The effect of infliximab on depressive symptoms in patients with ankylosing spondylitis

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ACTA REUMATOL PORT. 2015;40:262-267

ABSTRACT

Objectives: Ankylosing spondylitis is a chronic inflammatory disease which physically, psychologically, and socially affects the patient's life. Previous studies have reported a correlation between ankylosing spondylitis and depression. In this study we investigated the effect of infliximab on depression in ankylosing spondylitis patients.

Methods: A total of 29 patients with ankylosing spondylitis were enrolled in this prospective study. Infliximab was administered intravenously at a dose of 5 mg/ /kg at baseline, weeks 2 and 6. The measurements of morning stiffness, modified Schober's test, chest expansion, erythrocyte sedimentation rate, C-reactive protein, Bath ankylosing spondylitis disease activity index, Bath ankylosing spondylitis functional index and Beck depression inventory scores were compared between baseline and 12th week.

Results: The modified Schobers' quotes test and chest expansion increased, the morning stiffness duration, erythrocyte sedimentation rate and C-reactive protein levels decreased after infliximab treatment ($p < 0.001$, respectively). There was statistically significant decrease in Bath ankylosing spondylitis disease activity index, Bath ankylosing spondylitis functional index and Beck depression invantory scores of patients after 12 weeks ($p < 0.001$, respectively).

Conclusion: Infliximab can improve depression and its symptoms in patients with ankylosing spondylitis.

Keywords: Depression; Ankylosing Spondylitis; Infliximab.

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INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disorder of joints and spine. It is manifested clinically by pain and progressive stiffening of the spine. The disease is more common in males and the onset is generally in late adolescence or early adulthood. A back pain associated with morning stiffness that lasts hours, limited chest expansion, acute arthritis of the peripheral joints, enthesopathy, anterior uveitis may be the symptoms signs of ankylosing spondylitis[1]. The course is either continuously progressive or alternates with exacerbations and remissions[2]. In addition to the physical outcomes, AS also leads to psychological consequences such as depression[3].

Depression is one of the most common mental disorders. Depressed mood and anhedonia are major symptoms of this mental disorder. Increased prevalence of depression has found to be associated with chronic medical diseases[4-6]. In ankylosing spondylitis, proinflammatory cytokines like tumor necrosis factor (TNF) seem to play a central role in the pathogenesis of depression.

Anti-TNF agents represent an outstanding advance in the symptomatic control of patients with ankylosing spondylitis presenting an inadequate response to non-steroidal anti-inflammatory drugs. As a TNF antagonist, infliximab has established efficacy for AS patients[1,8]. In this study we aimed to investigate the effect of infliximab on depressive symptoms, in patients with AS.

MATERIAL AND METHODS

This observational-prospective study was carried out in the Rheumatology outpatient clinics of Ba kent University School of Medicine in Adana, from January 2011 to February 2012. The institutional review board

of the hospital approved this study and informed consent was obtained from all subjects. All procedures were followed in accordance with the Good Clinical Practice standards and ethical standards of the Responsible Committee on Human Experimentation, and with the Helsinki Declaration of 1975, as revised in 2008.

A total of 29 patients with ankylosing spondylitis, who met the modified New York criteria for AS, were enrolled[9]. All patients received a full history and complete physical examination. High disease activity was defined as a score of 4 or higher on the Bath ankylosing spondylitis disease activity index (BASDAI)[10]. Patients with other concomitant disorders like malignancies, infections, systemic disorders (endocrine, gastrointestinal, cardiac, neurological, renal, hepatic, respiratory or other rheumatological disorders) were excluded. Patients with a history or a diagnosis of mental disorder were also excluded. Patients with positive tuberculin skin test or abnormal chest x-ray findings were not included.

Infliximab was administered intravenously at a dose of 5 mg/kg at baseline, weeks 2 and 6. All patients were followed for 12 weeks.

