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Etanercept in Ankylosing Spondylitis: Effect on Some Hematological and Biochemical Parameters

Zahraa R. Albagoa[1], Imad A.Thanoon[2], Ali A. Younis[3,*]

[1]Ibn Sina Teaching Hospital

[2]Chief Director of Pharmacology Department- College of Medicine-University of Mosul

[3]Department of Medicine- College of Medicine-University of Mosul

[*]Corresponding author email: ali.younis7622@yahoo.com

ABSTRACT

PURPOSE: This study aimed to assess the effect of etanercept on the following hematological and biochemical parameters in a sample of Iraqi patients with AS: hemoglobin (Hb), white blood cell (WBC) count, neutrophil count, platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea and serum creatinine.

Methods: A single-center open-labeled prospective study conducted on 43 patients with AS diagnosed according to modified New York criteria of ankylosing spondylitis. Patients received etanercept 50mg once weekly and were assessed at baseline, at weeks 4 and 12. In all the patients the following laboratory tests were done: hemoglobin (Hb), WBC count, neutrophil count, platelet count, liver function tests including aspartate aminotransferase (AST), and alanine aminotransferase (ALT), and renal function tests including blood urea and serum creatinine.

Results: Mean age of patients was 36.55±8.47 years, males represented 90.7% of the cases, and the mean disease duration was 9.6±5.90 years. There was a significant reduction in WBC ($p=0.003$) and neutrophil count (0.000) after 4 and 12 weeks of treatment. However, there were no significant changes in serum SGOT, SGPT, urea, and creatinine ($p > 0.05$ for all).

Conclusion: Etanercept 50 mg once weekly for 12 weeks was associated with a reduction in WBC and neutrophil count after 4 and 12 weeks of treatment, with no significant changes in LFT and RFT. Leukopenia, neutropenia and elevated LFT were mild and each detected in 7% of the cases; they didn't result in discontinuation of treatment.

Keywords: ankylosing spondylitis, etanercept, TNF-α inhibitors, neutropenia

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INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory disease that is characterized by sacroiliac joints inflammation, chronic inflammatory back pain, enthesitis, and peripheral arthritis. Extra-articular features, such as inflammatory bowel disease, acute anterior uveitis, and psoriasis may also be present [1].Ankylosing spondylitis (AS) belongs to the group of diseases known as spondyloarthritides[2]. The disease usually begins in the second or third decade [3]; male to female prevalence is between 2:1 and 3:1[4].TNF-α inhibitors including etanercept have been verified as a significant breakthrough for managing patients with active AS and they can relieve symptoms caused by AS in a rapid manner for the majority of patients[5].

Etanercept is a receptor fusion protein composed of tumor necrosis factor receptor (TNFR) linked to the Fc portion of human IgG1[6]. TNF-α inhibitors are generally well tolerated. Common side effects, like rashes and injection site reaction, are usually mild and self- limiting, and generally do not lead to discontinuation of the drug[7]. However, significant hematologic reactions, in particular leukopenia and neutropenia, have been reported in patients treated with all TNF inhibitors including etanercept[7-12].Other cytopenias are uncommon[7]. In placebo-controlled trials, serious liver problems were rarely seen with TNF-α inhibitors[13].Elevations in aminotransferase have been seldom reported in case studies with the use of TNF-α inhibitors [14]. Data about the effect of TNF-α inhibitors on renal function in patients with AS are scarce[15].

This study aimed to assess the effect of etanercept on some hematological and biochemical parameters in a sample of Iraqi patients with AS. These include hemoglobin (Hb), white blood cell count (WBC), neutrophil count, platelet count, liver function tests including aspartate aminotransferase (AST), and alanine aminotransferase (ALT), and renal function tests including blood urea and serum creatinine.

