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Epidemiological and Clinical Factors Affecting the Response to Etanercept among Patients with Rheumatoid Arthritis

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ABSTRACT

Background: This study aimed to inspect the association between the response to etanercept among patients with rheumatoid arthritis and several epidemiological and clinical variables and medication adherence, as measured by medication possession ratio (MPR).

Methods: A cohort study that enrolls 120 active rheumatoid arthritis patients. The baseline values of disease activity score for 28 joints (DAS28) score,erythrocyte sedimmintation rate (ESR), WBC, tender joints count (TJC), swelling joints counts (SJC), and medication adherence, as measured by medication possession ratio (MPR), were identified. All patients received etanercept treatment for three months, and then the clinical response to etanercept was assessed after the end of the three months duration. Factors affecting clinical response were evaluated by univariate and multivariate logistic regression analysis. The predictive performance of a single independent predictor was then assessed using a receiver operating characteristic (ROC) curve.

Results: The results of the univariate logistic regression model showed that the smoking, disease duration, baseline DAS28, and MPR could predict the patients' proclivity for being non-responder. The multivariate logistic regression model showed that only baseline DAS28 (P< 0.0001, OR=32.239, 95%CI: 4.941–210.338) and MPR (P=0.002, OR=0.00063, 95%CI: 0.00001–0.032) were independent predictive factors for the tendency of patients to be non-responder. ROC curve analysis disclosed that baseline ESR and DAS28 have a good area under the curve (AUC) with the optimal cut-off for the baseline ESR threshold was 52 mm/hr., whereas the baseline DAS28 threshold was 5.79.

Conclusion: Current smoking is the main epidemiological factor that can predict the tendency for being non-responder. The potential of baseline ESR and DAS28 values as biomarkers for clinical response to etanercept in RA patients was identified by Receiver operating characteristic(ROC) analysis.

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Introduction

In the last decade, several international clinical guidelines have approved biologic therapies for moderate to severely active rheumatoid arthritis (RA) patients (1).

The most effective biological agent for dramatically improving the prognosis of RA patients was tumor necrotic factor (TNF) blockers(2) which most guidelines should consider for RA patients with moderate to severe activity after failure with Methotrexate monotherapy (3). Nonetheless, using these TNF inhibitors carries a cost, as they can raise the risk of infection, tuberculosis reactivation, psoriasiform skin changes, exacerbation of demyelinating

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diseases, drug-induced lupus, non-melanoma skin cancer, and injection site or infusion reactions(4).

Additionally, these agents are prohibitively expensive with a cost that varies by region and nation (5). Moreover, a spectrum of responses to these drugs has been seen, ranging from complete remission to delayed or even complete nonresponse. While patients who do not respond to or experience adverse effects from one anti-TNF treatment may respond to a second anti-TNF medication with a different mechanism of action, this may involve additional costs and expose the patient to unwanted side effects (6).

Etanercept (ETN), one of the most widely used TNF inhibitors globally, has been shown to improve physical function and slow the course of bone and cartilage erosion in RA patients(7)(8). Still, a significant proportion of RA patients do not respond well to ETN. Besides the high cost of ETN and the possibility of adverse effects, it imposes a significant burden on both patients and society (9). Actually, ETN takes 12 weeks for etanercept to produce a complete response, at which point the patient's therapy must be discontinued if there is no response (10).

As a result, viable biomarkers for predicting clinical response to ETN in patients with RA are essential to prevent subjecting individuals or health care systems to all of these drawbacks (11).

Numerous studies have examined the predictive value of age, gender, concurrent medications, body mass index (BMI), and smoking status for biological DMARD response. The majority of them included TNF inhibitors (12).

The purpose of this study is to examine the association between the response to etanercept among patients with rheumatoid arthritis and several epidemiological and clinical variables, including age, gender, weight, disease duration, smoking history, baseline values of disease activity score for 28 joints (DAS28) score, ESR, WBC, tender joints count (TJC), swelling joints counts(SJC), and medication adherence, as measured by medication possession ratio (MPR) depending on the number of doses taken by patients during the three-month study period.

