Rheumatol Int (2012) 32:323–330
DOI 10.1007/s00296-010-1616-x

ORIGINAL ARTICLE

Infliximab, a TNF-alpha antagonist treatment in patients with ankylosing spondylitis: the impact on depression, anxiety and quality of life level

I. Ertenli · S. Ozer · S. Kiraz · S. B. Apras · A. Akdogan · O. Karadag · M. Calguneri · U. Kalyoncu

Received: 20 December 2009 / Accepted: 13 October 2010 / Published online: 16 November 2010

Abstract The objective of this study was to assess the effect of infliximab on depression, anxiety and quality of life in patients with active ankylosing spondylitis (AS). In this 6-week longitudinal study, 16 patients with AS were assessed. Active disease as defined by BASDAI $\geq$4.0 was sought for inclusion. Infliximab was administered 5 mg/kg at 0, 2 weeks and 6 weeks. Collected data included age, sex and date of onset of rheumatologic disease. Activity of disease was measured using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Biological activity was evaluated with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). ESR and CRP were assessed at baseline and day 42. The Hospital Anxiety and Depression scale (HADS), Beck Depression Inventory (BDI) and 36-item Short Form Health Survey (SF-36) were used to evaluate anxiety, depression and quality of life. BASDAI, SF-36, HADS and BDE were assessed prior to the initial infliximab dose and at 2nd, 14th and 42nd day. Seven (43.8%) AS patients had depression scores above the cut off value for both the HADS depression (HADS-D) and BDI and 4 (25 %) had high HADS anxiety scores at baseline. Significant time effect for BDI and HADS-D scores were observed. Although significantly lower BDI scores were found after first, second and third infusions of infliximab, compared to initial score, the significant decrease in HADS-D appeared after second and third infusions. A significant time effect for HADS-anxiety scores were found as well. All of the subscales of SF-36 improved significantly during the course, with an exception of role emotional, for which the difference approached to the significance. The change in BASDAI scores and CRP and ESR, in the treatment process, were not correlated with the change in depression and anxiety scores. Infliximab which is an anti-TNF-α drug, may be effective in the treatment of depression accompanying AS. Possible implications for the treatment of major depressive disorder were discussed, as well.

Keywords Ankylosing spondylitis · Infliximab · Major depressive disorder · Cytokines

I. Ertenli · S. Kiraz · S. B. Apras · A. Akdogan · O. Karadag · M. Calguneri · U. Kalyoncu (✉)
Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Hacettepe University, 06100 Sihhiye, Ankara, Turkey
e-mail: umutkalyoncu@yahoo.com.tr

S. Ozer
Department of Psychiatry, Faculty of Medicine, Hacettepe University, Ankara, Turkey

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease of joints and spine. The course is either continuously progressive or alternates with exacerbations and remissions. It may lead to significant functional impairment, physical disability and reduced quality of life (QOL). The disease has a substantial effect on the mood of the patients. Patients may be depressed, apathetic and even reluctant to undertake treatment and rehabilitation. Although reduced physical functioning is well recognized, the impact of disease on psychosocial health has been less evaluated in patients with AS [1]. Barlow et al. found that about one third of patients with AS reported symptoms of depression [2]. Some of the studies report a significant association between disease status and anxiety or depression in AS [3]. Clinically anxious or depressed subgroups were found to have significantly worse Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores, and it has been suggested that

disease process affects different aspects of QOL via pain and decreased physical functionality [4].

In general, it is known that medically ill patients are at a markedly increased risk for the development of several depressive symptoms such as sadness, anhedonia, insomnia, anorexia and fatigue [5]. Although depression in medically ill patients often has been attributed to the psychological stressors and physical impairment that accompany the illness, recent data suggest that intrinsic physiological processes of the sickness is involved in the pathogenesis of depressive symptoms. One such process is the activation of the immune system with the subsequent production and release of cytokines, such as interferon alpha (IFN-α), interleukin (IL)-1, IL-6 and tumor necrosis factor alpha (TNF-α) [6]. Furthermore, it is known that patients with depression that are otherwise healthy, seem to have activated inflammatory pathways and several lines of evidence indicate that proinflammatory cytokines participate in the pathophysiology of major depressive disorder [6]. Most frequent findings are elevated serum and/or plasma concentrations of interleukin (IL)-6 and/or C-reactive protein (CRP) [7], although elevations in IL-1-beta [8] and tumor necrosis factor-alpha (TNF-α) [9] have also been described, both in the peripheral blood circulation and in the central nervous system. In addition, antidepressants have been shown to have anti-inflammatory activity and may work—at least in part—by reducing inflammatory activity, given evidence that clinical response is associated with reductions in cytokine levels [10]. Indeed, some depressed patients exhibit increased TNF-α levels, which normalize upon treatment with antidepressants [11]. Lanquillon et al. reported that pretreatment levels of TNF-α were increased in patients with depression, with a significant decrease after amitriptyline treatment only in responder subgroup [10]. Similarly, Tuglu et al. reported that treatment with antidepressants is accompanied by significant decreases in TNF-α as well as CRP level and leukocyte count [9]. To sum up, increased concentrations of TNF-α are associated with major depression, and it has been suggested that reducing the effect of these cytokines may reverse depressive symptoms [12].

