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Etanercept is Effective and Relatively Safe in a Sample of Iraqi Patients with Ankylosing Spondylitis

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Abstract
Objective: To evaluate the efficacy and safety of etanercept in a sample of Iraqi patients with ankylosing spondylitis patients.
Patients and methods: A single center open labeled prospective study conducted on 74 patients with ankylosing spondylitis diagnosed according to modified New York criteria of ankylosing spondylitis. Patients received etanercept 25mg twice weekly and were assessed at baseline, at month1, 3, and 6 thereafter. Disease activity was evaluated by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and functional status by Bath Ankylosing Spondylitis Function Index (BASFI) at each visit. Safety assessments included adverse events and laboratory tests.
Results: Mean age of patients was 35.2 ± 10 years, males represented 92% of the cases, and the mean disease duration was 9.29 ± 7.1 years. A significant decrease in BASFI and BASDAI was found after 1month,3 months, and 6 months compared to baseline($p<0.001$). Multiple logistic regression analysis revealed no significant association between age of patients, disease duration, HLA-B27, family history of psoriasis or inflammatory bowel disease, nonsteroidal anti-inflammatory drugs intake, and duration of smoking with the changes in BASDAI and BASF of the patients. Drug related adverse effects included three patients developed injection site reaction, 10 patients upper respiratory tract infections, and no serious infections occurred **Conclusion:** Etanercept was effective and relatively safe in treatment of ankylosing spondylitis patients. Further investigation of longer term treatment with etanercept is warranted to further define its therapeutic utility.
Keywords: Ankylosing spondylitis; Etanercept; Efficacy; Safety; BASDAI, BASFI

1. Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease characterized by inflammatory backpain, peripheral arthritis, enthesitis, and extraarticular features such as uveitis and inflammatory bowel disease(IBD) [Braun and Sieper , 2007].The disease has a relatively early onset, presenting at a mean age of 26 years, and occurs somewhat more frequently in men than in women [Feldtkeller et al, 2003]. Disease progression may result in loss of mobility and function, and therefore patients can experience a heavy disease burden, with pain and stiffness, loss of physical function, and severe impairment in quality of life [Davis et al, 2005; Zink et al, 2000].

Therapeutic options for patients suffering from AS have been limited over the last decades. There is no evidence that disease modifying anti-rheumatic drugs (DMARDs) work in axial manifestations of [Roychowdhury et al, 2002; Braun et al, 2006]. Tumour necrosis factor (TNF) blockers have greatly improved the condition of patients with active inflammatory spinal disease [Heiberg et al, 2005]. The short-term efficacy and safety of the recombinant 75-kd tumour necrosis factor (TNF) receptor IgG1 fusion protein etanercept (Enbrel) has been demonstrated in clinical studies of patients with active AS [Brandt et al, 2003; Gorman et al, 2002; Davis et al, 2004; Brandt et al, 2005].

This study was designed to assess the efficacy and safety of etanercept in a sample of Iraqi patients with ankylosing spondylitis

2. Patients and Methods

2.1 Study design

This was a single center, single group open labelled prospective study conducted at Rheumatology Unit in Baghdad Teaching Hospital from the 1st of January to the 1st of August, 2013.Patients received etanercept 25 mg twice weekly and evaluated at baseline and after 1month, 3 months, and 6 months for its efficacy and safety. Informed consent was obtained from all participants and this study was approved by the ethical committee of Baghdad University, College of Medicine -Medical Department.

2.2 Sample selection

Patients were included in the study if they had proved diagnosis of AS according to modified New York criteria of ankylosing spondylitis [Vander Linden et al, 1984] regardless the age or gender. Patients were excluded from

the study if they were currently on etanercept, refused to participate in the study, left the treatment or withdrew from the study, and those who developed serious complications.