Methods

A cohort study was conducted at Baghdad Teaching Hospital's Rheumatology Unit in Baghdad, Iraq. This research enrolled a convenient cohort of Iraqi RA patients who have been taking etanercept for at least three months.

The Europian Leage Againist Rheumatism (EULAR) response criteria (13) determined by calculating the DAS28-ESR (13) value to see whether the patient responds [when the change in DAS28 is more than 1.2 or between 0.6 and 1.2 but the value of DAS28 after three months is lower than 5.1] or fails to respond to etanercept[when the change in DAS28 from the baseline is less than 0.6 or the value of DAS28 after three months was lower than 5.1], then the patients divided into two groups based on their EULAR response into responsive and non-responsive. The author collected clinical and epidemiological data such as age, geneder, weight ,smoking history ,disease duration,baseline and after three months values of (ESR ,WBC, DAS28,TJC and SJC), from medical records as well as direct interviews with patients.

Inclusion criteria:

1-Participants must have been diagnosed with RA according to the classification criteria of the American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) (13)

2- Patients with moderate to severe disease, defined as a disease activity score of 28 joints and ESR (DAS28-ESR) (14) more than 3.2 at baseline.

3-Patients who had received etanercept subcutaneously for a minimum of three months.

The exclusion criteria:

1- Patients who are using a biological therapy other than etanercept.

2- Patients taking a combination of traditional disease modifying antirheumatic drugs (DMARDs) and etanercept

3-Patients who also have other connective tissue diseases.

Ethical approval with the number (RECACPUB-3102020B) on the 3rd of October 2020 was obtained from the Scientific and Ethical Committee in College of Pharmacy- the University of Baghdad and Rheumatology Medical Department at Baghdad Teaching Hospital. In addition, written consent was obtained from all the participants.

Statistical analysis was completed using SPSS 26.0 software (IBM, USA). Continuous variables are reported as frequency and percentages or as (means ±SD). A Shapiro–Wilk test was used to test the normality of the results. Comparison between two groups was made by

unpaired t-test for normally distributed data or Mann-Whitney U test for skew data. Factors affecting clinical response were assessed by univariate and multivariate logistic regression analysis. The predictive performance of a single independent predictor was then evaluated using a receiver operating characteristic (ROC) curve and 95 % confidence intervals (CI) to calculate the area under the curve (AUC). A probability that equals or less than 0.05 was considered significant.

Results

Table 1 summarizes the demographic characteristics of all study participants. There were significant differences in specific parameters between the responsive and non-responsive groups, like smoking and MPR. However, WBC and SJC became significant just three months later. Additionally, both the baseline and three-month ESR, TJC, and DAS28 values were significant (p.value< 0.01) for all .

Before introducing etanercept, the most frequently used DMARDS were methotrexate and steroids, followed by methotrexate alone. In contrast, the combination of infliximab and methotrexate was a less frequently used DMARDS, as shown in Figure 1.