As a matter of fact, Persoons et al. have shown the beneficial effects of infliximab a TNF-α inhibitor on depression and psychological well-being in active Crohn's disease (CD) [13]. Lichtenstein et al. have found that infliximab significantly improved QOL in patients with active CD, increasing their ability to work and participate in leisure activities and decreasing fatigue, depression and anger [14]. Likewise, Minderhoud et al. have shown that the administration of infliximab in CD significantly reduced depression scores and improved the QOL as well as fatigue in a 4-week follow-up study although a clear role of cytokines could not be substantiated [15]. Also, administration of etanercept, another TNF-α antagonist, has been found to be associated with the improvement in symptoms of depression in psoriasis but was not strongly correlated with the improvement in objective clinical measures of psoriasis severity [16].

The objective of this study was to assess the effect of infliximab on depression, anxiety and QOL in patients with active AS and to test the hypothesis that the improvement in psychological status was not associated with the decrease in the disease activity, in a longitudinal study design.

Materials and method

Study design

In this longitudinal study, 16 patients with AS were assessed. The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki. All participating patients provided written informed consent. The study protocol and informed consent were approved by local ethics committee.

Patient selection

Patients with AS who were regularly attending at the tertiary referral center (Hacettepe University Faculty of Medicine Hospital) were invited to participate. The patients who received infliximab treatment between February and November 2006 were enrolled in the study. Diagnosis of AS was based on the criteria of the American College of Rheumatology [17]. Patients aged 18 years or older were recruited. Active disease as defined by BASDAI $\geq$ 4.0 [18] was sought for inclusion. Exclusion criteria were pregnancy or breast feeding and previous treatment with any protein-based TNF-α inhibitors. Patients were also excluded if they had any uncontrolled, clinically significant systemic disease (e.g., chronic obstructive pulmonary disease, congestive heart failure or stroke), malignancy, active tuberculosis within the previous 2 years or other chronic inflammatory disease (e.g., psoriatic spondyloarthropathy or inflammatory bowel disease).

Study medication

Infliximab, human/mouse neutralizing chimeric monoclonal antibody, was administered 5 mg/kg at 0, 2 and 6 week.

Assessment tools for clinical and biological status

Collected data included age, sex and date of onset of rheumatologic disease. Measurements of disease status

were taken using Turkish version of BASDAI for patients with AS [19]. The BASDAI is scored using a 10-cm visual analog scale (VAS) for each of five major symptoms over the past week. The scores range from 0 to 10, with lower scores indicating less active disease. Biological activity was evaluated with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The ESR (normal $\leq$ 20 mm/h) was conventionally determined. The CRP value (normal $\leq$ 0.5 mg/dl) was evaluated by nephelometry. ESR and CRP were assessed at baseline and day 42.

Assessment tools for psychological status

Psychological status was measured using three questionnaires. The Hospital Anxiety and Depression scale (HADS) is one of the most commonly used instruments for screening clinically significant anxiety and depression in patients attending a general medical clinic with physical illness [20]. This self-administered scale consists of two subscales, one assessing anxiety (HADS-A) and the other evaluating depression (HADS-D). Each subscale consists of seven items. The items scored from 0 (no distress) to 3 (maximum distress). Total score ranges between 0 and 21 for each subscale. The higher score reflected the higher level of either anxiety or depression, respectively. The validity and reliability of HADS in Turkish language were reported by Aydemir et al. [21]. The cutoff scores are estimated as 10 and 7 for anxiety and depression scale, respectively. Accordingly, the patients presenting higher scores than the cutoff values are defined as at risk.

Beck Depression Inventory (BDI) is a self-rating instrument developed by Beck and his colleagues, and psychometric properties were evaluated rigorously [22]. It is used to identify potential cases of depressive illness and to measure the severity of depressive symptoms. Twenty-one symptoms of depression (sadness, feeling of discourage, failure, dissatisfaction, guilt, punishment, disappointment, blaming themselves, suicidal thoughts, crying, irritability, loss of interest in people, difficulty in making decisions, changes in appearance, changes in work productivity, sleep problems, fatigue, loss of appetite, weight gain/loss, feeling worried and interest in sex) are evaluated on a 4-point scale ranging from 0 to 3. The total maximum score is 63. The optimum cutoff point was found to be 16/17, in the reliability and validity study of Turkish version, in accordance with the original study [23].

