

Effect of Infliximab on Major Depressive Episode in a Sample of Iraqi Patients with Ankylosing Spondylitis at Baghdad Teaching Hospital

Corresponding Author:

Dr. Adnan Sadkhan Guber

Rheumatology diploma

Al-Kindy College of Medicine

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ABSTRACT:

Background: Infliximab is a biological therapy used to treat ankylosing spondylitis, may be effective in the treatment of depression accompanying it. **Objectives:** To assess the effect of infliximab on depressive disorder and severity in patients with ankylosing spondylitis (AS). **Patients and Methods:** A randomly selected study enrolled AS patients diagnosed according to the modified New York criteria for ankylosing Spondylitis. Activity of disease was measured using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Active disease as defined by BASDAI ≥ 4.0 . every patient assessed mentally by mini-international neuropsychiatric interview (MINI) and if there is depressive episode then diagnosed according to ICD-10 criteria for depression. Beck Depression Inventory (BDI) was used to evaluate depression severity. Infliximab was administered (5 mg/kg) at 0, 2 weeks and 6 weeks and then every 6weeks. Collected data include age, education, employment. BASDAI and BDI were assessed prior to the initial infliximab dose and at the subsequent doses. Data were collected in period between 1st October 2013 to 15 march 2014. **Results:** A total of 46 patients with ankylosing spondylitis were enrolled in this study, the mean age was 35.1 ± 8.5 years, 63% aged 30-39 years. The majority of patients (71.7%) had secondary school and lower level of education, employed patients were 18(39.1 %). Severe depression was found in 69.6%, moderate depression in 28.2%, mild depression in 2.2%. It had been found that frequency of severe depression reduced significantly with the advancing doses of infliximab ($p < 0.001$). After the last dose of infliximab, depression was improved in majority of patients (73.9%). No significant association had been found between the improvement in depression neither with age, level of education nor the occupation. ($p > 0.05$). **Conclusion:** The improvement of depression was among two thirds of AS patients, after three doses of Infliximab, and this improvement of depression was associated significantly with inactivity of ankylosing spondylitis disease.

Keywords: Ankylosing spondylitis, Depression, Infliximab.

INTRODUCTION:

Ankylosing Spondylitis: AS is a chronic, progressive inflammatory disease that affects primarily the sacroiliac joints and the axial skeleton(spine)and less frequently, peripheral joints and other extra-articular organs such as the eyes, skin and heart. The major functional losses occur during the first ten years of disease.(1) AS commonly starts in the second or third decade of life.(2, 3) The clinical picture of early (Juvenile Onset) AS differ from that of adult onset by the more frequent involvement of peripheral joints.(2) Men are afflicted with AS approximately two to three times more frequently than women.(3) 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). Patients may be depressed, apathic and reluctant to undertake treatment and rehabilitation. Infliximab (anti TNF- α) indicated in the treatment of disparate immune-inflammatory

disorders like AS, may offer broad- spectrum symptomatic benefits for mood disorders across affective, cognitive, and somatic domains. As ankylosing spondylitis being a chronic, painful, highly disabling and deforming disorder with frustrating treatment outcome and poor quality of life, it has a lot of impact on the psychological wellbeing of the individual (4, 5). Therefore, infliximab may lead to improvement of both ankylosing spondylitis and depression.

AIM OF STUDY:

To assess the effect of infliximab on improvement of depression in AS patients. To analyze the association between the efficacy of infliximab on depressive episodes in AS patients and the demographic characters of them.

PATIENTS AND METHODS:

In this longitudinal study, 46 patients with age range 20 – 66 years, the study subjects were chosen from the patients who attended the of Rheumatology unit of Baghdad Teaching Hospital in medical city between October 2013 to March 2014.