METHODS

Study design

This open-labeled prospective study was conducted at the Rheumatology unit in Ibn Sina Teaching Hospital between October 2020 and March 2021. The study was conducted in keeping with the principles stated in the Helsinki Declaration and was approved by the Medical Research Ethical Committee, Department of Medicine, College of Medicine, University of Mosul (Ref. no. : UOM/COM/MREC/20-21 (24)). Written informed consent was obtained from all participants. All the included patients were given etanercept at a dose of 50 mg weekly by subcutaneous injection and evaluated at baseline and week 4 and week 12 for its effect on some hematological and biochemical parameters.

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Sample selection

Forty patientswith a proven diagnosis of AS according to modified New York criteria of ankylosing spondylitis will be included in this study[16]. Eligible patients have had an active axial disease, defined as a BASDAI score of ⩾4 and a spinal pain score of ⩾4 (numerical rating scale 0–10) with an inadequate response to initial therapy with two different nonsteroidal anti-inflammatory drugs (NSAIDs) used consecutively in an adequate dose for at least two to four weeks each[17].They were previously treated with etanercept or adalimumab for a variable period, and their treatment was interrupted for 3-4 months because of the unavailability of the drugs. Treatment with etanercept was resumed if the patient had disease relapse, defined as BASDAI ⩾4. Patients were permitted to continue NSAIDS on demand.

Patients will be excluded from the study if they refuse to participate in the study, left the treatment, and develop serious complications.

Lab evaluation

In all the patients the following laboratory tests were done: hemoglobin (Hb), white blood cell count (WBC), neutrophil count, platelet count, liver function tests including aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and renal function tests including blood urea and serum creatinine. These lab tests were done at baseline, after 4 weeks, and 12 weeks. All the patients were evaluated for the presence of leukopenia, neutropenia, thrombocytopenia, and any increase in RFT and LFT above the upper limit of normal at weeks 4 and 12. Leukopenia is defined as a reduction in the WBC count to $< 4 \times 10^3/ \mu L$). Neutropenia is usually defined as an absolute neutrophil count (ANC) $<1.5 \times 10^3/ \mu L$ in an adult.[18].Neutropenia can be categorized as[18]:

•Mild – ANC ≥ 1 and $<1.5 \times 10^3/ \mu L$

•Moderate – ANC ≥ 0.5 and $<1 \times 10^3/ \mu L$

•Severe – ANC $<0.5 \times 10^3/ \mu L$

Thrombocytopenia is defined as a platelet count below the lower limit of normal (ie, 150 x $10^3/ \mu L$] for adults) [19].

The upper limit of normal (ULN) cutoffs for ALT and AST concentrations were 39 and 40 U/L respectively. An ALT and/or AST >1 × ULN was defined as reflecting an elevation in LFT, >2 × ULN was regarded as indicating abnormality, and >5 × ULN was considered indicative of hepatotoxicity[20].The upper limit of normal for blood urea and serum creatinine were7.1 mmol/L and 124 μmol/L respectively.

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Statistical analysis:

The data were collected and organized in Microsoft Excel 2007, and then the Statistics Package for Social Sciences (SPSS 26.0 for Windows) was used for analyzing the data. Data were presented as mean and standard deviation for continuous variables. Categorical variables were presented as numbers and percentages. Analysis of variances (ANOVA) test was used to compare the means of different parameters and to assess the significance of changes in these variables at a different time of follow-up. A post hoc test was conducted to find the honest statistical differences. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

Of 43 AS patients enrolled in this study, 40 patients completed the study. One patient developed uveitis and 2 patients developed a covid-19 infection. The baseline characteristics of them were shown in table 1. The mean age of the patients was 36.55±8.47 years and the mean disease duration was 9.6±5.90 years. Thirty-nine (90.7%) patients were males. More than half (58.1%) of the patients were current smokers, 90.7% of the patients were using NSAIDs, and 67.4% and 32.6% were previously using adalimumab and etanercept respectively.

