

Efficacy and Safety of Etanercept in Severely Active Rheumatoid Arthritis: 6-month, Open Label, Prospective, Observational Study from Iraq

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Abstract

Objective: To assess the efficacy and safety of etanercept in severely active rheumatoid arthritis (RA) in a sample of Iraqi patients.

Patients and methods: An open labeled single group prospective observational study was conducted over 15 months on 190 Iraqi patients with RA diagnosed according to 1987 American College of Rheumatology criteria. All the included patients were given etanercept at a dose of 50 mg by subcutaneous injection on weekly bases. Disease activity score at 28 joints (DAS28) and functional class of RA were measured at baseline and after 6 months.

Results: There was significant improvement in disease activity (DAS28) ($p < 0.001$) with percent of change (-29.26%) and functional disability ($P = 0.001$) with etanercept use over a period of 6 months. Elevated liver transaminase were 3.68%, leucopenia 3.15%, headache 2.11%, itching 2.11%, serious chest infection 1.57%, leg abscess 0.52%, injection site reactions 1.05%, breast cancer 0.52, and drug induced psoriasis 0.52%.

Conclusion: Etanercept was effective and relatively safe in treatment of RA patients among Iraqi patients.

Keywords: Etanercept, Rheumatoid arthritis, Diseases activity score 28 (DAS28).

1. Introduction

Rheumatoid arthritis (RA) is a chronic progressive autoimmune disease that dramatically impairs quality of life [1]. Affected individuals experience significant morbidity, disability, and excess cardiovascular mortality [2]. The advent of targeted therapies, mainly against tumor necrosis factor alpha (TNF- α) have substantially changed the management and hence the prognosis of RA. Etanercept (ETN) was the first biologic response modifier to be approved by the US Food and Drug Administration (FDA) for use in RA [3]. Many clinical trials have reported that etanercept was safe and efficacious in active RA [4-9].

In Iraq, literature review revealed efficacy and safety of etanercept in ankylosing spondylitis patients, however there was no reports on its use in RA patients [10]. This study aimed to assess efficacy and safety of etanercept in a sample of Iraqi patients with severely active RA.

2. Patients and Methods

2.1 Study design

This is an open labeled single group prospective study that was conducted over 15 months period on Iraqi patients with RA who were seen consecutively in the Rheumatology Clinic in Baghdad Teaching Hospital from May 2012 to July 2013. All the included patients were given etanercept at a dose of 50 mg by subcutaneous injection on weekly bases from the start of the study to its end and patients were checked for efficacy and safety of the drug after 6 months.

The study was approved by the ethical committee of Medical Faculty in Baghdad Teaching Hospital and all patients gave their written informed consent prior to enrollment in the study

2.2 Sample selection

Patients were included in the study if they met the 1987 American College of Rheumatology criteria for the classification of RA, or had history of methotrexate intake for at least 3 months, patients with DAS28 should be equal to or greater than 5.1 (severe disease activity).

Patients were excluded from the study if they were less than 18 years old, or were taking other forms of disease modifying antirheumatic drugs (DMARDs), or had a previous history of biologic agents intake or had other connective tissue diseases overlapping with RA.

2.3 Data collection and measurements

For each patient, a baseline data were collected during the first visit and after six months. The collected data

included: patients' age, sex, phone number, smoking status, disease duration, and previous and current RA medications (DMARDs, corticosteroids and biologics). Assessment of disease activity was done by using DAS28 [11] and the functional status of the RA according to the American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis [12].

Laboratory data which include rheumatoid factor (RF) and hemoglobin (Hb) level, white blood cell (WBC) count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea and serum creatinine levels. (Performed during the first visit (baseline) and every subsequent visit). The side effects are checked and recorded for every patient in each visit.

2.4 Statistical analysis

A statistical software SPSS version 18 was used for analysis. A target sample size of 183 patients was calculated to provide approximately 90% statistical power with medium effect size of 30% and α error probability of 0.05 as a significant level. Descriptive statistics were presented as mean, standard deviation, frequencies and percentages. Paired t test was used to compare the change of mean DAS28 at baseline and after six months while Chi square test (X^2) was used to compare the change in functional class. $p < 0.05$ was considered as significant.

