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A Prospective Open Label Trial of Clinical Efficacy and Safety of Etanercept in Juvenile Idiopathic Arthritis: Study from Iraq

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Abstract
Objective: To evaluate the efficacy and safety of etanercept (ETN) in Iraqi patients with juvenile idiopathic arthritis (JIA).**Patients and Methods:** This open labeled single group observational study included 42 Iraqi patients who fulfilled International League of Associations for Rheumatology (ILAR) criteria of JIA. All the patients were given ETN 0.8 mg/kg (max: 50 mg) subcutaneous injection once weekly. Baseline data were collected during the first visit and patients were followed during the study at regular intervals: one month, three months, and six months. Outcome measures included juvenile arthritis disease activity score3-27 joints (JADAS3-27), functional class, and drug adverse effects were measured and recorded at each follow up time.**Results**: The mean age of patients was (11.91±3.78 years). Female patients were 22 (52.4%). The mean JADAS3-27 at base line was 20.29 ± 10.4 and reduced significantly after six months to reach 8.79 ± 6.6 ($P<0.001$). The overall number of patients who had advanced functional class (III and IV classes) at baseline changed significantly to lower classes after six months of follow up ($P=0.001$). Adverse events were leukopenia in two patients (4.8%), elevated liver enzymes in one patient (2.4%) and mild transient local skin rash at site of injection in five patients (11.9%).**Conclusion:** Etanercept drug was effective and relatively safe in treatment of Iraqi patients with JIA patients.
Key words: Juvenile idiopathic arthritis, JADAS 3-27, Functional class, Etanercept

1. Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory rheumatic disease and a major cause of chronic disability in children. It comprises a clinically heterogeneous group of disorders characterized by persistent joint inflammation and onset before age 16 years. JIA is associated with functional disability [1,2] due to joint manifestations, morning stiffness, and fatigue [3].

Treatment of children with JIA mostly relies on nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs). For patients who do not adequately respond to conventional treatment, anti-TNF-α agents are an important alternative. The introduction of anti-TNF drugs into the treatment of rheumatic diseases has created the need for long-term monitoring of patients and, as a result, a number of JIA registries have been established across the world [4-8]. Etanercept (ETN) is a soluble dimeric fusion protein consisting of the human p75 TNF receptor fused to the Fc region of human IgG1 and it has appeared to have a major impact on outcome [9] and has become an important treatment option for children with JIA who did not respond or were intolerant to the conventional disease-modifying antirheumatic drug (DMARD) methotrexate [10].

In Iraq, literature review revealed efficacy and safety of etanercept in rheumatoid arthritis, however there was no reports on its use in JIA patients [11]. This study was designed to assess the efficacy and safety of ETN in Iraqi patients with JIA.

2. Patients and Methods

2.1 Study design

This open labeled single group observational study was conducted from September 2012 to June 2013 at the Rheumatology Unit, Department of Medicine in Baghdad Teaching Hospital. All the included patients were given ETN at a dose of 0.8 mg/kg (max: 50 mg) subcutaneous injection once weekly during the study period. The baseline and follow up data were collected and assessed for efficacy and safety. The informed written consents of parents and patients (as appropriate) were obtained according to the Declaration of Helsinki and ethical approval was obtained from Medical Faculty in Baghdad Teaching Hospital.

2.2 Patients' selection

Patients were included in the study if their age was below 16 years old with proved diagnosis of JIA according to the International League of Associations for Rheumatology (ILAR) 2001 classification criteria [12]. Patients had an inadequate response to the treatment with NSAIDs, corticosteroids (systemic or intra-articular) and DMARDs for at least 3 months. The exclusion criteria were**:** Patients with a previous history of biologic agent intake or had septic arthritis or arthritis related to malignancy, trauma or connective tissue disease.

2.3 Data collection and measurements

Baseline data included age, sex, smoking status, age at disease onset, disease duration, medical history, previous medication, concomitant drugs at start of ETN, disease activity and functional status. Follow-up data for disease activity, functional status and adverse effects were collected at one month, three months, and six months after the first visit.

Juvenile disease activity was measured by JADAS3-27 which included number of active joints of articular joint counts (AJC) (joints with swelling not caused by deformity, or joints with limited motion, and with pain, tenderness, or both).Overall assessment of disease activity by the doctor through the visual analogue scale VAS (range 0–10 cm).Parent/patient global assessment of well-being VAS (range 0-10 cm).