2.3 **Clinical and laboratory evaluation**

Data were collected using a questionnaire form including age, gender, occupation, smoking habits, disease duration, medication used, and family history of psoriasis or IBD). Efficacy measures were assessed at baseline of the study (Month 0) and at month 1,3, and 6 and included 0-100 scale assessments of Disease activity by using Bath ankylosing spondylitis disease activity index (BASDAI) [Garrett et al, 1994] and functional status using Bath ankylosing spondylitis functional index (BASFI) [Calin et al, 1994].

The safety of etanercept was assessed at each study visit in all patients who received at least one dose of study medication. Safety assessments included adverse events, premature discontinuations and laboratory tests were done for measuring hemoglobin (Hb), erythrocyte sedimentation rate(ESR), White blood cell count(WBC), liver function tests (ALT,AST) and renal function tests(Blood urea, serum creatinine).

2.4 **Statistical Analysis:**

Data of all patients were done using the statistical package for social sciences software for windows (SPSS v 18, Chicago, IL, USA). Data were presented as mean and standard deviation for continuous variables: age, disease duration, BASDAI, BASFI and laboratory findings. Categorical variables were presented as numbers and percentages including gender, job, smoking, medication use, family history, and HLA-B27. Analysis of variances (ANOVA) test was used to compare the means of BASDAI, BASFI and laboratory findings and to assess the significance of changes in these variables at different time of follow up. Chi-square test (χ^2) was used for testing the significance of differences in the categorical variables variable. . Findings with P value ≤ 0.05 were considered significant.

3. Results

Of 75 AS patients enrolled in this study, 70 patients completed the study, three patients switched to another biological therapy (infliximab) and two patients lost follow up(figure 1). The baseline characteristics of them were shown in table 1. Mean age of the patients was 35.2 ± 10 years and mean disease duration was 9.29 ± 7.1 years. Sixty nine (92%) patients were males. More than one-third (34.7%) of the patients were current smokers, 3 (4%) patients were ex-smokers and 46 (61.3%) patients were never smokers. Positive HLA-B27 was present in 41 (54.7%) studied AS patients, two patients (2.7%) had family history of IBD, and 60 (80%) patients were NSAIDs users.

The Mean baseline BASDAI of the patients was 5.4 ± 0.24, after one month of weekly treatment with etanercept medication, mean BASDAI of the patients was 4.3 ± 0.20, after three months the mean BASDAI changed to 3.0 ± 0.19, reached to 2.2 ± 0.12 after six months. There was a significant decrease in BASDAI of the studied AS patients through the period of follow up of the patients after treatment with etanercept medication ($p < 0.001$). Mean difference in BASDAI vs the baseline value was 1.1after one month, 2.4 after 3 months and 3.2 after 6 months. The difference in BASDAI was highly significant ($p < 0.001$), indicating the good effect of etanercept, table 2.

Mean baseline BASFI of the studied AS patients was 5.93 ± 0.23, decreased after one month to 5.1 ± 0.21, after three months to 3.8 ± 0.20 and after six months it was 2.9 ± 0.10, with a highly significant decrease in BASFI as compared to baseline ($p < 0.001$). The mean difference in BASFI of the compared to baseline was 0.83 after one month 2.13 after 3 months and after 6 month the mean difference in BASFI was 3.03, and this difference was significant at all times of follow up ($p < 0.001$), table 2. These findings indicate the effectiveness of etanercept in reduction of both disease activity and functional status.

Multiple logistic regression analysis revealed no significant association between each of age of the patients, disease duration, HLA-B27, family history of psoriasis/IBD, NSAIDs intake and duration of smoking with changes in BASDAI, BASFI and functional class ($P>0.05$) indicating that these changes were mainly due to the effect of etanercept (table 3).

Drug related adverse effects included three patients developed injection site reaction, 10 patients upper respiratory tract infections, and no serious infections occurred(Not shown in table).

Finally, Etanercept effect on laboratory blood test of the patients showed significant reduction in WBC and ESR after 6 months of treatment ($p< 0.001$, Table 4).

