Effectiveness and Safety of Biosimilar Etanercept (Altebrel) in Iraqi Rheumatoid Arthritis Patients: A Prospective Observational Study

Nourhan Ali Kadhim, MSc* Fadia Thamir Ahmed, PhD** Zakaria Moayad Al-Ghazaly, FIBMS***

ABSTRACT

Patients in Iraq with rheumatoid arthritis (RA) still face challenges accessing advanced biologic treatments. Biosimilars, highly similar to original biologics in efficacy and safety, have emerged as cost-effective alternatives to improve access in low- and middle-income countries. Barriers like limited availability and referral delays hinder access to appropriate biologics. Recent years have seen growing interest in real-world data on biosimilar effectiveness. The study aimed to Assess the effectiveness and safety of the biosimilar etanercept (Altebrel) in Iraqi RA patients. Thirty-five adult RA patients eligible for Altebrel treatment participated in a prospective, real-world study in Hilla, Iraq. Clinical outcomes (DAS28-ESR, ESR, TNF-α, IL-6), laboratory safety profiles, and PROMIS-HAQ assessments were recorded at baseline and after 12 weeks of treatment. The mean age of patients was 51.31 ± SD years. Significant decreases were observed in DAS28-ESR, TNF-α, and ESR IL-6 levels showed no significant decrease. All PROMIS-HAQ domains showed meaningful improvements. Physical function showed the most significant improvement (median T-score increased from 50 to 60.5; $p < 0.001$). Most adverse events were moderate, and no new safety issues emerged. PROMIS improvements in physical function and pain are modestly correlated with DAS28 decreases ($r = -0.41$ and -0.47, respectively). The study concluded that short-term treatment with Altebrel was effective and well-tolerated in RA patients. PROMIS-HAQ was valuable in capturing changes in quality of life. These data support the use of PROMIS-HAQ in routine RA assessments. Further long-term, larger sample size studies are needed to support these findings.

Keywords: Rheumatoid arthritis; biosimilar etanercept; Altebrel; DAS28; TNF-alpha; IL-6

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic multiorgan autoimmune disease identified by chronic inflammatory arthritis and extra-articular involvement[1]. Genetics, autoimmune and environmental factors may lead to synovial inflammation and RA progression[2]. Recently, novel biological and targeted agents have been utilised more frequently in clinical practice of RA, these agents have been shown to substantially relive the clinical symptoms and slow down the progression of the disease in patients when compared to conventional disease-modifying anti-rheumatic drugs (DMARDs)[3].

In 1998, the FDA approved the first fusion protein for RA, Etanercept, under the trade name Enbrel[4]. Although tumor necrosis factor inhibitors (TNFis) such as etanercept have developed RA management, access remains limited in low- and middle-income countries like Iraq due to high cost[5]. A biosimilar medication is produced to be extremely comparable to its reference medication in terms of effectiveness and safety. Despite potential slight variations arising from the complex nature and manufacturing processes, the active components of a biosimilar medication and its reference biologic are identical[6].

The latest guidelines for rheumatoid arthritis treatment suggest for the rapid use of TNF inhibitors in patients who fail to attain remission with methotrexate alone[7,8]. Altebrel is a proposed biosimilar of etanercept developed by AryoGen Pharmed in Iran, that has been approved for use in Iraq[5], but clinical evaluation in the Iraqi population is lacking. The aim of the study is to evaluate the effectiveness and safety of biosimilar etanercept (Altebrel) in Iraqi patients with rheumatoid arthritis through assessment of clinical outcomes (DAS28-ESR, ESR, TNF-α, IL-6), patient-reported quality of life (PROMIS-HAQ), and laboratory safety parameters, along with monitoring and analysis of adverse effects during a 12-week prospective real-world follow-up.