3. Results

Of a total 272 patients with RA, 195 patients met the inclusion criteria and 5 of those were lost during follow up leaving a total of 190 patients who successfully completed the study. The mean age of patients was (47.43 ± 11.9) years with a range of (20 - 95) years. The age was distributed into two categories; 52 patients (27.4%) were aged ≤ 40 years and 138 patients (72.6%) were aged > 40 years. Females were 158 (83.2%) and males were 32 (16.8%). Patients with disease duration < 10 years were 111 (58.4%) and those with disease duration ≥ 10 years were 79 (41.6%). Smokers were 18 patients (9.5%), RF was positive in 119 patients (62.6%), and 162 patients (85.3%) were taking MTX as in Table 1.

Etanercept significantly reduced DAS28 after 6 months (Mean difference -1.75 ± 0.117 , percent of change (-29.26%) , $p < 0.001$) as in figure 1. Also there was significant improvement in functional class with advancing treatment time. At baseline, 23 patients (12.1%) were functional class I, 70 patients (36.8%) were class II, 69 patients (36.3%) were class III and 28 patients (14.7%) were class IV. After sixth month of follow up the figures were changed to 106 patients (55.8%) in class I and only 9 patients (4.7%) in class IV which is significant ($P = 0.001$) as in Figure 2.

The most common adverse effects reported in this study were elevation in liver transaminases (3.68%) then leucopenia (3.15%), and other side effects were shown in Table 2.

Table 1. Baseline characteristics of rheumatoid arthritis patients (N=190)

Variable		N	%
Age (years)	≤ 40	52	27.4
	> 40	138	72.6
Sex	Male	32	16.8
	Female	158	83.2
	Smoker	18	9.5
Smoking	Non-smoker	172	90.5
Disease duration (years)	< 10	111	58.4
	≥ 10	79	41.6
	Positive	119	62.6
Rheumatoid Factor	Negative	71	37.4
Methotrexate	Use	162	85.3
	Not uses	28	14.7

N, number; %, percentage

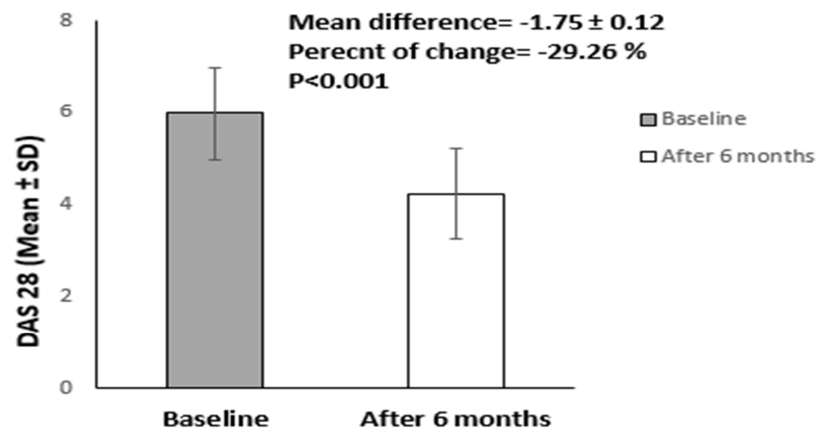


Figure 1. Disease activity index at 28 joints (DAS28) in severely active rheumatoid arthritis (N=190) at baseline and after 6 months of etanercept therapy; N, number; SD; standard deviation, P significant < 0.05