INCLUSION CRITERIA:

Male patients age 20 years or older

- Ankylosing spondylitis patients diagnosed according to criteria of the American college of Rheumatology
- Currently meets ICD-10 criteria for depression
- Patients received infliximab treatment freely between October 2013 and march 2014.
- Exclusion criteria
- Unwilling to participate in the study.
- Prior use of a TNF- antagonist or immune suppressants.
- Current use of Aspirin or NSAIDS, or COX-2 inhibitors.
- History of chronic diseases or organic brain disorders.
- History of previous psychiatric diseases.
- History of steroid using.

Study Medication:

Infliximab, human / mouse neutralizing chimeric monoclonal antibody, was administered 5 mg /kg at 0, 2 and 6 weeks. Prior to data collection, a signed consent from each of the participant was obtained after explaining the purpose of the study and ensuring privacy of the data. The study protocol was reviewed; approval and official permission were obtained from the Ministry of Higher Education and Scientific Research; Baghdad University, College of Medicine to conduct the present study.

Methods:

1. Sociodemographic data include age, employment status, education level, residence, phone number.
2. Measurement of ankylosing spondylitis severity were taken using Arabic version of BASDI for patients with AS, the BASDI 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.

3. Assessment tool for mental status

All patients with AS were screened by MINI screening test (6) and if there is depression then diagnosed according to ICD 10 criteria (7). Arabic version questionnaire then asses severity by using Beck Depression Inventory (BDI) Arabic version (8).

The AS patient, assessed initially before the first dose of infliximab for severity, depressive episodes and severity, and at each subsequent doses of infliximab (0, 2 weeks, 6 weeks then every 6 weeks). Statistical analysis: The data of the 46 patients were analyzed by using the statistical package of social sciences (SPSS) version 20. Descriptive statistics were presented as mean (SD), frequencies (No.) and proportions (%). By using the cross-tabulation, Chi square test (X^2) was used to assess the significance of differences in frequencies, Fisher's exact test was used alternatively when chi square couldn't be applied.

Analysis of variances (ANOVA) test was used to compare mean value of BASDAI at different doses of Infliximab.

Level of significance of ≤ 0.05 considered significant (sig) and ≤ 0.001 considered highly significant (HS). The results and findings were presented in tables and figures (graphs) with appropriate explanatory paragraphs.

RESULTS:

A total of 46 patients with ankylosing spondylitis were enrolled in this study, the baseline characteristics of the patients are shown in table 1;

The mean age of the studied group was 35.1 ± 8.5 years, further distribution of the age into 3 categories revealed that 9 patients (19.6%) aged ≤ 29 years, 29 (63%) aged 30 – 39 years and the remaining 8 patients (17.4%) aged ≥ 40 .

Regarding the education 12 patients (26.1%) had primary school level of education, 21 (45.6%) had secondary and 13 patients had college or higher education, employed patients were 18 (39.1%) while 28 patients were not employed.

All AS patients were screened for depression. The distribution of patient according to the severity of depression, revealed that 32 patients (69.6%) had severe depression, 13 (28.2%) had moderate depression and only one patient had mild depression. These findings are shown in table 1.

Table 1. Baseline characteristics of the studied group.

| Characteristic | No. | % |
|----------------|-----|------|
| Age | | |
| ≤ 29 | 9 | 19.6 |
| 30 – 39 | 29 | 63.0 |
| ≥ 40 | 8 | 17.4 |

| | | |
|-------------------|------------|------|
| Mean (SD*) | 35.1 (8.5) | |
| Education | | |
| Primary | 12 | 26.1 |
| Secondary | 21 | 45.6 |
| College or higher | 13 | 28.3 |
| Employment | | |
| Employed | 18 | 39.1 |
| Not employed | 28 | 60.9 |
| Depression | | |
| Mild | 1 | 2.2 |
| Moderate | 13 | 28.2 |
| Severe | 32 | 69.6 |