Additionally, all patients completed the Turkish version of the 36-item Short Form Health Survey (SF-36) [24]. SF-36 is a self-administered questionnaire assessing problems experienced during the previous 4 weeks in eight domains of QOL. Thirty-six questions yield 8 multi-item subscales (physical functioning, role functioning physical, role functioning emotional, bodily pain, vitality, social functioning, mental health and general health). Six subscales are formed of Likert scales with 3–6 answer categories and verbal anchors for each answer category. Two subscales are designed as Guttman scales (with 4 yes/no items each). The scores for each subscale are transformed to a 0–100 scale, with lower values representing a lower functioning.

BASDAI, SF-36, HADS and BDE were applied prior to the initial infliximab dose and after the 1st, 2nd and 3rd injections, at 2nd, 14th and 42nd day, respectively.

Statistical analysis

Statistical analysis was performed using SPSS (version 13.0) statistical software. Data are expressed as mean (SD) or frequency (percentage). Data were tested for normal distribution using the Kolmogorov–Smirnov test. Initially, the variables that did not show normal distribution were transformed as needed. Positively skewed variables (ESR and CRP) were subjected to power (logarithmic) transformations to normalize their distribution. Some of the variables (physical functioning, role physical and role emotional subscale scores of SF-36 and BDE scores) could not be transformed in a reliable manner; so, for the evaluation of these variables nonparametric tests were undertaken. After Mauchly's test of sphericity, repeated measures analysis of variance (ANOVA) was performed on the normally distributed variables among four consecutive measurements of depression, anxiety and QOL to explore the difference between baseline, 2nd, 14th and 42nd day. If sphericity could not be assumed, the Greenhouse–Geisser adjustment was used for the numerator and denominator degrees of freedom in the F test. The overmentioned 3 subscales of SF-36 and BDI scores (which were determined at baseline and 2, 14 and 42 day) were evaluated by nonparametric Freidman test. When a significant time effect was demonstrated in the Friedman test, the Wilcoxon signed-rank test for paired samples was used as a follow-up procedure to make post hoc pairwise comparisons. For the Wilcoxon tests, the overall experimental alpha of 0.05 was preserved by a modified Bonferroni procedure, that is, adjusted critical alpha $= 0.05/6 = 0.008$.

Paired t test was used for the comparison of the measures that were determined at baseline and at the end of the study (log ESR, log CRP and BASDAI). Moreover, we explored whether the difference between baseline (day 0) and final measures (day 42) of disease activity, biological activity and psychopathological status was correlated by using Spearman rank correlation test. Change scores from day 0 to day 42 were calculated by taking the difference between means at two time points.

Results

Demographic data

Sixteen (male/female: 13/3) patients with mean ± SD age 36±10 and mean disease duration 12.8 ± 9.5 were assessed in the study (Table 1).

Clinical disease activity and acute-phase reactants

The mean scores and values of BASDAI, CRP and ESR were shown in Table 1. The difference between the initial and final BASDAI scores was found to be significant (6.03 ± 1.18 vs. 2.28 ± 1.18, $P < 0.001$). Merely one patient had a VAS score over 4 at the end of the study. Similarly, CRP (3.7 ± 3.5 vs. 0.55 ± 0.47, $P < 0.001$) and ESR (36 ± 20 vs. 8 ± 7, $P < 0.001$) significantly differed from the baseline values.

HADS anxiety

Mean HADS anxiety scores were shown in Table 1. Four of 16 (25%) patients with AS had high anxiety scores at baseline. On follow-up period, 2 of 16 patients (12.5%) at day 2, and neither of patients at day 14, and 42 had high anxiety scores.

There was a significant time effect in repeated measures of ANOVA ($F = 4.3$, $P = 0.03$, $df = 1, 7$; as sphericity could not be assumed, the Greenhouse–Geisser adjustment was used). Pairwise comparisons using the Bonferroni adjustment did not revealed a significant difference between either evaluation.

HADS depression

Mean HADS depression scores were shown in Table 1. Seven of 16 (43.8%) patients with AS had high depression scores at baseline. Eight of 16 patients (50%) at day 2, 5 of 16 (33.3%) at day 14 and 4 of 16 (25%) at day 42 had high depression score.