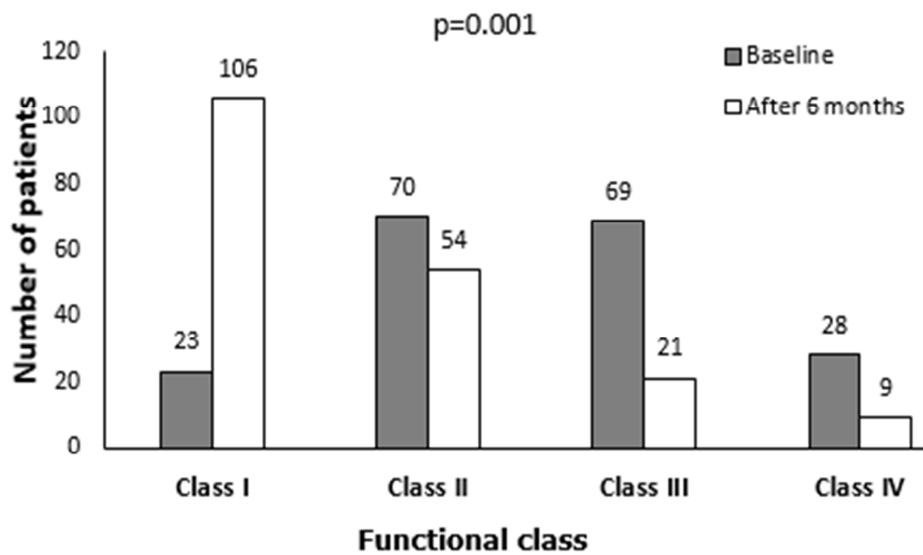


Figure 2. Functional class of rheumatoid arthritis patients at baseline and after 6 months of etanercept treatment.

Table 2: Frequency of adverse effects of etanercept treatment among 190 patients with rheumatoid arthritis in this study

Adverse effects	N	%
Elevated Liver transaminases	7	3.68
leucopenia (<3000)	6	3.15
Headache	4	2.11
Itching	4	2.11
Serious chest infection	3	1.57
Leg abscess	1	0.52
Injection site reactions	2	1.05
Breast cancer	1	0.52
Drug induced psoriasis	1	0.52

N, number; %, percentage

4. Discussion

This study assessed efficacy and safety of etanercept in severely active RA patients in Iraq. It showed clinically important and statistically significant reduction in disease activity (DAS28) ($p < 0.001$, percent of change (-29.26%) and significant with relevant improvement in the functional disability ($p = 0.001$) with etanercept use over a period of 6 months. In addition, etanercept was relatively safe with little adverse effects ranged from transient elevation of liver transaminases (3.68%) and leucopenia (3.15%) which restored back to normal after withdrawing of etanercept for an average of 2 weeks duration to non-serious infections (chest infection (1.5%) and leg abscess (0.5%), injection site reaction (1.05%) and drug induced psoriasis (1.05%).

Similar findings were reported by other studies. Weinblatt et al [13] evaluated safety and efficacy of etanercept beyond 10 years of therapy in North American patients with early and longstanding rheumatoid arthritis in open-label extension studies following initial double-blind trials of etanercept and found that etanercept was well tolerated and effective as a long-term, continuous therapy for the treatment of RA, with a favorable risk/benefit ratio.

Another study from Japan, one of the largest observational trials conducted thus far in RA patients treated with biologics, evaluated the safety and effectiveness of etanercept in a 6-month postmarketing surveillance study covering all Japanese patients with rheumatoid arthritis (RA) who received etanercept during a 2-year period. Data for 13,894 patients (1334 sites) enrolled between March 2005 and April 2007 were collected and it showed that etanercept was effective and safe in Japanese patients [14].

In addition, Koike et al reported that Combination therapies with etanercept plus methotrexate or other DMARD were reasonably well tolerated, and a combined etanercept with methotrexate at higher doses was more effective than etanercept monotherapy in Japanese patients with RA [15].

Recently, Machado et al [16] compared in an open label observational study the addition of etanercept versus a conventional DMARDs in subjects with active RA despite methotrexate therapy in the Latin American region and concluded that adding etanercept to methotrexate demonstrated better efficacy than adding one other conventional DMARD to methotrexate. No new safety issues were observed. A combined etanercept with methotrexate provided a favorable benefit-risk profile among RA patients from LA region.

The interpretation of the response to etanercept treatment may be related to no immunogenicity or insignificant immunogenicity against etanercept treatment as compared to other TNF blockers [17].

Notably, in the current study one patient developed breast cancer, although we were not sure whether this was an accidental finding or not because similar complication have not been reported in other studies.

The main limitations of this study are open label study and no control arm was included. This makes it difficult to distinguish outcomes relating to etanercept treatment from those caused by other factors (like: patient expectations, natural history of the disease, or concomitant treatments) but longer-term blinded studies with

control arm may solve these problems. However this is the first study evaluating the efficacy and safety of etanercept in combination with methotrexate in inadequate responders to methotrexate with a sufficient sample size among Iraqi patients.

5. Conclusion

Etanercept was effective and relatively safe drug in treatment of a sample of Iraqi patients with severely active RA. This may suggest that early initiation of etanercept treatment to control inflammation in patients with active RA thus warrants consideration.

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