.8	67.2 ± 41.5	**<.001**	**<.001**
Role-emotional scores	Mean ± SD	35.2 ± 39.2	52.1 ± 45.5	53.3 ± 44.1	66.7 ± 41.5	60.2 ± 44.3	62.8 ± 43.9	**<.001**	**.001**
Vitality scores	Mean ± SD	46.9 ± 26.9	54.9 ± 27.0	55.7 ± 25.3	59.5 ± 24.3	61.7 ± 22.5	58.6 ± 20.8	**.006**	**.019**
Mental health scores	Mean ± SD	53.6 ± 23.6	58.7 ± 23.2	59.3 ± 21.9	61.2 ± 22.6	64.6 ± 21.7	63.0 ± 16.6	.095	**.017**
Social functioning scores	Mean ± SD	58.6 ± 27.4	69.5 ± 25.4	69.5 ± 27.3	72.8 ± 27.4	72.0 ± 25.5	70.3 ± 22.6	**.001**	**.007**
Bodily pain scores	Mean ± SD	51.9 ± 30.0	71.0 ± 25.3	67.7 ± 27.8	69.5 ± 27.4	69.8 ± 26.3	73.0 ± 23.7	**<.001**	**<.001**
General health scores	Mean ± SD	44.8 ± 22.2	50.5 ± 24.3	50.4 ± 23.6	50.6 ± 23.6	54.4 ± 22.0	54.9 ± 19.7	**<.001**	**.005**

*Friedman test.
**Post hoc test results comparing baseline and the 12th-month visits with Wilcoxon test.
IBDQ, Inflammatory Bowel Disease Questionnaire; SD, standard deviation; SF-36, Short-Form Health Survey.

agents demonstrated improvement in their QoL in terms of IBDQ and SF-36 when compared to baseline. Similarly, in a randomized clinical study, substantial improvement was observed from baseline to week 26 with regard to total IBDQ score and as well as individual IBDQ domains for both certolizumab pegol treatment groups.[21]

On the other hand, this study included the results of the generic health-related QoL questionnaire, SF-36, and we obtained significant improvements for 8 measures of SF-36 including physical functioning, role-physical, role-emotional, vitality, mental health, social functioning, bodily pain, and general health. However, Coteur et al[22] have defined and applied minimal clinically important difference estimates for the SF-36 based on results from the randomized clinical trial study of PRECiSE 1 and PRECiSE 2. The analyses indicated that certolizumab pegol treatment provided sustained health-related improvement in QoL for CD patients.

Moreover, CD patients generally tend to maintain their anti-TNF therapy with the same agents such as certolizumab, adalimumab, and infliximab.[23,24] It should be considered that attenuation of the anti-TNF therapy response can be observed in further months of the treatment in CD patients who respond to anti-TNF agents. Schreiber[25] reported that disease relapse was observed in all 3 anti-TNF agents among active CD patients.

Since this was a noninterventional observational study, lost-to-follow-up patients were not replaced. A dropout rate of 10% was anticipated while calculating the sample size; however, actual dropout rate was approximately 30% at the end of the study, causing a reduction in the number of patients toward the end of the study. Therefore, patient selection bias and a lower number of patients completing assessment questionnaires at later visits might be considered as limitations of this study. Also, as there was no control group in this observational study, it is difficult to correlate the improvement in QoL to anti-TNF treatment; however, the results observed in this study are consistent with the results of other controlled studies.

Our study results indicate that patients receiving long-term anti-TNF treatment experience a significant improvement in their work productivity and QoL when compared to baseline. These improvements were significant for all components of the applied questionnaires [WPAI, IBDQ, and SF-36]. We assumed that, in patients with CD, direct and indirect costs on the country's economy will decrease

Table 4. Extraintestinal Symptoms of Crohn's Disease

		Skeletal Symptoms Present	Dermatological Symptoms Present	Hepatobiliary Symptoms Present	Ocular Symptoms Present	Oral Symptoms Present
Baseline	n [%]	20 [18.9]	7 [6.6]	0 [0.0]	1 [0.9]	4 [3.8]
Month 1	n [%]	15 [15.5]	3 [3.1]	0 [0.0]	0 [0.0]	0 [0.0]
Month 2	n [%]	5 [5.4]	1 [1.1]	1 [1.1]	0 [0.0]	0 [0.0]
Month 4	n [%]	11 [13.1]	1 [1.2]	1 [1.2]	0 [0.0]	0 [0.0]
Month 6	n [%]	10 [11.5]	4 [4.6]	0 [0.0]	0 [0.0]	0 [0.0]
Month 12	n [%]	8 [11.0]	3 [4.1]	0 [0.0]	0 [0.0]	0 [0.0]

with the increase in QoL and work capacity. Among the extraintestinal symptoms of CD, a reduction in skeletal symptoms was observed at the end of the study compared to baseline; however, collected data were insufficient and inconclusive for dermatologic, hepatobiliary, and ocular symptoms, due to low prevalence of these types of symptoms. Results of this study did not indicate any new safety signal for any anti-TNF agent.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of İbni Sina University on September 9, 2012 (approval number: 14-493-12).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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This study was registered in a publicly accessible database (ClinicalTrials.gov Identifier: NCT01860846) and results were presented at the 12th Congress of ECCO – European Crohn's and Colitis Organisation, Barcelona, 2017.

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