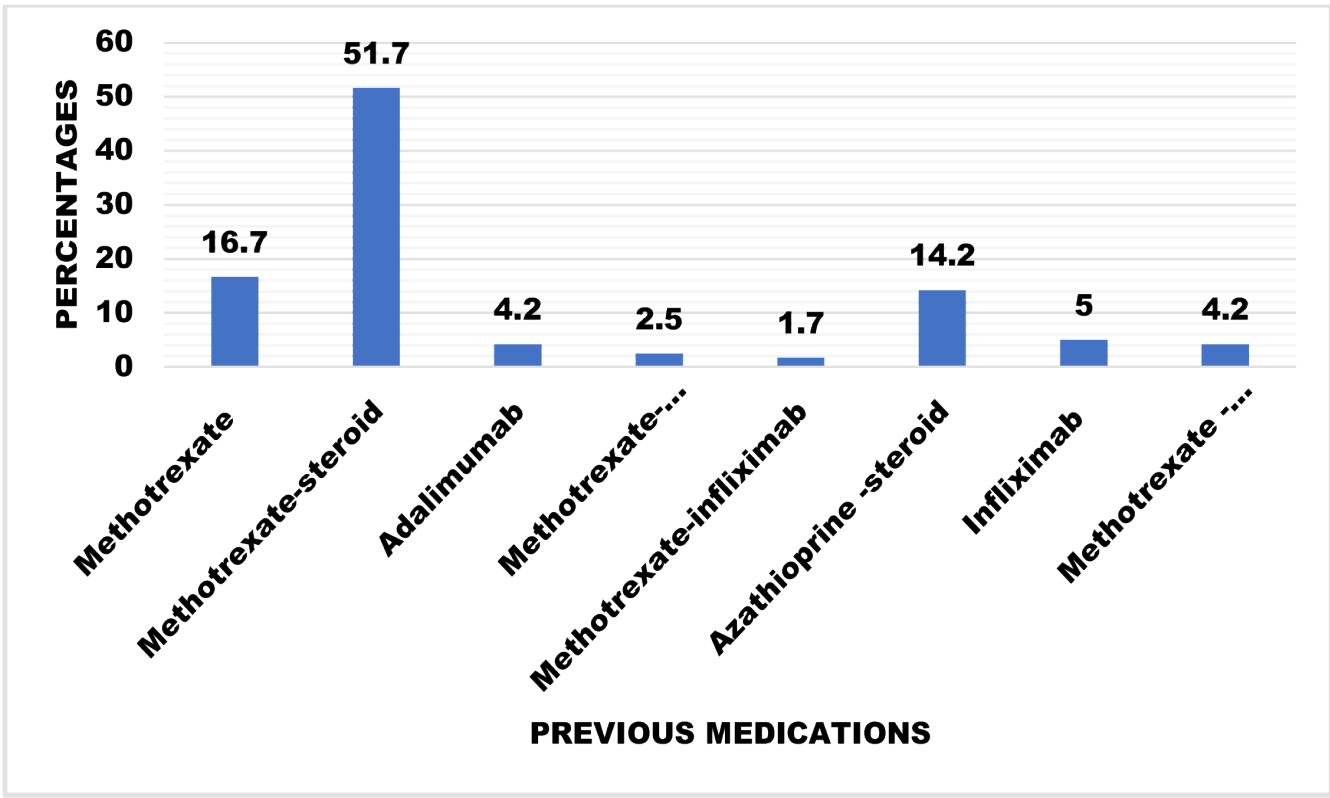

Figure 1. Previous medication is taken before etanercept for all participants. n=120.

Factors predicting clinical response to etanercept therapy

The results of the univariate logistic regression model showed that the smoking (P=0.002, OR=7.75, 95%CI: 2.108–28.487), disease duration (P=0.032, OR=0.918, 95% CI: 0.848–0.993), baseline ESR (P< 0.01, OR=1.055, 95% CI: 1.030– 1.080),baseline DAS28 (P< 0.01, OR=43.068, 95% CI: 11.305–164.076), and MPR((P=0.001, OR=0.00035, 95% CI: 0.00004–0.033) predicted the patients' proclivity for being non-responder as seen in Table 2.

Additionally, a multivariate logistic regression model evaluated all variables with a p-value of ≤ 0.1 in the univariate model. As seen in Table 3. Only baseline DAS28 (P< 0.0001, OR=32.239, 95%CI: 4.941–210.338) and MPR (P=0.002, OR=0.00063, 95%CI: 0.00001–0.032) were independent predictive factors for the tendency of patients to be non-responder to etanercept therapy.