We prospectively collected the following data at baseline and week 12: the duration of morning stiffness (min), modified Schober's test (cm), chest expansion (cm), erythrocyte sedimentation rate (ESR) (mm/h), C-reactive protein (CRP) (mg/L). ESR and CRP levels were determined using the Westergreen method and immunoturbidimetry, respectively. Disease activity was assessed by using BASDAI, while functional capacity was evaluated with Bath ankylosing spondylitis functional index (BASFI)[11]. The ankylosing sondylitis disease activity scores (ASDAS-CRP and ASDAS-ESR) were calculated. ASDAS-CRP was calculated according to the "0.12 x Back Pain + 0.06 x Duration of Morning Stiffness + 0.11 x Patient Global + 0.07 x Peripheral Pain/Swelling + 0.58 x Ln(CRP+1)" formule. ASDAS--ESR was calculated according to the "0.08 x Back Pain + 0.07 x Duration of Morning Stiffness + 0.11 x Patient Global + 0.09 x Peripheral Pain/Swelling + 0.29 x √ (ESR)" formule[12].

All patients had a Beck Depression Inventory (BDI) evaluation at baseline and week 12. The BDI is a 21-question multiple-choice, self-report inventory. Reliability and validity of BDI in Turkey were studied by Tegin[13] and Hisli[14] previously. It is one of the most widely used instruments for measuring depression severity. A value of 0 to 3 is assigned for each answer, and then the depression severity is determined by the total score. Higher total scores indicate more severe depressive symptoms. Correspondingly, BDI scores of 0–9, 10–18, 19–29 and 30–63 are considered as minimal, mild, moderate and severe depression, respectively[15].

Statistical analyses were performed using the MedCalc software version 13.0. The variables were investigated using Kolmogorov-Smirnov test to determine whether or not they are normally distributed. Descriptive analyses were presented using means and standard deviations. Paired Student's t-test was used to compare the normally distributed measurements at two time points (baseline and 12 weeks). As a non-parametric test, Wilcoxon test was conducted to compare non-normally distributed parameters, between baseline and 12 weeks. The correlation coefficient was used to analyse the degree of association between BDI and BASDAI, BASFI, CRP, ESR, ASDAS-CRP and ASDAS--ESR (Pearson correlation coefficient (r) with p-value and 95% CI for r). A log transformation was used for variables that were not normally distributed. Multiple regression test (backward method) was used to analyse the relationship between a dependent variable (BDI) and one or more independent variables (predictor variables or explanatory variables). The probability of making a type I error (alpha, significance) is 0.05 in all tests.

RESULTS

Twenty-nine patients with AS were enrolled in this prospective observational study. The mean age was 34.4±10.3 years old. Males to females ratio was 23:6 (79.3% vs. 20.7%). The mean disease duration was 48.6±74.7 months. HLAB27 was found in 17 (58.6%) of patients. Table I shows the demographical and clinical characteristics of the patients. There was statistically significant differences in the modified Schober's test, chest expansion, morning stiffness duration, ESR, CRP, ASDAS-CRP and ASDAS-ESR levels after infliximab treatment. While the modified Schober's test and chest expansion increased after 12 weeks; the morning stiffness duration, ESR, CRP, ASDAS-CRP and ASDAS-ESR levels decreased ($p < 0.001$, respectively, Table I). Additionally, there was a statistically significant decrease in BASDAI and BASFI scores of patients after 12 weeks ($p < 0.001$, respectively, Table I).

BDI scores of the patients were significantly higher at baseline in comparison with end of the study. (ave-

TABLE I. DEMOGRAPHICAL AND CLINICAL PROPERTIES OF THE PATIENTS

	Baseline	12 weeks	p
Age	34.4±10.3		
Male N (%)	23 (79.3%)		
Smoking N (%)	15 (51.7%)		
Duration of disease (months)	48.6±74.7		
HLAB27 N (%)	17 (58.6%)		
Schober test (cm)	2.6±1.2	4.1±1.8	<0.001
Chest expansion (cm)	3.0±1.1	4.6±1.7	<0.001
Morning stiffness (min)	93.7±26.4	16.0±10.6	<0.001
ESR (mm/h)	25.8±19.8	10.4±10.5	<0.001
CRP (mg/L)	26.0±46.8	6.5±5.9	<0.001
BASDAI	7.0±0.9	1.9±1.0	<0.001
BASFI	6.2±1.4	2.1±1.5	<0.001
BDI score	27.0±8.7	10.3±8.4	<0.001
ASDAS-CRP	4.2±0.55	1.8±0.6	<0.001
ASDAS-ESR	3.9±0.5	1.5±0.7	<0.001

rage BDI scores were 27.0 ± 8.7 vs. 10.3 ± 8.4, at baseline vs. 12th week, respectively, $p < 0.001$, Table I). While patients with minimal depression scores were not detected (0%) at the baseline, the majority of these patients had minimal depression scores (55.1%) at 12th week. Additionally, 37.9% of the patients had a severe depression score at baseline; however, this ratio was reduced to and this 3.4% at 12th week. The difference was statistically significant ($p < 0.001$, Table II).