There was a time effect in repeated measures of ANOVA (Greenhouse–Geisser adjustment was used as the sphericity could not be assumed) at a trend level ($F = 3.39$, $P = 0.058$, $df = 1.7$). Similar to anxiety score, no significant difference was found after Bonferroni adjustment of pairwise comparisons in this first analysis. In a second analysis, we evaluated changes over 42 days in HADS depression scores with a repeated measures of ANOVA statistic with time as the within-subject factor and risk regarding anxiety (basal HADS anxiety score over or under the cutoff point 10) as the between-subject factor. Significant effects of time ($F = 10$, $P < 0.01$, $df = 2.1$; as sphericity could not be assumed, the Greenhouse–Geisser

Table 1 Demographic features, tools of psychological status and activity markers of patients with ankylosing spondylitis

	At baseline	2 day	14 day	42 day
Age mean (SD)	36.4 (10.3)	–	–	–
Sex (male/female)	13/3	–	–	–
Disease duration (years) mean (SD)	12.8 (9.5)	–	–	–
SF-36 subscale scores				
Mean (SD)				
Physical functioning	47.2 (16.5)	63.7 (21.9)	72.0 (24.3)	74.4 (23.5)
Role physical	17.2 (35.0)	32.8 (42.5)	46.7 (44.2)	62.5 (50.0)
Body pain	.28.2 (17.4)	40.5 (22.2)	53.7 (21.1)	63.1 (20.4)
General health	29.1 (19.5)	39.7 (25.1)	50.1 (18.9)	55.0 (27.3)
Vitality	49.7 (17.1)	54.1(22.0)	65.3 (22.2)	71.2 (22.1)
Social functioning	39.8 (13.8)	47.6 (23.4)	60.0 (25.5)	71.9 (25.6)
Role emotional	41.6 (43.0)	37.5 (46.9)	44.4 (43.0)	66.6 (43.8)
Mental health	36.2 (13.3)	49.7 (20.0)	58.9 (19.1)	62.5 (19.4)
HAD anxiety mean (SD)	8.7 (4.9)	7.1 (3.9)	5.1 (2.8)	5.5 (3.4)
HAD depression mean (SD)	7.6 (4.1)	6.6 (3.6)	5.0 (3.4)	4.6 (3.9)
BDI mean (SD)	15.4 (7.1)	10.1 (7.2)	6.7 (7.5)	7.1 (7.8)
BASDAI mean (SD)	6.03 (1.18)	–	5.1 (1.2)	2.28 (1.18)
ESR mean (SD)	36 (20)	–	–	8 (7)
CRP mean (SD)	3.7 (3.5)	–	–	0.55 (0.47)

BASDAI Bath Ankylosing Spondylitis Disease Activity Index, *BDI* Beck Depression Inventory, *CRP* C-reactive protein, *HAD* The Hospital Anxiety and Depression Scale, *ESR* erythrocyte sedimentation rate, *SD* standard deviation

adjustment was used) and time × anxiety risk interaction ($F = 7.43$ $P = 0.002$ $df = 2.1$), but no significant effect of anxiety risk ($F = 1.17$ $P = 0.29$ $df = 1$) were found. In this analysis, pairwise comparisons showed significantly lower HADS depression scores on evaluation at day 14 ($P = 0.009$) and at day 42 ($P = 0.01$) compared to initial score.

BDI

Mean BDI depression scores were shown in Table 1. At baseline, 7 of 16 (43.8%) patients with AS was found to be depressed (above the cut-off point) as measured by BDI. At day 2, 4 of 16 (26.7%), at day 14, 1 of 16 (6.7%), and at day 42, 2 of 16 (12.5%) patients with AS were above the cut off point.

The Friedman test revealed significant time effects for BDI scores (chi-square 20.8, $df = 3$, $P < 0.01$). Pairwise comparisons (Wilcoxon rank order tests) revealed significantly lower BDI scores on evaluation at 2nd day ($P = 0.007$, $z = -2.7$), at day 14 ($P = 0.001$, $z = -3.24$) and at day 42 ($P = 0.002$, $z = -3.13$), compared to initial score, whereas no significant differences could be demonstrated in BDI scores between 2nd and 14th day, between 2nd and 42nd day, and between 14th and 42nd day ($P >$ critical $\alpha = 0.05/6 = 0.008$).

SF-36

Mean SF-36 subscale scores were shown in Table 1 and Fig. 1. The Friedman test revealed significant time effects for "physical functioning" scores ($P = 0.004$). Pairwise comparisons (Wilcoxon rank order tests) showed significantly higher physical functioning scores on evaluation at second day ($P = 0.011$), 14th day ($P = 0.001$), and day 42 ($P = 0.002$) compared to initial (pretreatment) score. No significant difference could be found between second and 14th day, 2nd and 42nd day, and 14th and 42nd day ($P >$ critical alpha).