Table 1: Baseline characteristics of the ankylosing spondylitis patients

"Variable"		"Value"
Age (mean± SD)		36.55±8.47
Duration (mean± SD)		9.6±5.90
Weight in kg, mean (SD)		70.5 ±12.6
Smoking, n (%)	Ex-smoker	2 (4.7%)
	never	16 (37.2%)
	current	25 (58.1%)
NSAID	Yes n (%)	39 (90.7%)
	No n (%)	4(9.3%)
MTX users'	Yes n (%)	6 (14%)
	No n (%)	37 (86%)
Steroid users'	Yes n (%)	5 (11.6%)
	No n (%)	38(88.4%)
Previous TNF- α inhibitors	ADA n (%)	29 (67.4%)
	ETN n (%)	14 (32.6%)

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The effect of etanercept on some hematological parameters is shown in table 2. There was a significant reduction in mean WBC (p=0.003) and mean neutrophil count (0.000) after 4 and 12 weeks of treatment. The post hoc test clarifies that the real difference regarding the WBC count was between the baseline and the 12 weeks visit only (p-value=0.002); regarding the neutrophil count, there was a significant difference between the baseline visit and the week 4 (p=0.002) and week 12 (p=0.000) visits, however, the difference was not significant between the week 4 and week 12 visit (p=0.55). There was no significant change in Hb level and platelet count after 4 and 12 weeks of treatment (p > 0.05). Leukopenia and neutropenia were detected in 3 patients (7%) only; they were mild and treatment with etanercept was continued.

Table 2: Effect of etanercept on some hematological parameters

Lab test	Baseline	Week 4	Week 12	p-value*
Hb	13.61±1.70	13.705±1.72	13.67±1.67	0.969
WBC× 10^3	8.44 ±3.16	6.98±2.79	6.32±2.35	0.003
Neutrophils× 10^3	5.2±2.2	3.9±1.5	3.5±1.3	0.000
Platelets× 10^3	291.9±100.2	288.48±95.89	283.48±86.90	0.923

The effect of etanercept on some biochemical parameters is shown in table 3. There were no significant changes in serum SGOT, SGPT, urea, and creatinine after 4 and 12 weeks of treatment (p > 0.05 for all). Only 3 (7%) patients had an elevation in LFT (>1 × ULN and <2 × ULN), and they continued treatment with etanercept.

Table 3: Effect of etanercept on some biochemical parameters

Lab test	Baseline	Week 4	Week 12	P value*
SGOT	**26.93±6.77**	**26.90±6.79**	**27.55±7.51**	**0.896**
SGPT	27.43± 8.47	26.8± 8.15	27.18 ± 8.43	0.944
Urea	4.29±1.16	4.27±1.17	4.27±1.17	0.994
Creatinine	74.65±16.80	74.53±16.89	74.30±16.41	0.996

AST, aspartate transaminase; ALT, alanine transaminase.

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DISCUSSION

In this 3 month study, once-weekly subcutaneous injections of 50 mg etanercept resulted in a reduction in WBC (p=0.003) and neutrophil count (0.000) after 4 and 12 weeks of treatment. There was no significant effect on platelet count and Hb level. Leukopenia and neutropenia were detected in 7% of patients only. However, they were mild and didn't lead to treatment discontinuation. Our finding was in agreement with Alosami M et al (2013), who conducted a single-center prospective study on 74 patients with ankylosing spondylitis [21].They found a significant reduction in WBC count after 6 months of treatment, with no significant effect on hemoglobin and platelet count. They didn't assess neutrophil count. Xiong W et al in their study which was designed to identify the frequency of leukopenia in patients on anti-TNF alpha therapy at a tertiary care institution for various indications, and found that 19% developed leukopenia during anti-TNF alpha therapy [8]. The higher frequency of leukopenia in this study may be explained by the longer duration of treatment, concomitant use of methotrexate, and the inclusion of different TNF inhibitors for a variety of indications. Hastings R. et al conducted a study to assess the rates of and risk factors for neutropenia in a cohort of patients treated with a tumor necrosis factor (TNF) inhibitor for different types of inflammatory arthritis including AS.[7].They found that 18.8% had at least one episode of neutropenia during TNF inhibitor therapy and that 6% of them developed serious infections. In patients with AS, 15.8% developed neutropenia. They found that after the initial drop in the neutrophil count after 2 weeks of treatment with TNF inhibitor, the mean neutrophil count decreased to a consistent level over the following 12 months. This pattern of drop in the neutrophil count was seen in both the group thatdeveloped at least one episode of neutropenia and the group that did not.