BDI score was positively correlated with BASDAI ($r = 0.532$, $p = 0.0029$, Table III), BASFI ($r = 0.563$, $p = 0.0014$), ASDAS-CRP ($r = 0.392$, $p = 0.035$), and with ASDAS-ESR ($r = 0.430$, $p = 0.019$, Table III) at baseline while it was not correlated with CRP, and with ESR ($p = 0.898$, $p = 0.729$, respectively). Similarly, BDI score was positively correlated with BASDAI ($r = 0.456$, $p = 0.0012$, table IV), and with BASFI ($r = 0.426$, $p = 0.025$, table IV) at 12th week while it was not correlated with CRP, ESR, ASDAS-CRP, and with ASDAS-ESR ($r = 0.398$, $p = 0.165$, $r = 0.303$, $p = 0.577$, respectively).

Multiple regression analyses (backward method) was performed with BDI as a dependent variable and with ESR, CRP, BASFI, BASDAI, ASDAS-CRP and ASDAS-ESR as independent variables. A significant correlation persisted between BDI and ESR ($p = 0.015$), and between BDI and BASDAI ($p = 0.003$), and between BDI and ASDAS-ESR ($p=0.050$) at baseline (Ta-

TABLE II. FREQUENCY OF PATIENTS ACCORDING TO THE BDI SCORES AT BASELINE AND 12TH WEEK

	0-9	10-18	19-29	30-63	p
Baseline	0 (0%)	4 (13.7%)	14 (48.2%)	11 (37.9%)	<0.001
12th week	16 (55.1%)	7 (24.1%)	5 (17.2%)	1 (3.4%)	

TABLE III. CORRELATION OF BDI SCORES WITH BASDAI, BASFI, CRP, ESR, ASDAS-CRP AND ASDAS-ESR AT BASELINE

	BASDAI	BASFI	CRP	ESR	ASDAS-CRP	ASDAS-ESR
BDI-scores	r = 0.532 p = 0.0029	r = 0.563 p = 0.0014	r = 0.024 p = 0.898	r = -0.066 p = 0.729	r = 0.392 p = 0.035	r = 0.430 p = 0.019

TABLE IV. CORRELATION OF BDI SCORES WITH BASDAI, BASFI, CRP, ESR, ASDAS-CRP AND ASDAS-ESR AT 12TH WEEK

	BASDAI	BASFI	CRP	ESR	ASDAS-CRP	ASDAS_ESR
BDI-scores	r = 0.456 p = 0.0012	r = 0.426 p = 0.025	r = -0.162 p = 0.398	r = -0.264 p = 0.165	r = 0.398 p = 0.165	r = 0.303 p = 0.577

TABLE V. A MULTIPLE REGRESSION ANALYSIS AT BASELINE

Independent variables	Coefficient	Std. Error	rpartial	t	P
(Constant)	-28.3618				
ESR	-0.2074	0.07988	-0.4609	-2.597	0.015
BASDAI	5.5995	1.7062	0.5487	3.282	0.003
ASDAS-ESR	5.3647	2.6056	0.3808	2.059	0.050

TABLE VI. MULTIPLE REGRESSION ANALYSIS AT 12 WEEKS

Independent variables	Coefficient	Std. Error	rpartial	t	P
(Constant)	3,0018				
BASDAI	3,8438	1,3016	0,4941	2,953	0,006

ble V). A significant correlation persisted between BDI and BASDAI (p = 0.006), at 12th week (Table VI).

DISCUSSION

Depression may be the final expression of genetic factors, personality problems or psychosocial stress[16]. However, the prevalence of depression is going up with the increased prevalence of the chronic medical conditions[4]. AS is a chronic inflammatory disorder which negatively affects the patients' life in terms of physical, social and psychological aspects[17].