The Friedman test revealed significant time effects for "role functioning physical" scores ($P = 0.0012$) as well. Pairwise comparisons (Wilcoxon rank order tests) revealed significantly higher role functioning physical scores only at day 42 ($P = 0.002$) compared to initial (pretreatment) score but not at day 2 or 14 ($P >$ critical alpha). Second and 14th day, 2nd and 42nd day, and 14th and 42nd day comparisons did not reveal significant differences as well after modified Bonferroni procedure was applied ($P >$ critical alpha).

Repeated measures of ANOVA revealed a significant improvement in SF pain scores ($F = 14$, $P < 0.01$, $df = 3$). Significantly higher day 14 ($P = .003$) and day 42 ($P < 0.01$) scores were found compared to initial score.

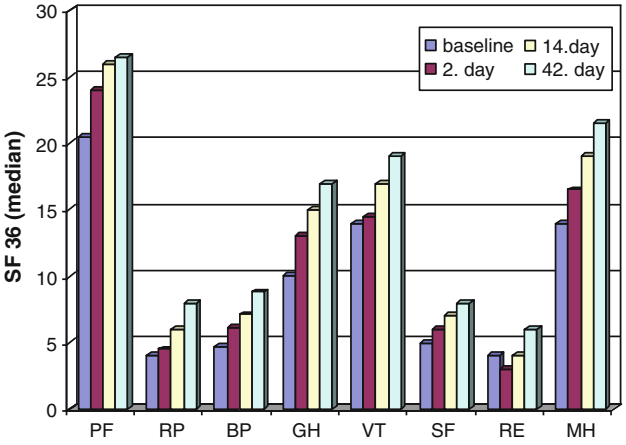

Fig. 1 The change in SF-36 subscale after infliximab treatment

The improvement from day 2 to day 42 was significant as well ($P = 0.037$). The time effect was significant for general health as well ($F = 10.9$, $P = .0$, $df = 1.92$; as sphericity could not be assumed, the Greenhouse–Geisser adjustment was used). The improvement from initial evaluation to day 14 ($P = 0.002$) and to day 42 ($P = 0.002$) was found to be significant. The improvement in vitality scores was significant as well ($F = 8$, $P = 0.004$, $df = 1.6$; as sphericity could not be assumed, the Greenhouse–Geisser adjustment was used). There was a significant change from initial evaluation to day 42 ($P = 0.02$) and approached to significance at day 14 ($P = 0.061$). Repeated measures of ANOVA revealed a significant improvement in SF social functioning scores ($F = 8.4$, $P < 0.01$, $df = 3$).The increase from initial evaluation to day 42 was found to be significant ($P = 0.004$). There was change from day 0 to day 14 at trend level ($P = 0.08$). The scores increased from day 2 to day 42 with a trend ($P = 0.08$) as well. The Friedman test revealed that the scores for "role emotional" improved with a trend toward significance ($P = 0.056$). Pairwise comparisons (Wilcoxon rank order tests) showed significantly higher role emotional scores on evaluation at day 42 ($P = 0.007$) compared to initial (pretreatment) score. No significant change was found between evaluations at other time points. Mental health scores improved significantly as well ($F = 12.74$, $P < 0.01$, $df = 3$). The changes from the initial evaluation to day 2 ($P = 0.025$), day 14 ($P = 0.003$) and day 42 ($P = 0.001$) were found to be significant.

Correlations between the change scores of psychopathological measures, measures of biological and disease activity

Moreover, we explored whether the difference between baseline (day 0) and final measures (day 42) of disease

activity, biological activity and psychopathological status was correlated by using Spearman rank correlation test. Change scores from day 0 to day 42 were calculated by taking the difference between means at two time points.

The change in BASDAI scores was not correlated with the change in BDI, HADS depression and HADS anxiety scores from day 0 to day 42 (Table 2). Besides, the basal BASDAI scores did not correlate with initial BDI ($P = 0.43$), HADS-depression, ($P = 0.27$), HADS-anxiety ($P = 0.69$) scores. Basal ESR and CRP levels were not correlated with pretreatment depression and anxiety as measured by BDI and HAD-A (data not shown), as well. However, a significant correlation was found between merely basal ESR and pretreatment HAD-D scores ($\rho = 0.57$, $P = 0.02$).

Discussion

To our knowledge this is the first study which has examined the effect of infliximab—a TNF-α antagonist—on depression, anxiety and QOL, in patients with active AS. It was found that 43.7% of patients eavaluated by BDI or HADS-D were depressed in this study. Depression is highly comorbid to patients with chronic medical diseases. The studies, which assessed depression as a separate categorical diagnosis, found prevalence rates of 6–14% [25, 26]. The frequency of depressed patients in our study was higher. It could be partly explained by the inclusion of only the active AS patients in this study. Additionally, the patients with scores above the cut-off points for both scales were assigned to depressive group; official diagnostic criteria for major depressive disorder were not applied. Our results show that depression scores as measured by BDI significantly decreased after first (and also second and third) infusion of infliximab acutely. A significant effect of infliximab infusion on depression scores evaluated by HADS (after controlling for anxiety scores) was found as well, but only after the second (after 2 weeks) and third (after 6 weeks) infusion. In the same way, anxiety scores are significantly reduced after the second and third infusion of the anti-TNF treatment.