MATERIALS AND METHODS

This was a prospective, observational, real-world study conducted at the Biologic Therapy Center of Merjan Teaching Hospital, Hilla, Iraq. Initially, sixty–five adult patients diagnosed with rheumatoid arthritis (RA) and prescribed Altebrel 50 mg injected subcutaneously once a week, were enrolled in the study as the baseline population. These patients met the eligibility criteria for treatment with biosimilar etanercept (Altebrel) and were evaluated before the initiation of therapy. However, during the 12-week follow-up period, the sample

* Pharmacy Department, Babil Health Directorate,
Iraqi Ministry of health, Babil, Iraq.
Email: nurhan.Ali2200m@copharm.uobaghdad.edu.iq
** Assistant Professor, Department of Clinical Pharmacy
College of Pharmacy, University of Baghdad, Baghdad, Iraq.
*** Specialist Rheumatologist and Lecturer
College of Medicine, University of Babylon, Babylon, Iraq.

size was reduced due to several reasons, including loss to follow-up, patient non-compliance, discontinuation due to personal or medical reasons, and incomplete data collection. As a result, the final sample size was 35 patients who completed both baseline and post-treatment assessments as shown in the Figure 1.

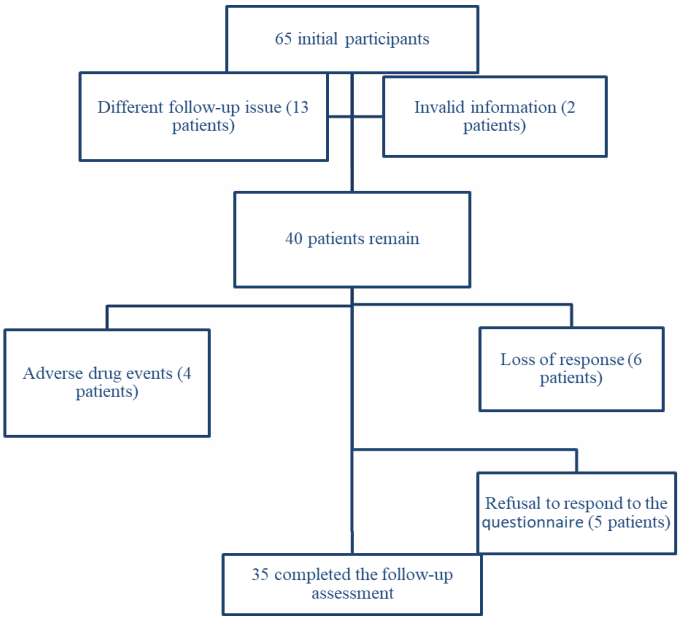

Figure 1. Sample Size Flow Chart

Inclusion criteria were an adult patients more than 18 years, diagnosed with RA according to the 2010 ACR/EULAR classification criteria. Patients were excluded if they had a history of prior biologic therapy, were under 18 years old, pregnant or lactating, discontinued Altebrel or switched treatments during the study, or had coexisting autoimmune diseases, active infections, or malignancies. The study population was divided into two groups, group I: newly diagnosed RA patients who were prescribed biosimilar etanercept (Altebrel) as first-line biologic therapy and group II: patients with established RA who received biosimilar etanercept (Altebrel) as an add-on to their existing treatment with conventional synthetic DMARDs, primarily methotrexate (MTX tab at 10 mg weekly dose).

The demographic data were collected from each participant, including (age, gender and educational level), disease severity and duration duration also had been taken. All patients were screened for latent tuberculosis infection (LTBI) prior to the initiation of biosimilar etanercept (Altebrel) therapy. Screening was conducted using the Interferon-Gamma Release Assay (IGRA). Screening for latent tuberculosis (TB) infection prior to use of tumor necrosis factor (TNF) antagonists is a recommended approach to decrease the risk of reactivation of latent Mycobacterium tuberculosis infection[9]. Each participant underwent clinical evaluation at baseline and at a 3-month follow-up.

The Disease Activity Score 28 (DAS28): is a validated composite index that includes tender joint count (TJC), swollen joint count (SJC), patient global assessment using a visual analogue scale (VAS), and erythrocyte sedimentation rate (ESR). Scores range from 0 to approximately 10; higher scores reflect higher disease activity. DAS28 is widely accepted in clinical and research settings for evaluating RA disease activity. The VAS Pain Score is the visual analogue scale for pain is used to measure the intensity of pain reported by the patient, ranging from 0 (no pain) to 10 (worst imaginable pain)[10,11].