In this study, we have shown that the infliximab treatment improves and decreases the depressive symptoms in patients with AS. In our study population, the majority of patients with AS had depressive symptoms at baseline. Moreover, a substantial part of them had severe depression. After infliximab treatment both depressive symptoms and frequency of depression decreased. In contrast to the baseline a substantial part of the patients had minimal depression scores at the end of the study. Additionally, BASDAI and BASFI scores of patients were positively correlated with BDI scores both at baseline and 12th week.

World Health Organization offers to evaluate psychological and social well being, as well as physical well being, to determine the health status of a patient. AS was studied in many studies and depression was found to be associated with this chronic inflammatory disorder in some of the previous studies, as well as in the current study[17-20]. However, the effect of infliximab on depressive symptoms in patients with AS was investigated in a very few studies. Ertenli et al. conducted a longitudinal study on 16 AS patients[18]. They reported lower BDI scores after first, second and third infusions of infliximab. The study design of their study is different from ours. Our study is an observational-prospective study. We tested the patients with BDI at baseline (before treatment) and 12th week (after 6 weeks from the third infusion of infliximab). Additionally, the sample size of our study is larger than that study. In the study of Arısoy *et al.* they studied 9 AS patients and reported that TNF blockers had potential antidepressant effect besides their anti-inflammatory effect in patients with AS[21]. In that study the sample size was also small and, they tested depressive symptoms with Hamilton Depression scale. They also controlled the patients at 6th week. However, the result of our study is supported by these two previous studies.

In our study, we controlled the patients at 12th week, evaluating the effect of infliximab in a longer period.

Patients with AS treated with infliximab, a chimeric IgG1 antibody against TNF, have shown rapid, profound, and sustained reductions in all clinic and laboratory measures of disease activity[22]. In accordance with this link, in this study, we showed that modified Schober's test and chest expansion increased, serum levels of ESR, CRP, ASDAS-CRP, and ASDAS-ESR, scores of BASDAI, BASFI and BDI decreased after infliximab treatment.

Previous studies have shown that, as a common mental disorder, depression is associated with an enhanced production of cytokines, such as IL-1, IL-6 and TNF. These cytokines are potent modulators of corticotropin-releasing hormone which produces heightened hypothalamic-pituitary-adrenal axis activity characterized by increases in adrenocorticotropic hormone (ACTH) and cortisol, both of which are reported elevated in major depression. A successfully pharmacological treatment of depression decreases the elevated cytokine levels[23-25]. In the study by Tuglu *et al.*, was reported that patients with major depression had higher serum TNF levels compared to controls[24]. According to the other studies in the literature, Uguz et el. have reported that anti-TNF therapy is associated with less depressive symptom and anxiety disorders in rheumatoid arthritis patients[26]. Additionally, in the study by Iglesias *et al.*, they concluded that infliximab therapy in Crohn's disease patients is associated with fewer depressive symptoms[27].

In the current study, we have found a correlation between BDI scores and BASDAI, and BASFI at baseline. Martindale *et al.*, analysed 89 AS patients and reported that BASDAI and BASFI scores correlated with depression scores[19]. Similarly, Ortancil *et al.* reported that BASDAI and BASFI correlated with depression in their study[20]. Our results are reinforced with both of these previous studies. Additionally, we have also found a correlation between BDI scores and ASDAS-CRP, and ASDAS-ESR at baseline. On the other hand, we have found also a correlation between BDI scores and BASDAI, and BASFI at 12th week. This result may be attributed the duration of the follow-up of the patients. As a difference from other studies we follow-up the patients for 12 weeks. Decrease in depression scores in our study might be due to the decrease in disease severity with TNF treatment.

This study had some limitations. First, it would have been beneficial if the sample size had been larger. Second, patients with lower BASDAI and BASFI scores have less pain and this could be the major determinant for BDI improvement and not only infliximab treatment. Third, BDI is a self-rated instrument. So, the scores of BDI can be exaggerated or minimized by the patients completing them.

CONCLUSION

Proinflammatory cytokines like TNF play a central role in the pathogenesis of depression which is a common mental disorder and detected in the majority of AS patients. Infliximab is an effective medicine in the treatment of AS. It can improve depression and its symptoms by blocking TNF.

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