JADAS3-27= AJC (27joints) + Physician global (10 cm VAS) + Parent/patient global (10 cm VAS) [13]

Functional status was assessed using the criteria for classification of functional status in rheumatoid arthritis [14]. Laboratory data included rheumatoid factor (RF) and antinuclear antibody (ANA) (performed at the first visit) and erythrocyte sedimentation rate (ESR), hemoglobin (Hb) level, white blood cell (WBC) count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea and serum creatinine levels (performed at the first visit (baseline) and every subsequent visit).

2.4 Statistical analysis

A statistical software SPSS version 18 was used for analysis. A target sample size of 36 patients was calculated to provide approximately 95% statistical power with medium effect size of 25 % and α error probability of 0.05 as a significant level for a single group and 4 numbers of repeated measurements. Descriptive statistics were presented as mean, standard deviation, numbers and percentages. ANOVA test was used to compare the change of mean JADAS3-27 at baseline, one month, three months, 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 55 patients, only 42 met the inclusion criteria, of these: 10 patients were lost during the follow up after six months. The mean age of patients was (11.91±3.78 years). Female patients were 22 (52.4%). Nonsmokers were 39 patients (92.9%), the mean disease duration was (7.8 ± 6.6 years), RF was positive in four patients (9.52%), ANA was positive in only two (4.76%) patients, methotrexate and prednisolone were the dominant medications used by patients, they were used by 37 (88.1%) and 33 (78.57%) patients respectively as shown in table 1.

The mean disease activity score 3-27(JADAS3-27) at base line was 20.29 ± 10.4 and reduced significantly after six months to reach 8.79 ± 6.6 ($P<0.001$) as shown in figure 1. The overall number of patients who had advanced functional class (III and IV classes) at baseline changed significantly to lower classes after 6months of follow up ($P=0.001$) as shown in figure 2.

Adverse effects found among patients were leukopenia in two patients (4.8%) and one patient (2.4%) had elevated liver enzyme, the treatment was postponed in those three patients for one month and reconstituted later. Another five patients (11.9%) had reported mild transient local skin rash at site of injection.

Table 1. Baseline characteristics of study group (N=42)

Variable		Value
Age Mean ± SD (years)		11.91±3.78
Females n (%)		22 (52.4)
Smoking n (%)	Never	39 (92.9)
	Ex-smoker	3 (7.1)
Disease duration Mean ± SD (years)		7.8 ± 6.6
RF n (%)	Positive	4 (9.52)
ANA n (%)	Positive	2 (4.76)
Medications		
Methotrexate n (%)		37(88.1)
Sulfasalazine n (%)		13(30.95)
Chloroquine n (%)		4(9.52)
Leflunomide n (%)		3 (7.14)
Azathioprine n (%)		3 (7.14)
Prednisolone n (%)		33 (78.57)
IAS (Methyl-prednisolone) n(%)		7 (16.6)

RF, rheumatoid factor; ANA, antinuclear antibody; n, number; IAS, intra-articular steroids, SD, standard deviation

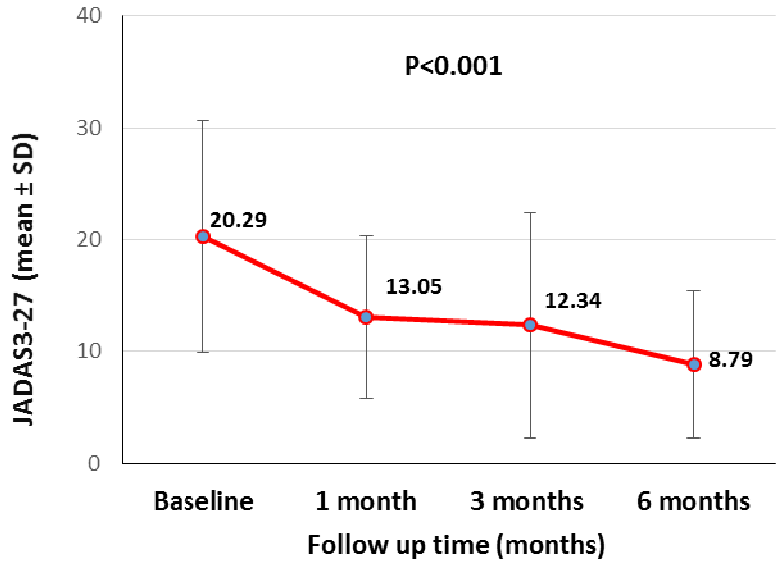

Figure 1. Changes in mean JADAS3-27 score throughout follow up period. JADAS3-27, Juvenile Arthritis Disease Activity Score3-27 joints.