SD: Standard Deviation

Table 2, shows the distribution of cases according to their depression status across the different doses of Infliximab; it had been found that frequency of severe depression reduced significantly with the advancing doses of infliximab; at baseline time (before administration of treatment) severe depression was found in 32 (69.6%) patients, in 15 patients (32.6) after the 1st dose, in 10 patients (21.7%) after the 2nd dose, in 6 patients (13%) after the 3rd dose and at the last dose only 3 patients (6.5%) had severe depression, in contrast the number of patients who didn't have depression increased dramatically from none (0%) at baseline to 25 (54.3%) at the last dose, the same trends in those with mild and moderate depression, (Fig. 1)

Table 2. Frequency distribution of depression with advancing doses of infliximab

| | Severe No. (%) | Moderate No. (%) | Mild No. (%) | No depression No. (%) |
|------------------------------|-------------------|---------------------|-----------------|--------------------------|
| Baseline | 32 (69.6) | 13 (28.3) | 1 (2.2) | 0 (0.0) |
| Dose 1 | 15 (32.6) | 24 (52.2) | 4 (8.7) | 3 (6.5) |
| Dose 2 | 10 (21.7) | 18 (39.1) | 5 (10.9) | 13 (28.3) |
| Dose 3 | 6 (13.0) | 14 (30.4) | 9 (19.6) | 17 (37.0) |
| Last dose | 3 (6.5) | 9 (19.6) | 9 (19.6) | 25 (54.3) |
| $X^2 = 92.5, P < 0.001 (HS)$ | | | | |

X^2 ; chi square, df; degree of freedom, HS; highly significant

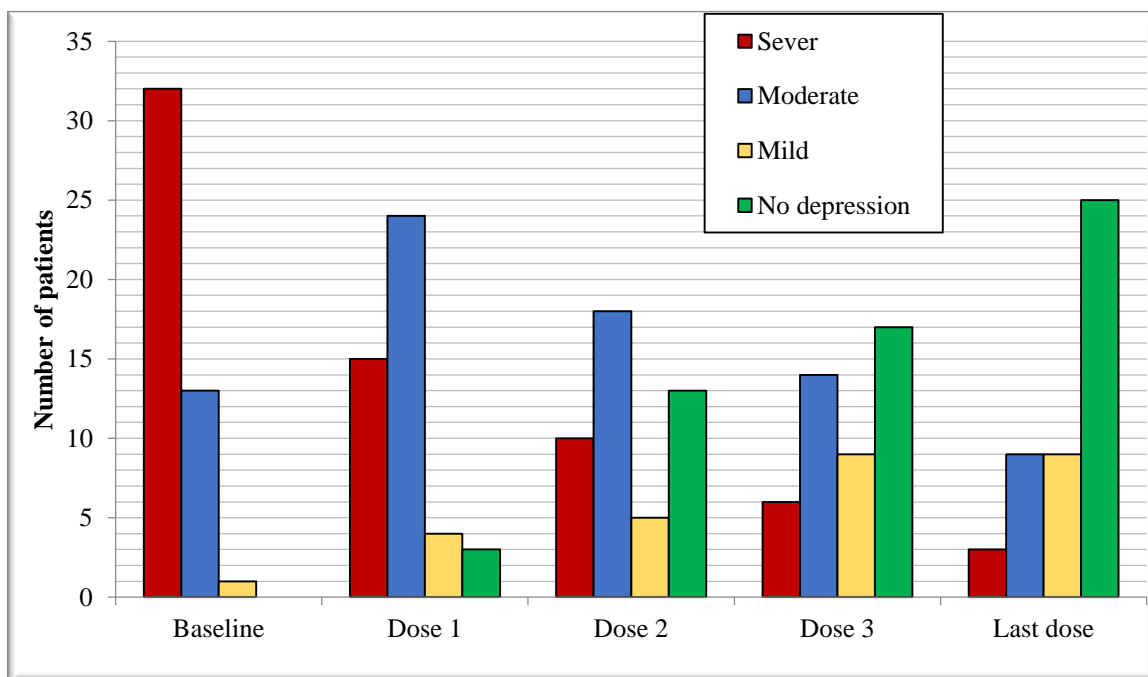


Figure 1. Changes in depression status across the doses of Infliximab

As it shown in figure 2, at the last dose depression was improved in 34 patients (73.9%) and not improved in the remaining 12 patients (26.1%), furthermore, the distribution of improvement according to age is shown in table 3; no

