ISSN: 2457-0400

Impact Factor: 6.711

WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

www.wjahr.com

Volume: 9, Issue: 11

Page N. 112-116

Year: 2025

Original Article

Coden USA: WJAMA3

EFFECT OF ETANERCEPT ON BLOOD INVESTIGATIONS IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Article Received: 01 October 2025 **Article Revised:** 20 October 2025 **Article Published:** 01 November 2025

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DOI: https://doi.org/10.5281/zenodo.17490198

How to cite this Article: Dr. Ashraf Ibrahim Gandary*, Dr. Fakhir Yousif Hussain, Dr. Ali Abdul-Rahman Younis. (2025). Effect Of Etanercept On Blood Investigations In Patients With Rheumatoid Arthritis. World Journal of Advance Healthcare Research, 09(11), 112–116.

ABSTRACT

Background: Rheumatoid arthritis (RA) is a chronic inflammatory disorder affecting synovial joints of the hands and feet, primarily caused by TNFα. Etanercept, a fusion protein, acts as a competitive inhibitor, reducing pro-inflammatory effects. Treatment results in hematological changes, such as anemia and leukocyte levels. **Aim:** To study the association of blood investigation with etanercept in patients with Rheumatoid Arthritis. **Patients and Methods:** This study analyzed 100 Iraqi patients with rheumatoid arthritis who were referred to the biologics committee in Ibn-Sena Teaching Hospital from April-2019 to April-2020. The patients were diagnosed as RA by their physicians and referred to the biologic drug dispensing committee who made the final decision. Patients were given 50 mg of etanercept weekly and checked for effectiveness and safety after 3 and 6 months. Data was collected from the patients with rheumatic diseases treated with biological agents in the rheumatology department. **Results:** A study of 190 patients with RA found that 107 met inclusion criteria, leaving 100 who completed the study successfully. The mean age was 48.29 ± 12.81, with a mean disease duration of 12.05 ± 8.40. Rheumatoid factor was positive in 76% of patients, and ACCP positive in 9.3%. The mean MTX dose was 14.67 ± 3.58mg, and no significant changes in HB and WBC count were observed after treatment. **Conclusion:** Etanercept was associated with a reduction in platelet count after 6 months of treatment, with no significant changes in hemoglobin, WBC, serum SGOT, SGPT, urea, and creatinine.

KEYWORDS: Blood Investigations, Etanercept, Rheumatoid Arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory condition that predominantly targets the synovial joints of the hands and feet. Due to the extensive expression of the pro-inflammatory cytokine tumor necrosis factor-α (TNFα) in the joints of individuals with RA, therapies that inhibit the activity of this cytokine are highly effective and constitute standard clinical practice.[1]

The musculoskeletal manifestations of RA include synovitis, joint tenderness and swelling, with subsequent structural damage leading to joint destruction, which may result in deformity and disability. Patients with RA frequently complain of fever, weight loss and extreme tiredness. As a consequence, the ability to carry out activities of daily living is markedly impaired. In addition to the articular manifestations of RA, the vast majority of patients develop extra-articular disease, which involves the cutaneous cysts, sjogren's syndrome and ocular disease. Moreover, other organs, such as the lung, kidneys, blood vessels and heart, may also be involved.[1, 2]

Etanercept is a fusion protein comprised of two extracellular domains of the tumour necrosis factor receptor 2 (p75) linked to the Fc portion of human immunoglobulin G1 (IgG1). It acts as a competitive inhibitor of tumour necrosis factor (TNF)-α by binding to both TNFα and TNFβ and preventing their interaction with cell-surface receptors thereby reducing pro-

inflammatory effects.[3] The incorporation of two TNF receptor moieties into a dimeric fusion protein enables etanercept to bind two TNFα molecules or one TNFα trimer resulting in a substantially higher affinity for TNFα compared with the monomeric receptor. In rheumatoid arthritis, the administration of etanercept reduces pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-1 and matrix metalloproteinases. There is also attenuated infiltration of neutrophils and macrophages and reductions in the expression of IL-1β that correlate with long-term improvements in arthritis. Furthermore, etanercept promotes bone formation and decreases bone resorption providing added joint protection. It has also been shown to down-regulate the percentage of B-cell subsets in peripheral blood.[4]

Etanercept treatment in RA patients results in hematological changes indicative of therapeutic effect. Anemia and leukocyte levels are important indicators due to their association with inflammatory activity.[5] Total white blood count, neutrophil, and platelet counts did not exhibit significant alterations during a 12-week period of treatment, remaining within normal limits; some patients with high baseline leukocyte and neutrophil counts experienced decreases to within the normal range. Despite the lack of significant inflections in leukocytes or neutrophils, continued improvements in clinical status according to the American Rheumatism Association (ARA) criteria were observed.[6]