Table 1. Demographic data for participants

Category		Responsive group n=66	Non -responsive group n=54	P-Value
Age(years)		49.812 ±11.14	51.5370 ±12.15	0.317
Gender	Male n (%)	19(28.7)	13(24.1)	0.783
	Female n (%)	47(71.3)	41(75.9)	0.54
Weight(kg)		82 ±13.6	79.648 ±11.41	0.267
Smoking n (%)		2(0.031)	15 (27.7)	0.001*
Disease duration		10.12± 6.027	8.11±3.440	0.239
Baseline WBC		11.323 ±2.135	11.713 ±1.803	0.122
WBC after 3 months		7.63 ±1.88	8.965 ±2.227	< 0.01*
Baseline ESR		49.265±18.464	67.33±19.392	< 0.01*
ESR after 3 months		23.48±15.269	57.388±18.707	< 0.01*
Baseline TJC		6.89±1.07	8.648±1.792	< 0.01*
TJC after 3 months		2.937± 1.562	8.0370 ±1.61319	< 0.01*
Baseline SJC		3.359 ±1.3137	3.852± 1.337	0.062
SJC after 3 months		1.0625±1.753	2.7963±1.2646	< 0.01*
Baseline DAS28		5.60± 0.333	6.094 ± 0.378	< 0.01*
DAS28 after 3 months		3.49 ±0.871	5.8146 ± 0.27775	< 0.01*
MPR		0.9486 ±.07706	0.8904 .10054	< 0.01*

Results are reported as means ±SD or count (percentage). WBC: White blood cell counts; ESR: erythrocyte sedimentation rate; TJC: Tender joints count; SJC: Swelling joints count; DAS28: disease activity score in 28 joints; MPR: Medication's possession ratio.

Table 2. Factors at baseline predicting response for etanercept by univariate logistic regression analysis

Parameter	OR	P-Value	95% CI.	
			Lower	Upper
Smoking	7.750	0.002*	2.108	28.487
Age	1.017	0.288	0.986	1.050
Gender	1.122	0.782	0.497	2.532
Disease duration	0.918	0.032*	0.848	0.993
Baseline WBC	1.129	0.203	.937	1.361
Baseline ESR	1.055	<0.01*	1.030	1.080
Baseline DAS28	43.068	<0.01*	11.305	164.076
MPR	0.00035	0.001*	0.00004	0.033

DAS28: disease activity score in 28 joints; ESR: erythrocyte sedimentation rate; MPR: medication possession ratio. Data were presented as odds ratios (OR), p values, and 95% confidence intervals (CI). A univariate logistic regression model was used to assess baseline factors associated with response prediction in rheumatoid arthritis patients treated with etanercept. A significance level of 0.05 was considered significant.

Predictive value of baseline ESR, baseline DAS28, MPR, and disease duration for clinical response to ETN

The ROC curve analysis includes the statistically significant predictive parameters for clinical response to ETN based on univariate logistic regression analysis (baseline ESR, baseline DAS28, MPR, and disease duration). ROC curve analysis disclosed that for baseline ESR (AUC: 0 .771, 95% CI :0.68-0.85), baseline DAS28 (AUC: 0.83, 95% CI:0.75-0.91), MPR (AUC: 0 .3, 95% CI :0.21-0.40) and disease duration (AUC: 0.43, 95% CI:0.33-0.54) as seen in Figure 2. Only baseline ESR and DAS28 have a good AUC with the optimal cut-off, defined as the highest value obtained by sensitivity plus specificity at the time (the baseline ESR threshold was 52 mm/hr., whereas the baseline DAS28 threshold was 5.79).

Table 3. Independent factors at baseline predicting response to etanercept by multivariate logistic regression analysis.

Parameter	OR	P-Value	95% CI.	
			Lower	Upper
Smoking	4.365	0.061	0.935	20.379
Disease duration	0.953	0.370	0.858	1.059
Baseline WBC	0.934	0.611	0.718	1.215
Baseline ESR	0.999	0.962	0.964	1.035
Baseline DAS28	32.239	< 0.0001*	4.941	210.338
MPR	0.00063	0.002	0.00001	0.032

DAS28: disease activity score in 28 joints; ESR: erythrocyte sedimentation rate; MPR: medication possession ratio. Data were presented as odds ratios (OR), p values, and 95% confidence intervals (CI). All factors with a p<0.1 in the univariate model in Table 2 were analyzed by the multivariate logistic regression model. A p<0.05 was considered significant.