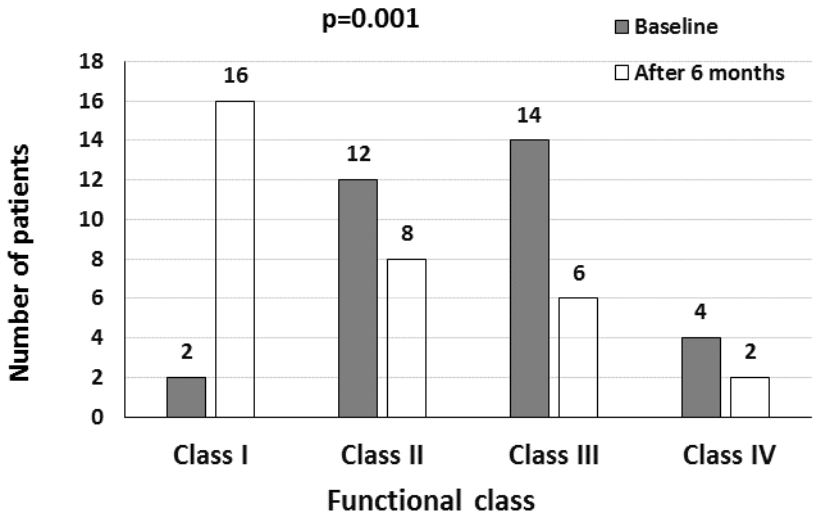

Figure 2. Functional class of patients with Juvenile idiopathic arthritis (JIA) at baseline and after 6 months of follow up.

Table 2: Adverse effects among JIA patients who received ETN

Adverse effect	n	%
Leukopenia	2	4.8%
Elevated liver enzyme	1	2.4%
Local skin rash	5	11.9%

n, number

4. Discussion

This study was designed to evaluate the efficacy and safety of ETN in Iraqi patients with JIA and showed that the mean disease activity score 3-27(JADAS3-27) was significantly reduced with significant improvement in the functional class after 6 months of follow up (P=0.001). In addition, ETN was relatively safe and well tolerated.

Similar findings were reported by many other studies. Horneff et al [15] described the efficacy and safety of open-label ETN on extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis and psoriatic arthritis: part 1 (week 12) of the CLIPPER study and found that ETN treatment for 12 weeks was effective and well tolerated in these pediatric subjects with no unexpected safety findings. Klotsche et al [16] investigated the 12-month course of health related quality of life (HRQOL) in patients with JIA after the start of therapy with ETN and identified its determining factors. They concluded that HRQOL was dramatically improved in children who started ETN treatment. Inactive disease and lower pain were important predictors for improvement of HRQOL over time.

Dore [17] reviewed the clinical utility of ETN in the treatment of arthritides in children and adolescents and reported that ETN has significantly improved the quality of life of children with JIA and has an acceptable safety profile. Minden et al [18] assessed the outcome of adult patients with JIA who received ETN during childhood and demonstrated that the first data from the JuMBO register indicate an improved long-term outcome of patients with severe JIA treated in the biologic era and an acceptable safety profile of ETN. Another study evaluated the long-term safety and efficacy of ETN in Japanese children with JIA and showed that ETN is an effective therapeutic option for Japanese children with polyarticular-course JIA [19].

Recently Windschall et al [20] assessed safety and efficacy of ETN in a total of 1,678 JIA patients with the JIA categories and reported that administration of ETN in patients with the JIA categories is safe and very efficacious in children.

A number of limitations of the current study must be pointed out: the relatively small sample size of the study must be noted. In addition to the relatively short study period could not confirm the sustained remission in JIA patients. However these limitations may be solved by a larger sample and longer study follow up. Despite these limitations, our findings call attention to the effectiveness and safety of ETN treatment in Iraqi patients with JIA for the first time with strict inclusion and exclusion criteria.

5. Conclusion

In conclusion, ETN was effective and comparatively safe in Iraqi patients with JIA. This is important because it

may have economic impact and can improve functional quality of life of the patients.

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