Non-serious infections during treatment (urinary tract infections, respiratory tract infections, vulvovaginal candidiasis, and Herpes simplex) were managed without discontinuation of PEG-etanercept. One patient exhibited a transient unexplained thrombocytopenia that resolved spontaneously, while another presented a mild decrease in neutrophil count concurrent with evidence of streptococcal infection. All other patients maintained platelet and neutrophil values within the normal range throughout the study.[7]

Increases in total hemoglobin and hematocrit values were significant in patients treated with 25 and 50 mg of PEG-etanercept and were accompanied by parallel reductions in the inflammatory markers ESR and CRP, consistent with improvement in the underlying disease. These changes were still evident at day 84 in the month 1 and 2 treatment groups despite a period of placebo dosing. Hematological descriptors and platelet counts were unchanged in the month 3 treatment group, for which clinical improvement was not significant during the PEG-etanercept treatment period.[8]

AIM OF THE STUDY: To study the association of blood investigation with etanercept in patients with Rheumatoid Arthritis.

PATIENTS AND METHODS

From April 2019 to April 2020, 100 Iraqi patients with RA who were referred by rheumatology seniors to the biologics committee in the rheumatology sector at Ibn-Sina Teaching Hospital participated in an open-labeled, single group retrospective research. The biologic medicine distribution committee at Ibn Sina Teaching Hospital was referred to all of the patients after their physicians diagnosed them with RA. Five expert rheumatologists make up this committee, which makes the ultimate determination on a patient's appropriateness for biologic treatment, including etanercept. The committee adheres to national RA treatment standards that were approved by the Ministry of Health but not yet publicly published. From the beginning of the trial to its conclusion, all enrolled patients received weekly subcutaneous injections of etanercept (Enbrel) at a dose of 50 mg. Patients were evaluated for the drug's safety and efficacy at three and six months.

Information was gathered from the rheumatology registry at Ibn-Sena Teaching Hospital. Initiated in 2019, the Rheumatology Patient Registry is a prospective longitudinal cohort. It includes all rheumatic illness patients who have received biological agent treatment at the rheumatology department. Participants in the research were those who satisfied the 2010 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) categorization criteria for RA.

Exclusion criteria

1. Patients less than 18 years old
2. Taking other forms of DMARDs
3. The patient had a previous history of biological agent intake
4. The patient had other connective tissue diseases overlapping with RA

Data collection and measurements

Baseline data were gathered on the initial visit for every patient. Patients' age, sex, phone number, smoking status, length of illness, and current and past use of RA drugs (DMARDs, corticosteroids, and biologics) were among the information gathered. Evaluation of laboratory data, such as blood urea, serum creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), hemoglobin (Hb) level, white blood cell (WBC) count, platelet count, and so on. (Conducted on baseline, the initial visit, and each follow-up visit).

Data analysis

The data were entered in computer using Microsoft excel program and analysis was done using the software SPSS23 (Chicago, IL), p-value considered when appropriate to be significant if less than 0.05 by using analysis variants (ANOVA).

RESULTS

Of a total of 190 patients with RA (at time of the study), 107 met the inclusion criteria, and 7 of them were lost during follow up leaving 100 patients who completed the study successfully. Females were 89(89%) and males

11(11%). The mean age was 48.29 ± 12.81. The mean duration of disease was 12.05±8.40. Rheumatoid factor (RF) was positive in 76 (76%), ACCP positive in 93(9.3%) patients. MTX dose 14.67±3.58mg. Smoking were 4(4%), Ex-smoker 6(6%), never 90(90%), as shown in table (1).

Table (1): Baseline characteristic of rheumatoid arthritis patients.

		No.	%
Age	> 40	25	25.0
	< 40	75	75.0
Gender	Male	10	10.0
	Female	90	90.0
Disease duration	< 10	39	41.5
	> 10	55	58.5
RF	NEG	23	23.0
	POS	77	77.0
ACCP	NEG	7	7.0
	POS	93	93.0
Smoking	Current	4	4.0
	Ex-Smoker	6	6.0
	Never	90	9.0

After three and six months of therapy, there was no discernible improvement in the HB and WBC counts. The table (2) indicated that there was a substantial shift in platelets between the baseline and six months of the condition.

Table (2): Effect of etanercept on some hematological parameters.

	Baseline	3 Month	6 Month	P value
HB	11.87 + 1.73	13.14 + 2.88	12.04 + 2.02	0.189NS
WBC	9.25 + 7.13	8.47 + 3.02	8.12 + 2.56	0.223 NS
PLAT	306.36 + 76.42 a	280.85 + 90.55 b	301.81 + 73.11 ab	**0.05***
* refer to significant difference between groups at (P < 0.05) (a.b.) aim to significant difference bet. Means at (P<0.05), according to Duncan test. NS refers to no significant difference between groups at (P < 0.05).				