significant differences had been found in improvement according to different age groups ($P>0.05$). Regarding the association between depression improvement and level of education it had been found that patients with college and higher levels of education had better improvement than those with secondary and primary levels of education; (92.3%) vs. (71.4%) and (58.3%) respectively, however, the difference was statistically insignificant ($P>0.05$), Table 3.

According to the employment status of the patients, 16 patients (88.9%) of the 18 employed patients had been improved compared to 18 (64.3%) of the 28 not employed patients, however the difference was statistically insignificant ($P>0.05$), Table 3.

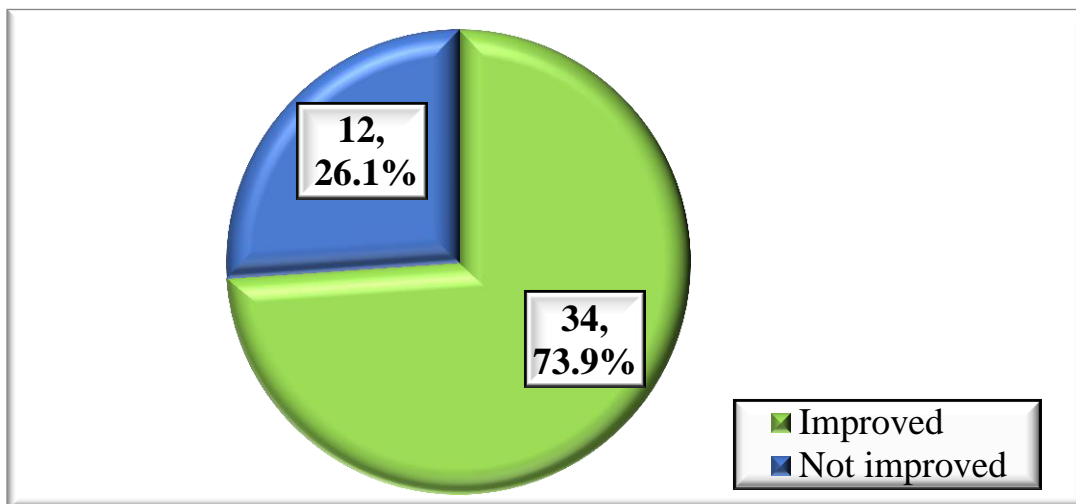


Figure 2. Distribution of overall improvement of patients

Table 3. Distribution of improvement of depression according to age, Education Employment

| | Depression | | | | P |
|-------------------|------------|------|--------------|------|------------------------------|
| | Improved | | Not Improved | | |
| | No. | % | No. | % | |
| Age | | | | | |
| ≤ 29 | 7 | 77.8 | 2 | 22.2 | 0.55 (NS) <i>Fisher's</i> |
| 30 – 39 | 20 | 69.0 | 9 | 31.0 | |
| ≥ 40 | 7 | 87.5 | 1 | 12.5 | |
| Education | | | | | |
| Primary | 7 | 58.3 | 5 | 41.7 | 0.14 (NS) <i>Fisher's</i> |
| Secondary | 15 | 71.4 | 6 | 28.6 | |
| College or higher | 12 | 92.3 | 1 | 7.7 | |
| Employment | | | | | |
| Employed | 16 | 88.9 | 2 | 11.1 | 0.13 (NS) |
| Not employed | 18 | 64.3 | 10 | 35.7 | |

NS; not significant

At baseline (pre-medication) 44 patients (95.7%) had active disease and only 2 patients (4.3%) had inactive disease, at the last dose there were 25 patients (54.3%) remained with active disease and 21 (45.7%) had inactive diseases, the changes in disease activity between the baseline and the last dose was statistically highly significant ($P<0.001$), Table 4 and Fig. 3.