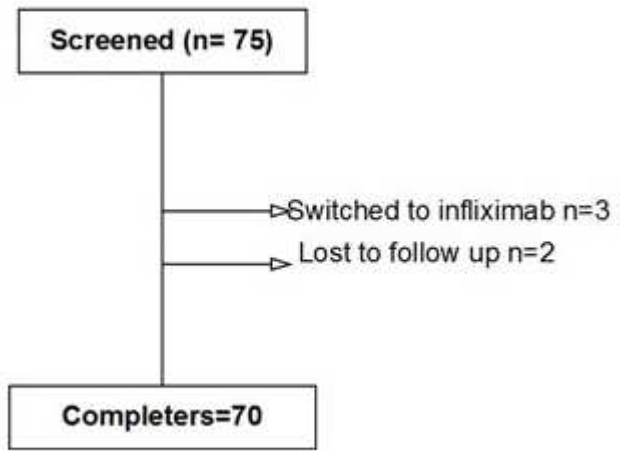

Figure1: Flow chart of the study

Table1. Baseline characteristics of ankylosing spondylitis patients

Variable		Value
Age\ mean ± SD (range) years		35.2 ± 10 (18 -59)
Males n (%)		69 (92)
Disease duration \ mean ± SD (range) years		9.29 ± 7.1
Smoking n (%)	Current	26 (34.7)
	Ex-smoker	3 (4.0)
	Never	46 (61.3)
Positive HLA-B27 n (%)		41 (54.7)
Family History of IBD n (%)		2 (2.7)
NSAIDs users n (%)		60 (80)

SD, standard deviation; IBD, inflammatory bowel disease; NSAIDs, nonsteroidal anti-inflammatory drugs

Table 2. Comparison in mean BASDAI and mean BASFI at different follow up time.

Variable	Baseline (n=75)	1 month (n=72)	3 months (n=68)	6 months (n=66)	*P*
BASDAI	5.4 ± 0.24	4.3 ± 0.20	3.0 ± 0.19	2.2 ± 0.12	<0.001*
Mean difference from Baseline	-	1.1	2.4	3.2	<0.001*
BASFI	5.93 ± 0.23	5.1 ± 0.21	3.8 ± 0.20	2.9 ± 0.10	<0.001*
Mean difference from Baseline	-	0.83	2.13	3.03	<0.001*

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Function Index, * p<0.05 is significant.

Table 3. Multiple logistic regression analysis of patients' characteristics and response to treatment.

Variable	Standardized correlation coefficients	*t*	P
Age	-0.027-	-0.092-	0.928
Disease Duration	0.219	0.914	0.377
HLA-B27	0.275	0.979	0.346
Family history of psoriasis \IBD	0.457	1.686	0.116
NSAIDs	-0.068-	-0.253-	0.804
Duration of Smoking	0.406	1.253	0.232

IBD, inflammatory bowel disease; NSAIDs, nonsteroidal anti-inflammatory drugs

Table 4. Effect of etanercept on laboratory blood tests

Test	Follow-up time				*P*
	Baseline (n=75)	1 month (n=72)	3 months (n=68)	6 months (n=66)	
Hb	13.2	13.3	13.4	13.2	0.85
WBC x 1000	8.5	7.5	6.9	6.6	< 0.001 *
ESR	31.2	19.86	18.19	16.12	< 0.001 *
AST	22.1	22.9	21.7	20.1	0.49
ALT	19.9	23.1	21.6	22.1	0.31
Blood urea	33.8	33.2	31.8	32.2	0.40
Serum Creatinine	0.77	0.83	0.81	0.87	0.12

Hb, haemoglobin; WBC, White blood cells; ESR, erythrocyte sedimentation rate; AST, aspartate transaminase; ALT, alanine transaminase.* P<0.05 is significant.

4. Discussion

AS is a chronic inflammatory disease often leading to permanent spinal damage, a considerable handicap, and a poor quality of life. Current treatments for AS are inadequate for most patients, especially treatments for axial skeletal involvement [Calin et al, 2004]. This study showed that etanercept 25mg twice weekly significantly reduced disease activity index and significantly improved the functional status of AS patients during the 6 months follow up period.