Treatment effectiveness was measured after 3 months using the 28-joint Disease Activity Score (DAS28), and the European League Against Rheumatism (EULAR) response criteria[12]. The DAS28 scores were divided into 4 categories: remission (< 2.6), low disease activity (≥ 2.6 to ≤ 3.2), moderate disease activity (> 3.2 to ≤ 5.1), and high disease activity (> 5.1). EULAR responses were based on DAS28 results. A good response was defined as an improvement (i.e., a reduction in DAS28 score) of > 1.2 from baseline and DAS28 ≤ 3.2 at evaluation. A moderate response was defined as an improvement of 0.6 to 1.2 and DAS28 ≤ 5.1 at evaluation. Non-response was defined as an improvement of ≤ 0.6 or an improvement of 0.6 to 1.2 and DAS28 > 5.1 at evaluation. Treatment was deemed effective in patients with EULAR ratings of moderate or good response[12].

The PROMIS-HAQ (Patient-Reported Outcomes Measurement Information System - Health Assessment Questionnaire): This tool assesses physical functioning and disability in RA patients, this assessment covers daily activities, including dressing, walking, and gripping. Higher scores indicate greater disability. The PROMIS-HAQ is a validated and standardized instrument used in RA studies[13].

The Arabic version of the PROMIS-HAQ was used to assess patients' quality of life and functional status. This version had been culturally adapted and validated for Arabic-speaking populations[14]. Patients completed the questionnaire themselves before and after 12 weeks of treatment, with assistance provided if needed.

Also, the participants were followed via mobile phone between visits to ask any question or to document any adverse events, the adverse events. Serum concentrations of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were quantified using available sandwich ELISA kits (USCN Life Science Inc., Wuhan, China; Catalog Nos. SEA079Hu for IL-6 and SEA133Hu for TNF-α) . Both assays were performed according to the manufacturer's protocol, which follows a similar workflow for all procedure steps[15].

RESULTS

Thirty-five patients completed the current study. The mean age of participating patients was 51.31±11.23 years. Most participants were females (77.14%), with short history of RA (85.71%). Nearly half of participating patients were illiterate. More than 90% of included patients have moderate to severe disease activity before starting therapy with biosimilars etanercept. All details are shown in (Table 1)

Table 1. Clinical and demographic characteristics of study participants

Parameter		Value
Age (in years)	Mean ± SD	51.31±11.23
Sex	Male N (%)	8 (22.86)
	Female N (%)	27 (77.14)
Educational level	Illiterate N (%)	17 (48.57)
	Primary N (%)	5 (14.29)
	Intermediate N (%)	4 (11.43)
	Secondary N (%)	5 (14.29)
	College N (%)	2 (5.71)
	Postgraduate N (%)	2 (5.71)
History of RA	Short (<1 year) N (%)	30 (85.71)
	Medium (1-5 years) N (%)	3 (8.57)
	Long (>5 years) N (%)	2 (5.71)
Disease activity before starting treatment	Mild* N (%)	2 (5.71)
	Moderate* N (%)	17 (48.57)
	Severe* N (%)	16 (45.71)

Current treatment	Etanercept only	11 (31.43)
	Etanercept with MTX	24 (68.57)

*Mild disease activity was defined as DAS28: 2.6-3.19; Moderate disease activity as DAS28: 3.2-5.1; and sever disease activity as DAS28>5.1.

Biosimilar etanercept demonstrated a high and statistically significant reduction in disease activity, as measured by DAS28, decreasing from 4.97 ± 0.95 to 4.24 ± 1.07 (P < 0.001). Additionally, ESR levels significantly declined following biosimilar etanercept treatment, from 39 to 27 mm/hr (P < 0.001). The levels of TNF-alpha also showed a significant decrease, with the median reduced from 281.23 to 198.55 pg/ml (P < 0.001). However, there was no significant change observed in IL-6 levels after treatment Table 2.