As for the QOL scores, similar results were established. Mental health subscale scores improved beginning from the first administration of the drug. The other two scales with the most mental factor content are social functioning and role emotional. The scores for these two increased after the third infusion (though only with a trend for role emotional). In factor analytic studies these two scales and mental health have been shown to be most responsive, when compared before and after recovery from depression [27] and change in the severity of depression [28]. The three scales with the most mental factor content are even found to be sensitive to interpersonal therapy, as well as drug treatment for depression [29]. The physical functioning significantly improved after the first, second and third infusion. Vitality and general health are relevant to both physical and mental scales. Vitality increased after the third and general health from the second and third infusion. Evaluation by BDI showed an acute decrease in depression scores even after the first infusion of infliximab, whereas it took 2 weeks time to notice the decrease in depression scores as measured by HADS-D. The study by Minderhood et al. [15] reported that a significant effect of infliximab infusion on feelings of depression was found 4 weeks after the infliximab infusion. In that study depression scores were assessed by CES-D. The Hospital Anxiety and Depression Scale specifically developed for use in patients with somatic comorbidity. To distinguish psychiatric presentations from physical illness, items focus on subjective disturbance of mood rather than physical signs. Depression subscale of HADS is oriented toward the anhedonic symptoms which are sensitive indicators of depression in medically ill [30]. However, BDI has somatic component as well as cognitive/affective components, so it may be the decrease in disease activity (given the improvement in

Table 2 Correlations between the change scores (psychopathological measures, measures of biological and disease activity) (Spearman's rho)

Change from day 0 to day 42	HADS anxiety	HADS depression	BDI	BASDAI	CRP	ESR
ESR	0.151	0.429	0.453	0.742**	0.773**	1.000
CRP	0.000	0.213	0.443	0.393	1.000	
BASDAI	−0.093	0.152	0.321	1.000		
BDI	0.531*	0.705**	1.00			
HADS depression	0.814**	1.000				
HADS anxiety	1.000					

* $P < 0.05$

** $P < 0.01$

physical functioning subscale of SF-36, was evident even after the first infusion of infliximab) that BDI has detected acutely, whereas HADS could not. In any case delayed (after second or third infusion) improvement of depression evaluated by all of the scanning tools (BDI and HADS-D particularly) including mental health, social functioning and role emotional subscales of SF-36, was evident. On the other hand, the acute impact of infliximab on depression cannot be posited unequivocally, in patients with AS in this study.

In this study, it was found that the change in BASDAI scores and the change in depression or anxiety scores were not associated and that basal BASDAI scores did not correlate with the pretreatment depression scores as well. On the contrary, it has been suggested that depression/anxiety and disease status scores are interrelated in previous studies [3, 4]. However, similar to our results Persoons and colleagues found that disease activity (excluding well-being, one of the subjective items of the CD activity index) was not correlated with depression score at baseline and after infliximab infusion [13].