Table (4) shows that improvement in depression was parallel to improvement in AS

Furthermore, the mean BASDAI at the last dose was 3.6 ± 1.9 (range: 1.2 – 6.3) which is significantly lower than those who Not improved (6.0 ± 1.6) (ranged 3.2 – 8) table 4

Table 4. Distribution of disease activity according to the improvement in depression.

| Disease activity | Improvement in depression | | P |
|------------------|---------------------------|--------------|---|
| | Improved | Not improved | |
| | | | |

| | No. | % | No. | % | |
|--------------------------|-----------|------|-----------|------|-------------------|
| Active | 14 | 56.0 | 11 | 44.0 | 0.003 |
| Inactive | 20 | 95.2 | 1 | 4.8 | |
| Total | 34 | 73.9 | 12 | 26.1 | < 0.001 |
| Mean BASDAI at last dose | 3.6 ± 1.9 | | 6.0 ± 1.6 | | |
| Range | 1.2 – 6.3 | | 3.2 – 8 | | |

From other point of view, in the improved depression patients the changes in BASDAI values across the doses of infliximab was approximately linear and significant (P=0.016) , while in those who were not improved the changes were statistically insignificant (P=0.39) , figure 3 .

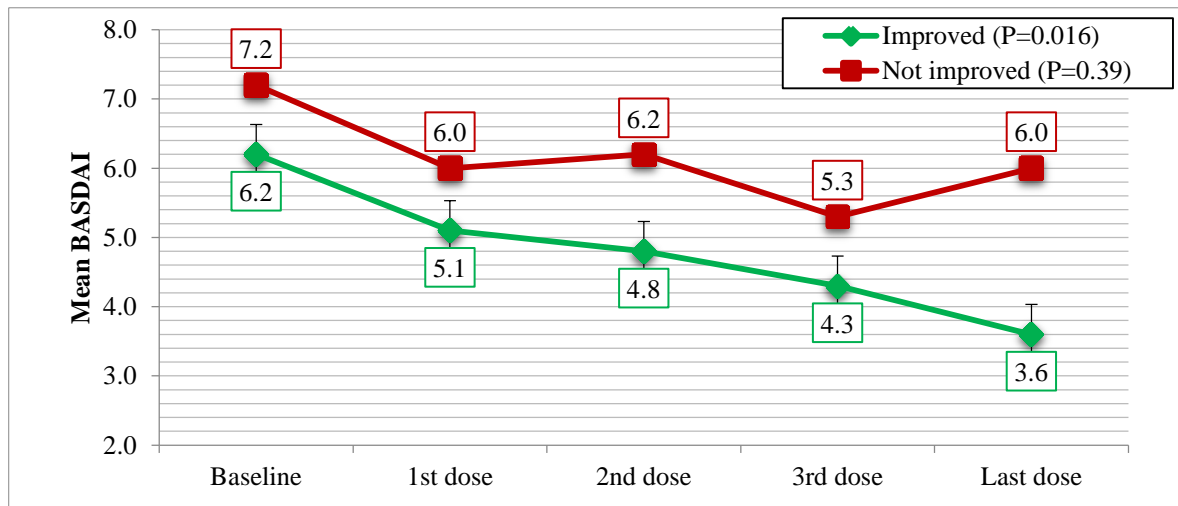


Figure 3. Changes in BASDAI across the different doses of Infliximab according to improvement in depression

DISCUSSION:

The present study revealed that mean age of AS patients was 35.1±8.5 years. This finding is close to results of Demirdal S, et al study in Turkey (2013) (9) that reported mean age of participated AS patients of 37.9±12.7 years. The mean age of present study (35.1) is lower than that reported by Ward et al study in USA (2005) (10) with mean age 55±10.7 years. This inconsistency might be attributed to low sample size of present study.