Table 2. Effectiveness of biosimilar etanercept

Parameter	Baseline level	Post treatment level	p. value
DAS-28 Mean ± SD	4.94±0.97	4.32±0.96	<0.001*
ESR Median (IQR)	39 (31-52) mm/hr	27 (18-35)	<0.001^
TNF-α Median (IQR)	281.23 (222.99-298.46) pg/ml	198.55 (177.40-219.56)	<0.001^
IL6 Median (IQR)	139 (107-165) pg/ml	144 (143-151)	0.082^

*Paired T test; ^Wilcoxon ranked test

The usage of biosimilar etanercept had a significant effect on increasing all quality-of-life domains. All details are shown in Table 3.

Table 3: The effect of biosimilars etanercept on patients' quality of life

Parameter	Baseline level	Post treatment level	p. value
Physical activity Median (IQR)	50 (39.5-56)	60.5 (50-69.5)	<0.001^
Pain severity Mean ± SD	41.71±12.12	48.57±12.10	<0.001*
Pain effect Median (IQR)	53.8 (38.8-65)	53.8 (50-65)	0.001^
Anxiety mean ± SD	57.5 (42.5-68.8)	61.2 (50-67.2)	0.002^
Depression Median (IQR)	65 (42.5-76.2)	72.5 (50-80)	<0.001^
Fatigue mean ± SD	48.61±14.63	52.24±13.68	<0.001*
Sleep disturbances Median (IQR)	47.54±13.17	49.27±12.62	0.024*

*Paired T test; ^Wilcoxon ranked test

All studied baseline values from laboratory tests (ESR, TNF-α, and IL6 level) did not influence getting a reduction in disease activity by the usage of biosimilar etanercept; details are shown in Table 4.

Table 4. The effect of baseline level of different laboratory test values on the response to biosimilar etanercept

Parameter	Odd ratio	p.value
Baseline ESR	0.966	0.156
Baseline TNF-α	0.992	0.230
Baseline IL6	0.982	0. 134

Table 5 shows that there were no statistically significant differences in response to biosimilar etanercept when comparing different patient subgroups. Specifically, responses did not significantly differ between patients younger than 50 years and those aged 50 years or older; between males and females; between patients receiving etanercept alone and those on combined therapy with methotrexate (MTX); or between patients with severe rheumatoid arthritis (RA) prior to treatment and those with mild to moderate disease activity. Although a higher proportion of patients with a disease duration of one year or more exhibited a better response (60%) compared to those with a shorter disease duration (26.67%), this difference was not statistically significant.

Table 5. Factors affecting the response to biosimilar etanercept

Parameter		Respond	Non respond	p. value
Age	≥50 Y	9 (39.13)	14 (60.87)	0.259^
	< 50 Y	2 (16.67)	10(83.33)	
Sex	Male	4 (50)	4(50)	0.226^
	Female	7 (25.93)	20 (74.07)	
Used treatment	Altebrel monotherapy	2 (18.18)	9 (81.82)	0.435^
	Etanercept +MTX	9 (37.5)	15 (62.5)	
Educational level	Illiterate	5 (29.41)	12 (70.59)	0.803*
	literate	6 (33.33)	12 (66.67)	
History of RA	< 1 year	8 (26.67)	22 (73.33)	0.297^
	≥ 1 year	3 (60)	2 (60)	
Severity of RA	Mild	1 (33.33)	2 (66.67)	0.271^
	Moderate	3 (18.75)	13 (81.25)	
	Severe	7 (43.75)	9 (56.25)	

*Statistical analysis by chi square test; ^ statistical analysis by Fisher exact test

The level of creatinine but not urea was significantly increased after the usage of biosimilar etanercept; yet the level of creatinine despite this increase is still within the normal range (Median changed from 0.63 mg/dl to 0.7mg/dl; P = 0.030). On the other hand, only AST was significantly reduced among users of biosimilar etanercept (P=0.049). The level of urea and ALT didn't show any statistical difference.