There were no significant changes in renal and liver function test after 3months and 6 months of treatment, as shown in table (3).

Table (3): effect of etanercept on renal and liver functions test.

	Baseline	3 month	6 month	P-Value
B.urea	13.33+15.34	15.25+20.12	16.02+18.35	0.593
S.Creatinine	48.31+34.47	44.3+34.51	41.77+32.01	0.458
SGOT	19.49+10.10	20.61+10.17	22.63+10.87	0.108
SGPT	17.43+9.87	18.16+9.25	20.5+12.09	0.125

DISCUSSION

According to the current study, there was an increase in Hb levels at the 3- and 6-month follow-up periods as compared to the baseline. Because TNF-α and IL-6 cytokines have a role in the pathophysiology of ACD, biotechnological medications such tocilizumab (a humanized monoclonal antibody that targets the IL-6 receptor) and TNF-α inhibitors may raise hemoglobin (HB) levels. Indeed, following therapy with IL-6 and TNF-α inhibitors, elevated HB levels were noted in a number of trials including patients with RA and other chronic inflammatory disorders.[9,10] DAS28 and CRP readings were considerably greater in RA patients than in PsA patients in the Corrado et al.[11] investigation. Additionally, RA patients had considerably lower HB levels than PsA patients. These findings can be explained by taking into account that HB levels in RA may be influenced by the alleged more severe inflammatory state. For all three anti-TNF-α medications, we have seen elevated HB levels in RA patients. Patients receiving ETN reported greater HB levels at the twelfth month compared to those receiving IFX and ADA. In contrast to a soluble TNF receptor fusion protein, like ETN, we have suggested that anti-drug antibodies likely contribute to the decreased effectiveness of monoclonal antibodies, such IFX and ADA, on anemia.[12] Even though the present examined sample's mean WBC level dropped over the follow-up period relative to the baseline, the difference was not statistically significant. Following 4 and 12 weeks of therapy, there was a substantial decrease in WBC (p=0.003) and neutrophil count (0.000) in the research by Albagoa et al.[13]

The current investigation revealed no discernible variation in the means of the liver and renal function tests at the follow-up intervals as compared to the baseline. Similarly, Albagoa et al.[13] demonstrated that serum SGOT, SGPT, urea, and creatinine did not alter significantly ($p > 0.05$ for all). Additionally, this is consistent with a prior research by Alosami et al.[14] that reported no discernible changes in LFT after six months of etanercept administration. According to van Denderen et al.'s research[15], 14% of AS patients who received etanercept for at least three months had elevated liver enzymes. The extended follow-up duration and the use of co-medications that may impact the liver, such as methotrexate, sulfasalazine, and NSAIDs, may be the cause of the greater incidence of elevated liver enzymes in this research. There may be additional variables at play, such as comorbidities, obesity, and alcohol use. When compared to comparator DMARDs, liver enzyme elevations were most typically seen with fliximab, less frequently discovered with dalimumab, and not seen with etanercept in a trial by Sokolove et al.[16] in patients with rheumatoid arthritis. The chemical structure, dosage, schedule, method of administration, half-life, and possible immunogenicity of TNF-α inhibitors vary. This might account for the variations in the increase of liver enzymes among TNF-αinhibitors.

The association of blood urea levels with etanercept treatment in rheumatoid arthritis (RA) patients is an emerging area of interest, particularly regarding the drug's efficacy and patient response. While the provided studies do not directly address blood urea levels, they highlight the relationship between etanercept serum concentrations, disease activity, and treatment response, which may indirectly influence urea levels. Higher serum etanercept levels correlate with better clinical responses in RA patients, as evidenced by a study where patients in remission had significantly higher drug levels compared to those with moderate disease activity which reported by Zivojinovic et al.,[17] In the Gehin et al.,[18] the median etanercept concentration was found to be 1.8 mg/L at three months, but no therapeutic range was established, indicating variability in patient responses. The association of serum creatinine levels with etanercept treatment in rheumatoid arthritis (RA) patients reveals a complex relationship. While etanercept is known to improve various clinical parameters in RA, its direct impact on renal function, as measured by serum creatinine, appears nuanced. In a study of Nakamura et al.,[19], the RA patients with amyloid A amyloidosis, etanercept treatment did not significantly improve overall serum creatinine levels; however, patients with baseline creatinine levels below 2.0 mg/dl experienced a notable decrease in creatinine over time ($P = 0.021$). Another study by Hanzu-Pazara et al.,[20] indicated that patients receiving biological therapies, including etanercept, had lower mean serum creatinine levels compared to those treated with DMARDs, suggesting a potential renal protective effect of biological therapies.

CONCLUSION

After six months of therapy, etanercept was linked to a decrease in platelet count, although there were no appreciable changes in hemoglobin, WBC, serum SGOT, SGPT, urea, or creatinine.

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