In the same way our results show that the changes in CRP and ESR (which are suggested to be a marker of disease activitiy in AS) were not correlated with the change in depression scores. Basal ESR and CRP levels were not correlated with pretreatment depression and anxiety as measured by BDI and HAD-A, as well. However, basal ESR was found to be associated with pretreatment HAD-D scores. On the contrary, in a cross-sectional study, it was reported that disease activity, either clinical or serological (measured by ESR and CRP levels) was associated with the severity of depression and anxiety in AS patients with heterogeneous treatments [31], though the change due to a unique treatment was not examined in that study. In view of these findings, it seems to be reasonable, to suggest that the improvement in depression is not associated with the improvement in physical functionality or pain, in this study. Then what other mechanisms may be involved in the improvement of depression? Is infliximab involved in this process and by implication TNF-α, in pathophysiology of depression? It has been suggested that disturbances in neurotransmitter metabolism, modulation of the hypothalamus–pituitaryadrenal (HPA) axis and the production of relevant CNS growth factors are some of the mechanisms by which cytokines may be involved in pathogenesis of depression. Bearing in mind the dysfunction in brain monoamine neurotransmitter systems has long been the focus of etiology and drug treatment for depression, the first of the above three mechanisms deserves mentioning thoroughly. Pro-inflammatory cytokines may cause reduction in tryptophan availability for serotonin synthesis by activating tryptophan degrading enzyme indoleamine-2,3-dioxygenase (IDO). IL-1 or TNF-α are potent inducers of IDO [32]. Tryptophan is the precursor of the so-called 'kynurenine' pathway, as well as serotonin. Cytokine-induced stimulation of IDO, an enzyme that switches the synthesis of serotonin from tryptophan to kynurenine and quinolinic acid, results in reduction of serotonin synthesis [33]. Moreover, in an in vitro study, it has been shown that the IL-1 and TNF-α increase the activity of the serotonin transporter; an effect mediated by activation of p38 mitogen-activated protein (MAP) kinase, in both a rat embryonic raphe cell line, and in mouse midbrain and striatal synaptosomes [34]. These data suggest that IL-1 or TNF-α in the brain, could contribute to decreased synaptic availability of serotonin which may lead to the development of depression. The findings in active CD [13–15] suggest that infliximab rapidly and significantly reduced depression scores, prior to any improvement in the intestinal pathology. Data regarding patients with CD are consistent with our findings in AS patients for whom the change in the activity of clinical disease was not associated with the change in depression scores. Infliximab might have been implicated in the pathogenetic mechanisms of major depressive disorder. Proinflammatory cytokines which are involved in the pathophysiology of depression, may represent promising targets for the pharmacological treatment of major depressive disorder in medically healthy patients, as well. Infliximab which is a TNF-α antagonist, might improve mood as a consequence of decreased inflammatory activity in depressive patients who have increased levels of pretreatment proinflammatory cytokines or other inflammatory markers. Accordingly, a randomized, double blind, placebo-controlled (phase IV) study is being conducted to evaluate the efficacy of the infliximab in acutely reducing symptoms of patients with treatment resistant depression who have elevated proinflammatory markers [35].

In conclusion, our results show that infliximab, an effective treatment for the clinical symptoms of AS, may be effective in the treatment of depression accompanying AS, as well. Additionally, we can tentatively suggest that infliximab provides a rapid improvement of mood. Infliximab may modulate the cytokines that are involved in the pathogenetic mechanisms of depression in AS and these findings might bear implications for the treatment of major depressive disorder, in otherwise healthy patients. As a matter of fact the lack of cytokine level determinations before and after infliximab treatment is the main limitation of our study which hinders us suggesting more clearly, the role of inflamatuary process and cytokines in the pathogenesis of depression in active AS. Small sample size is another limitation which might have given rise to type two error in the context of detecting clear acute effect of infliximab on mood.