Twenty-one patients of thirty-five totally experienced at least one side effect related to biosimilar etanercept. Six patients developed injection site reactions, and another six reported back pain. Rash was observed in four patients. Additionally, three patients experienced sinusitis, and two patients reported urinary tract infections (UTI). Other symptoms including (headache, respiratory tract infections, diarrhoea, fatigue) were noted in four patients, as in (Figure 2).

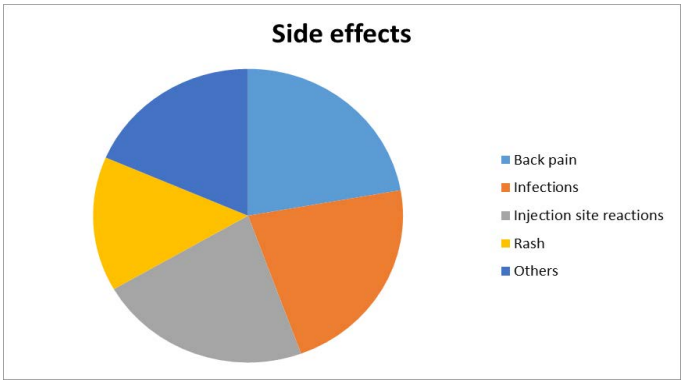

Figure 2. Side effects to biosimilar etanercept.

Table 6 indicates that the occurrence of side effects was not significantly different between young and older patients using biosimilar etanercept. Gender and educational level were not associated with an increased risk of developing side effects from biosimilar etanercept. The addition of etanercept to methotrexate did not appear to elevate the risk of side effects. Furthermore, the incidence of side effects was similar between patients with a short history of rheumatoid arthritis (RA) and those with a long-standing disease. However, the development of etanercept side effects was significantly higher among patients with mild to moderate disease activity (77.78%) compared to those with high disease activity (41.18%) (P = 0.041).

Table 6. Factors affecting the development of drug side effects

Parameter		Complaining of drug side effects	Not complaining of drug side effects	p. value
Age	Young (<50 years) N (%)	6 (54.5)	5 (45.5)	0.656*
	Old (50 or more) N (%)	15 (62.5)	9 (37.5)	
Gender	Male N (%)	4 (50.0)	4 (50.0)	0.685^
	Female N (%)	17 (62.96)	10 (37.04)	
Used treatment	Etanercept only N (%)	8 (72.72)	3 (27.28)	0.461^
	Etanercept plus MTX N (%)	13 (54.17)	11 (45.83)	
Educational level	Illiterate N (%)	10 (58.82)	7 (41.18)	0.890*
	Literate N (%)	11 (61.11)	7 (38.89)	
History of RA	Short N (%)	18 (60.0)	12 (40.0)	1.000^
	Medium and long N (%)	3 (60.0)	2 (40.0)	
Baseline disease activity	Mild and moderate N (%)	14 (77.78)	4 (22.22)	0.041^
	High N (%)	7 (41.18)	10 (58.82)	

*Statistical analysis by chi square test; ^ statistical analysis by Fisher exact test

Table 7. Correlation between Δ disease activity score with Δ quality of life domains

Parameter	Correlation coefficient	p. value
Physical activity (abnormal)	-0.408*	0.015
Pain severity (normal)	-0.468^	0.005
Pain effect (abnormal)	-0.237^	0.169
Anxiety (normal)	-0.205^	0.245
Depression (abnormal)	-0.247^	0.152
Fatigue (normal)	-0.341^	0.045
Sleep disturbances (normal)	^0.173	0.319

^Statistical test by Spearman Rho analysis; *statistical test by Pearson correlation test