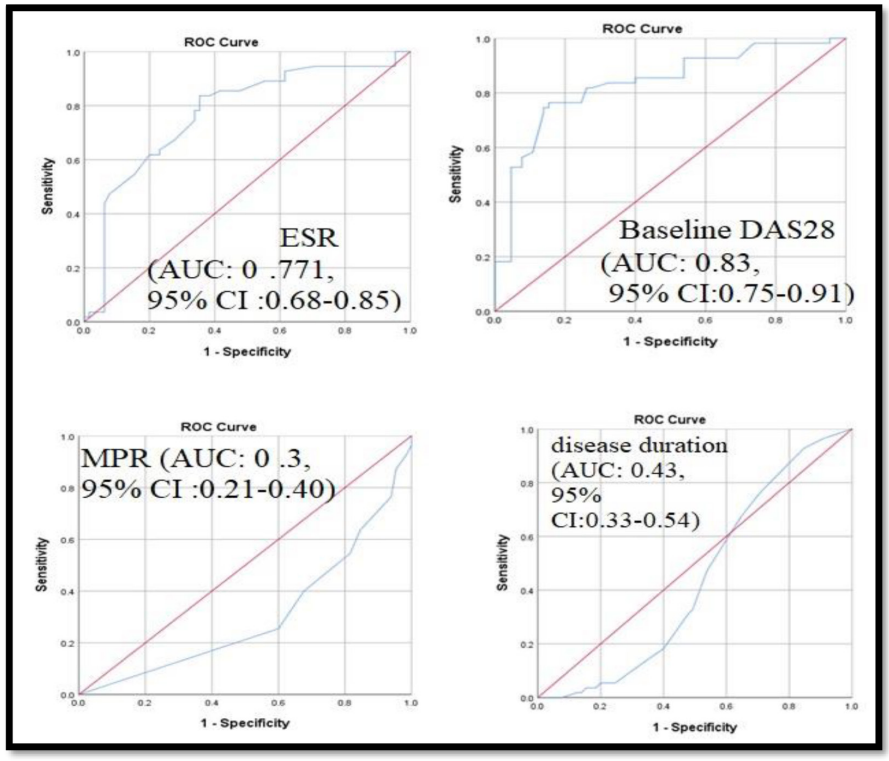

Figure 2. ROC curve analysis for baseline ESR, baseline DAS28, MPR, and disease duration.

Discussion

Until now, decisions about failure to respond to anti-tumor necrosis factor treatment were made only based on clinical outcome, without regard for circulating medication levels (15). However, both pharmacological and disease-related factors may influence the efficacy of a therapy (15).

It is critical to identify accurate predictors of therapy response in order to do so, both Katchamart et al., (16) and Callaghan et al., (17) conducted systematic reviews of 18 and 154 studies, respectively, and identified several potential predictors of rheumatoid arthritis remission and response to biologic therapy, including age, sex, disease duration, disease activity, smoking status, and concurrent methotrexate therapy (16,17).

According to the present study results, methotrexate and steroids were the most frequently used DMARDS, followed by methotrexate alone. In contrast, the combination of infliximab and methotrexate was less regularly used DMARDS before starting etanercept. These results align with many previous studies that confirm that methotrexate was the most widely used treatment of rheumatoid arthritis (18–20).

In medical practice, patients who do not respond to one TNF inhibitor are not encouraged to receive the same medication in the near future, implying that a TNF inhibitor's responsiveness is mainly constant. However, patients who do not respond to one TNF inhibitor are regularly treated with another, indicating that earlier treatment regimens do not affect the response (20).

The current study showed that 5% of patients who failed to respond to infliximab and 4.2% of patients who were unable to respond to adalimumab converted to etanercept.