In this study only 28.3% of AS patients were completed their higher education. This finding is consistent with results of Bonnen A, et al study in Netherlands (2001) (11). Although this disease usually starts in the third decade of life and affects men three times as often as women, there was a proved withdrawal of AS patients from completing their higher education in addition to their jobs(11).

More than half of AS patients (60.9%) were unemployed. Many literatures reported this physical and social problem (10, 11). Working at physically demanding jobs may affect long-term functional ability by stressing joints in the axial skeleton, thereby perpetuating inflammation (12). Alternatively, persons with physically demanding jobs may be less likely to perform therapeutic or recreational exercises, which then could lead to greater functional limitations in the future (13). Both of these factors may contribute.

About two thirds (69.6%) of the studied AS patients were complaining from severe depression. This finding is consistent with results Kar SK study in India (2013) (14). The major impact of AS on overall health and activity raises the possibility that psychological factors may influence disease status and outcome. If true, this would have important implications for both assessment and management of AS.

The present study recorded a significant improvement of depressive AS patients with advancing doses of infliximab (p<0.001). This finding is consistent with Raison CL, et al study in USA (2013) (15).

Given the association of inflammatory cytokines with treatment resistance, there has been interest in testing whether inhibiting inflammatory cytokines might have therapeutic potential in treatment resistant depression (TRD). One inflammatory cytokine, tumor necrosis factor (TNF)-alpha, may be especially relevant in this regard. TNF-alpha has been reliably shown to be elevated in depressed patients (16). Moreover, increases in TNF-alpha have been associated with depressive symptoms during chronic exposure to interferon (IFN)-alpha (17). In addition, peripheral administration of a TNF-alpha antagonist has been shown to improve depressed mood in patients with psoriasis (18, 19).TNF-alpha antagonism has also been found to resolve major depression in patients with Crohn's disease, and reduce fatigue in patients with

advanced cancer (20). Moreover, gene-targeted deletion of TNF- α receptors in mice leads to an antidepressant-like phenotype and reduced anxiety-like behavior during immune activation (21, 22).

The proportion of depressed patients' improvement was 73.9%. This finding is close to results of Ertenli L, et al study in USA (2012) (23) which reported an improvement of depression and anxiety among 72.5% of AS patients after 3 doses treatment with infliximab.

Although no statically significant association was observed between depression improvement of studied AS and their age, educational level and employment ($p>0.05$), a higher proportion (92.3%) of highly educated AS patients had depression improvement after treatment. Bayasal O, et al study in Turkey (2010) (24) reported significant negative correlation between depression scales among AS patients and their educational levels.

In the same direction, higher proportions (88.9%) of improved depressive AS patients in the present study were employed. This finding is consistent with results of Frauendorf R, et al study in Brazil (2013) (25) and Bonnen A, et al study in Netherlands (2001) (11). Occupational characteristics have been largely overlooked as potential risk factors, despite strong associations between functional limitations and work disability, and between physically demanding jobs and work disability (26).

The present study revealed significant association between improvement of depression and inactivity of ankylosing spondylitis disease ($p=0.003$). Mean BASDAI of AS patients was significantly declined among improved depressive AS patients ($p<0.001$). These findings are consistent with results of Günaydin R, et al study in Turkey (2009) (27) and Martindale J, et al study in UK (2006) (28). Our findings are consistent with the notion that self-report assessment tools may measure different facets of health status than tools which involve measurement by a clinician or metrologist. Whilst the issue of associations between disease scores with anxiety or depression not been previously investigated in AS, the limited extent to which patient-reported measures may capture overall disease status in AS has been raised⁽⁶⁴⁾, and the potential for patients' psychological status to influence completion of a self-complete questionnaire has been highlighted (28).

Our study revealed significant effect of infliximab (3doses) on both improvement of depression and ankylosing spondylitis ($p=0.016$). This finding is consistent with results of Mörck B, et al study in Sweden (2013) (29) which concluded that IFX treatment is effective in well-established active AS .

CONCLUSIONS:

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