References

1. Braun J, Sieper J (2007) Ankylosing spondylitis. Lancet 369: 1379–1390
2. Barlow JH, Macey SJ, Struthers GR (1993) Gender, depression, and ankylosing spondylitis. Arthritis Care Res 6:45–51
3. Martindale J, Smith J, Sutton CJ, Grennan D, Goodacre L, Goodacre JA (2006) Disease and psychological status in ankylosing spondylitis. Rheumatology 45:1288–1293
4. Zink A, Braun J, Listing J, Wollenhaupt J (2000) Disability and handicap in rheumatoid arthritis and ankylosing spondylitis—results from the German rheumatological database. J Rheumatol 27:613–622
5. Evans DL, Charney DS, Lewis L et al (2005) Mood disorders in the medically ill: scientific review and recommendations. Biol Psychiatry 58:175–189
6. Raison CL, Capuron L, Miller AH (2006) Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol 27:24–31
7. Alesci S, Martinez PE, Kelkar S, Ilias I, Ronsaville DS, Listwak SJ, Ayala AR, Licinio J, Gold HK, Kling MA, Chrousos GP, Gold PW (2005) Major depression is associated with significant diurnal elevations in plasma interleukin-6 levels, a shift of its circadian rhythm, and loss of physiological complexity in its secretion: clinical implications. J Clin Endocrinol Metab 90:2522–2530
8. Thomas AJ, Davis S, Morris C, Jackson E, Harrison R, O'Brien JT (2005) Increase in interleukin-1beta in late-life depression. Am J Psychiatry 162:175–177
9. Tuglu C, Kara SH, Caliyurt O, Vardar E, Abay E (2003) Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. Psychopharmacology 170:429–433
10. Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H (2000) Cytokine production and treatment response in major depressive disorder. Neuropsychopharmacology 22:370–379
11. Kubera M, Maes M, (2000) Serotonin–immune interactions in major depression. In: Patterson, Kordon, Christen (eds) Neuro–immune interactions in neurologic and psychiatric disorders. Springer-Verlag, Berlin, pp 79–87
12. O'Brien SM, Scott LV, Dinan TG (2004) Cytokines: abnormalities in major depression and implications for pharmacological treatment. Hum Psychopharmacol 19:397–403
13. Persoons P, Vermeire S, Demyttenaere K, Fischler B, Vandenberghe J, Oudenhove LV et al (2005) The impact of major depressive disorder on the short- and long-term outcome of Crohn's disease treatment with infliximab. Aliment Pharmacol Ther 22:101–110
14. Lichtenstein GR, Bala M, Han C, DeWoody K, Schaible T (2002) Infliximab improves quality of life in patients with Crohn's disease. Inflamm Bowel Dis 8:237–243
15. Minderhoud IM, Samsom M, Oldenburg B (2007) Crohn's disease, fatigue, and infliximab: is there a role for cytokines in the pathogenesis of fatigue? World J Gastroenterol 13:2089–2093
16. Tyring S, Gottlieb A, Papp K, Gordon K, Leonardi C, Wang A et al (2006) Etanercept and clinical outcomes, fatigue, and depression in psoriasis: double-blind placebo-controlled randomized phase III trial. Lancet 367:29–35
17. Van der Linden S, Valkenburg HA, Cats A (1984) Evaluation of diagnostic criteria for ankylosing spondylitis. Arthritis Rheum 27:361–367
18. Braun J, Pham T, Sieper J et al (2003) International ASAS consensus statement for the use of anti-tumour necrosis factor agents in patients with ankylosing spondylitis. Ann Rheum Dis 62:817–824
19. Akkoc Y, Karatepe AG, Akar S, Kirazli Y, Akkoc N (2005) A Turkish version of the Bath Ankylosing Spondylitis disease activity index: reliability and validity. Rheumatol Int 25:280–284
20. Zigmond AS, Snaith RP (1983) The hospital anxiety and depression scale. Acta Psychiatr Scand 67:361–370
21. Aydemir Ö, Güvenir T, Küey L, Kültür S (1997) The reliability and validity of Turkish form of Hospital Anxiety and Depression Scale. Turk psikiyatri Derg 8:280–287 (in Turkish)
22. Beck AT, Steer RA, Garbin MG (1988) Psychometric properties of the Beck depression inventory: twenty-five years of evaluation. Clin Psychol Rev 8:77–100
23. Hisli N (1989) Beck depression envanterinin üniversite öğrencileri için geçerliliği, güvenilirliği. A reliability and validity study of Beck Depression Inventory in a university student sample. J Psychol (Psikoloji Dergisi) 7:3–13 (in Turkish)
24. Koçyiğit H, Aydemir Ö, Ölmez N, Memiş A (1999) The reliability and validity of SF-36 for Turkish language. Ege Fizik Tedavi ve Rehabilitasyon Dergisi 12:102–106 (in Turkish)
25. Walker EA, Gelfand MD, Gelfand AN et al (1996) The relationship of current psychiatric disorder to functional disability and distress in patients with inflammatory bowel disease. Gen Hosp Psychiatry 18:220–229
26. Katon WJ, Ciechanowski P (2002) Impact of major depression on chronic medical illness. J Psychosom Res 53:859–863
27. Ware JE (1995) The status of health assessment 1994. Annu Rev Public Health 16:327–354
28. Beusterien KM, Steinwald B, Ware JE (1996) Usefulness of the SF-36 Health Survey in measuring health outcomes in the depressed elderly. J Geriatr Psychiatry Neurol 9:13–21
29. Coulehan JL, Schulberg HC, Block MR et al (1997) Treating depressed primary care patients improves their physical, mental, and social functioning. Arch Intern Med 157:1113–1120
30. Yonkers KA, Samson JA (2008) Mood disorders measures. In: Rush AJ, First MB, Blacker D (eds) Handbook of psychiatric measures, 2nd edn. American Psychiatric Publishing, Arlington VA, pp 499-528
31. Eren İ, Şahin M, Cüre E et al (2007) Interactions between psychiatric symptoms and disability and quality of life in ankylosing spondylitis patients. Arch Neuropsychiatry 44:1–9
32. Müller N, Schwarz MJ (2007) The immune-mediated alteration of serotonin and glutamate: towards an integrated view of depression. Mol Psychiatry 12:988–1000
33. Myint AM, Kim YK (2003) Cytokine-serotonin interaction through IDO: a neurodegeneration hypothesis of depression. Med Hypothesis 61:519–525
34. Zhu CB, Blakely RD, Hewlett WA (2006) The proinflammatory cytokines interleukin-1beta and tumor necrosis factor-alpha activate serotonin transporters. Neuropsychopharmacol 31:2121–2131
35. Raison C A study of infliximab for treatment resistant major depression emory university. http://clinicaltrials.gov/show/NCT00463580