Other studies have reported similar findings. Calin et al (2004) conducted a multicenter randomized double blind placebo controlled clinical trial in Europe, with 45 patients randomly assigned to etanercept 25 mg and 39 to placebo twice weekly for 12 weeks. They reported that scores on the BASDAI composite index and the BASDAI fatigue component improved 44% among etanercept patients (p=0.01 versus placebo) and had improved spinal flexion. In addition, a post hoc analysis of BASDAI responses showed that the percentage of etanercept patients with BASDAI scores, 40 increased from 9% at baseline to 71% at week12.

Braun et al (2007) assessed the humanistic impact of AS and compared the effect of etanercept 50 mg once-weekly, etanercept 25 mg twice-weekly and placebo on patient-reported outcomes in a 12-week, double-blind, placebo-controlled multicenter study conducted on 356 patients with active AS and reported significant improvement in BASFI and significant reduction in BASDAI of etanercept groups compared to placebo.

Another study in 2011 compared the efficacy and safety of etanercept with that of sulfasalazine after 16 weeks of treatment in 379 patients with axial and peripheral manifestations of AS in a randomized, double-blind trial and demonstrated that etanercept was significantly more effective than sulfasalazine in improving the signs and symptoms of AS in the axial skeleton and peripheral joints [Braun et al, 2011].

A recent meta-analysis of randomized, double-blind, placebo-controlled clinical trials that included 1,570 participants has investigated the efficacy of etanercept in Caucasian versus Chinese populations and reported that there was sufficient evidence to prove that etanercept has its advantages in both disease activity controlling and symptoms relieving, especially for axial joints compared with peripheral joints, without higher incidence of serious adverse events [Li et al, 2013].

In this study, the non-significant association between age, disease duration, HLA-B27, family history of psoriasis/IBD, NSAIDs and duration of smoking with response to treatment on multiple regression analysis may indicate that the response was due to etanercept therapy.

Notably, most laboratory findings were normal except leucocytes count which showed a significant decrease after 6 months of treatment with etanercept. Pancytopenia including leukopenia rarely has been reported. The causal relationship to etanercept therapy remains unclear. Although no high risk group has been identified, caution is recommended if the drug is to be used in patients with a previous history of significant hematologic abnormalities. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias or infection (e.g., persistent fever, bruising, bleeding, pallor) while on etanercept and the drug should be discontinued if patient developed significant hematologic abnormalities [Sandhu et al, 2007].

The current study revealed a significant decline in ESR of AS patients after 6 months of treatment with etanercept. This in line with other studies which reported significant improvement in ESR after etanercept treatment [De Sanctis et al, 2013; Bes et al, 2013]. ESR is an important measure for assessment of treatment of AS patients with peripheral arthritis in addition to strong correlation with BASDAI of AS patients [Heijde et al, 2002].

Additionally, in this study, etanercept was well tolerated with an acceptable safety profile in adult patients with AS. Drug related adverse effects included 10 patients upper respiratory tract infections, three patients developed injection site reaction, two patients lost follow up and three switched to another biological therapy (infliximab) due to non-responsiveness, and no serious infections occurred. In the randomized clinical trials, the rate of adverse events was similar between the treatment and placebo groups, except for injection site reactions, which were more frequent in the etanercept groups [Davis et al, 2008; Dijkmans et al, 2009]. Another open-label extension study demonstrated that number of etanercept discontinuations because of adverse events was very low. Overall, serious adverse events occurred in less than 5% of the patients, and were often unrelated to treatment [van der Heijde et al, 2009]. Recently an open-label extension involving 59 AS patients treated with etanercept for 264 weeks (original etanercept group) or 252 weeks (original placebo group) reported that serious infections occurred at a rate of 0.03 events per subject years, while no cases of tuberculosis or opportunistic infections were reported [artín-Mola et al, 2010].

Limitations of this open label extension study include small sample size and short duration of follow up which may solved by a larger and longer duration randomized prospective study.

5. Conclusion

Etanercept drug was effective and relatively safe in treatment of a sample of Iraqi patients with ankylosing spondylitis.

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