TNFα has a complex effect on neutrophils. This cytokine up- regulates other proinflammatory cytokines involved in the differentiation and maturation of hemopoietic progenitor cells, including granulocyte-macrophage colony- stimulating factor, interleukin- 1 (IL- 1), IL- 6, and IL- 8 [22].So it is possible that TNF inhibition could result in bone marrow suppression by inhibiting stem cell differentiation[23]. However, normal bone marrow examinations had been found in many cases of TNF inhibitors -induced neutropenia, suggesting that neutropenia could be mediated by increased peripheral consumption[11]. Furthermore, the drop in neutrophil count following TNF inhibitor therapy was not seen for other cells from the same lineage, namely basophils, eosinophils, and monocytes [7,11]. Owing to the risk of leukopenia and neutropenia among patients treated with TNF-alpha inhibitors, it seems wise to check a complete blood countwithin one month of starting TNF-alpha inhibitors, and then to repeat this test every three months, assuming that the patient's white blood cell count is stable.

There were no significant changes in serum SGOT and SGPT after 4 and 12 weeks of treatment with etanercept. Only 3 patients had an elevation in LFT (>1×ULN and <2 × ULN), and they continued treatment with etanercept. Our findings were in agreement with a previous study done by Alosami M et al, who found no significant changes in LFT over 6 months of treatment with etanercept in AS [21]. In their study, van Denderen JC et al found that increased liver enzymes

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were detected in 14 % of AS patients who were treated with etanercept for at least 3 months [13]. The higher frequency of increased liver enzyme in this study may be due to a longer period of follow-up, the use of co-medication which could affect the liver like methotrexate, sulfasalazine, and NSAIDs. Other factors like alcohol usage, obesity, and comorbidities may also be involved. In a study conducted by Sokolove J et al in patients with rheumatoid arthritis, liver enzyme elevations were most frequently observed with infliximab, less commonly detected with adalimumab, and not observed with etanercept compared with comparator DMARDs[20]. TNF-αinhibitors differ in their molecular structure, dosing, dose schedule, route of administration, and half-life as well as potential immunogenicity[20]. This may explain the difference in liver enzyme elevation between TNF-α inhibitors.

In the current study, there were no significant changes in serum urea and creatinine after 4 and 12 weeks of treatment. Our findings were in agreement with a previous study done by Alosami M et al, who found no significant changes in serum urea and creatinine over 6 months of treatment with etanercept in AS [21]. Similarly, in a study done by Swart I et al, TNF inhibitors themselves, were not associated with a significant decline renal function in AS patients, which means that use of anti-TNF is safe concerning renal function in patients with AS [15].

The main limitations of this study were the small sample size and short duration of follow-up. Longer-term studies with larger numbers of patients will be necessary to address the issue of safety further and to determine the effects of etanercept on more hematological and biochemical parameters in patients with AS.

CONCLUSION

Etanercept 50 mg once weekly for 12 weeks was associated with a reduction in WBC and neutrophil count after 4 and 12 weeks of treatment, with no significant changes in serum SGOT, SGPT, urea, and creatinine. Leukopenia, neutropenia, and elevated LFT were each detected in 7% of the cases; however, they were mild and didn’t result in discontinuation of treatment.

DECLARATIONS

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Contribution of authors : We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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