DISCUSSION

Evaluating the effectiveness and safety of biosimilars has become increasingly important due to their expanding use in treating inflammatory arthritis, especially rheumatoid arthritis (RA). Despite numerous studies addressing their real-world application, there is limited evidence from Middle Eastern populations, particularly Iraq, where access to biologic therapy remains restricted due to limited availability and referral delays. This highlights the importance of conducting local clinical trials with biosimilars like Altebrel, which is a proposed biosimilar of etanercept that should be similar to the reference product in terms of purity, effectiveness, and safety[16].In this study the participants' mean age of 51.31 years is similar to the regional studies like the one in Jordan (mean 51.86 years), and the fact that women were the majority of patients (77.14%) are aligned with what is known about RA epidemiology, according to which the disease is more frequent in women[17]. In terms of biomarkers, the established mechanism of TNF-α inhibitors was confirmed by the significant decrease in TNF-α levels seen after treatment with Altebrel (median 281.23 to 198.55; $p < 0.001$)[18]. Etanercept's selective activity, which doesn't directly block IL-6 pathways, possibly explains why it doesn't directly block IL-6 pathways, and didn't drop considerably ($p = 0.082$).

Similar findings have been reported in other studies, which suggest that IL-6 suppression may require longer follow-up or different biologic targets[19]. ESR, a key inflammatory marker, also declined significantly, supporting the anti-inflammatory effects of the biosimilar. These changes were accompanied by a meaningful reduction in DAS28-ESR scores (mean decrease of ~0.7), which is comparable to findings from large-scale real-world investigations such as the COMPACT study[20].

In addition to clinical outcomes, significant improvements were observed in PROMIS-HAQ domains, especially physical function and pain severity. Median physical function T-scores improved from 50 to 60.5 ($p < 0.001$), and pain severity improved significantly as well, which is consistent with previous studies demonstrating the sensitivity of PROMIS to changes in disease activity and functional status[21]. Domains including depression, anxiety, and fatigue also showed improvement, but their association with disease activity was less pronounced. This is probably because these symptoms are caused by several factors[22].

The safety profile of the biosimilar was also favourable. Apart from a slight rise in serum creatinine (still within normal range) and a decrease in AST, no clinically significant lab abnormalities were reported. Adverse drug events occurred in more than 60% of patients, consistent with the literature, and the majority were mild[23]. No serious events such as neurologic complications, sepsis, or hepatitis reactivation were observed. A notable observation was the higher rate of adverse events among patients with milder baseline disease, a pattern also described in other observational cohorts[24].

A moderate negative correlation was seen between DAS28-ESR decrease and improvements in PROMIS physical function ($r = -0.41$) and pain intensity ($r = -0.47$), highlighting PROMIS's importance as a validated tool for measuring patient-reported outcomes in addition to clinical measures. However, psychological domains had weaker relationships, which were most likely attributed to variables unrelated to direct inflammation, such as baseline psychological status, socioeconomic stresses, or chronic pain, as shown in (Table 7)[25].

The strength of the study is in its multi-dimensional assessment, which incorporates both validated patient-reported measures and objective disease activity scoring. Despite a very high attrition rate (46.2%), which is typical of real-world trials of biologics in chronic illnesses, the findings provide useful insights on Altebrel's efficacy in Iraqi RA. However, the results do provide light on Altebrel's effectiveness in Iraqi RA, even if the attrition rate was somewhat high at 46.2%. This rate is typical of real-world studies of biologics in chronic conditions. However, there are certain limitations to the study that might introduce

bias, such as a small sample size, a lack of a control group, a short duration, and the reliance on self-reported data. The withdrawal of non-responders might potentially lead to an exaggeration of the treatment's effectiveness. To confirm and expand upon these findings, more studies are needed with larger samples, extended follow-up times, immune system profiling, and radiographic findings.

CONCLUSION

The present study supported that Altebrel is safe and effective biosimilar for RA, since it has the potential to improve clinical and quality-of-life outcomes when tested with sensitive tool like PROMIS-HAQ. Personalised therapy and significant gains from the patient's point of view could be enhanced by incorporating such assessments into routine care. Long-term pharmacovigilance data and comparative studies of biosimilar drugs are recommended.

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Potential Conflicts of Interest: None

Competing Interest: None

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