The univariate logistic regression model results indicated that smoking is an excellent predictor of patients' predisposition to be non-responders to etanercept in Iraqi patients with rheumatoid arthritis. This result is comparable to previous studies, which confirm that smokers with rheumatoid arthritis are less likely to respond to an anti-TNF agent (21–23).

Smoking has been linked to increased disease activity and extraarticular consequences such as nodules and vasculitis in rheumatoid arthritis (RA)(24) and has been implicated in the illness's pathophysiology (25).

In previous investigations, etanercept's pharmacokinetics have not been proven to change with age (26). The current study's univariate logistic regression model revealed that the age of rheumatoid arthritis patients did not affect their responsiveness to etanercept. Similarly, Kim et al., (27), Naldi et al., (28), and Gordon et al.'s investigations corroborated the current study's findings. However, in a study conducted by Hetland et al., (29), older age was found to be a negative predictor of clinical response to etanercept.

Another factor that can predict the tendency for being non-responder to etanercept is RA disease duration, where the tendency of being non-responder increases with the increase in disease duration. The results align with Katchamart et al., (16) and Callaghan et al., (17) studies that confirm a positive correlation between the disease duration and the tendency to be non-responder. Nevertheless, the findings contradict those of Zhang et al., who found no link between disease duration and response (11).

Although no definitive serological indicators of non-responsiveness have been identified to date (23), the current investigation found that the baseline ESR level is a predictor of non-responsiveness when using univariate logistic regression, which is contrary to the findings of Zhang et al., (11)who discovered no correlation between disease duration and response.

The 28-joint DAS (DAS28) determines eligibility to begin and sustain anti-TNF medication treatment (30). Before RA patients are eligible for anti-TNF therapy, they must score 5.1 on two different occasions at least one month apart. At the same time, a response of 1.2 is necessary 6 months after initiation for biologic therapies to be sustained (30). The current study indicates that baseline DAS28 is an independent predictor of non-responsiveness to etanercept therapy in individuals. In contrast to Zhang et al., (16) study observed a non-significant difference in baseline DAS28 between responders and non-responders.

The optimal efficacy of biologic medications observed in randomized controlled trials may only occur if patients take their prescription with full adherence (31).

The majority of studies used the medication possession ratio (MPR), which is calculated as the percentage of days the patient had a supply of the medicine during the follow-up period. Adherence is measured using a cut-off MPR (usually 80%), although the cut-off values are arbitrary rather than a clinically meaningful MPR that has been proved to affect treatment response (32). The current investigation results show a significant difference in adherence between responders and non-responders. MPR might also be used to determine whether patients are likely to be non-responders according to the univariate logistic regression model.

Similarly, Bluett et al., (33) confirm that Patients with RA who reported poor adherence had worse clinical outcomes than those who did not report poor adherence. Following 6 months of anti-TNF medication, non-adherence was found to be related to a more inadequate DAS28 response. This disparity might be attributed to various variables, such as limited sample sizes, different response classifications criteria, and varied treatment durations.

ROC curve analysis displayed that only the baseline ESR and DAS28 values could distinguish responders from non-responders effectively. These findings might be explained by the fact that high ESR levels suggest a severe inflammatory process that may hinder etanercept's effective response. Furthermore, a high DAS28 indicates severe RA illness, which may be related to etanercept non-responsiveness.

The inclusion of other parameters such as baseline levels of inflammatory cytokine levels of interleukins, TNF, CRP, anti-CCP with RF levels, and the most essential measure etanercept concentration are the fundamental limitations associated with the current investigation, in addition to the small sample size.

Conclusion: high values of baseline WBC, ESR, TJC, and DAS28 are associated with a significant tendency for being non-responder to etanercept. Current smoking is the main epidemiological factor that can predict the tendency for being non-responder. Additionally, inadequate drug adherence can lead to non-responsiveness. The potential of baseline ESR and DAS28 values as biomarkers for clinical response to ETN in RA patients was identified by ROC analysis, which would aid in the identification of disease subgroups that would benefit from ETN, assisting in treatment decisions and supporting the rationale for the future development of personalized medicine for RA patients.

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