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ORIGINAL RESEARCH

Assessment of Treatment Safety and Quality of Life in Patients Receiving Etanercept Biosimilar for Autoimmune Arthritis (ASQA): A Multicenter Post-marketing Surveillance Study

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ABSTRACT

Introduction: Phase IV post-marketing surveillance studies are needed to evaluate the real-world safety and effectiveness of drug products. This study aimed to evaluate the safety and effectiveness of biosimilar etanercept (Altebrel, AryoGen Co., Iran) in patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA).

Methods: In this open-label, multicenter, prospective, observational, post-marketing surveillance study, 583 patients received biosimilar etanercept 25 mg twice weekly or 50 mg once weekly and were followed up to 12 months. The primary objective was to evaluate the safety of biosimilar etanercept by documenting all the adverse events in the case

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report forms throughout the study period. The secondary objective was to evaluate the effectiveness of biosimilar etanercept in study patients, where longitudinal changes in health assessment questionnaire (HAQ), pain, and disease activity scores were assessed.
Results: A total of 583 patients (44.80 ± 13.09 years of age) were included and followed for an average of 8.12 ± 3.96 months. Among all patients, 172 (29.50%) experienced at least one adverse event, and injection site reaction, abdominal pain, and upper respiratory tract infection were the most common. HAQ scores decreased from 1.32 ± 0.77 at baseline to 0.81 ± 0.61 at 12 months in patients with RA/PsA ($p < 0.01$) and from 0.82 ± 0.58 at baseline to 0.66 ± 0.63 at 12 months in patients with AS ($p = 0.18$). Pain scores decreased from 6.49 ± 2.41 at baseline to 3.51 ± 2.39 at 12 months ($p < 0.01$).
Conclusion: The results demonstrated the real-world safety and effectiveness of biosimilar etanercept in patients with RA, PsA, and AS.
Trial Registration: ClinicalTrials.gov identifier NCT04582084.

Keywords: Anti-TNF; Ankylosing spondylitis; Biologic; Biosimilar; Etanercept; Psoriatic arthritis; Rheumatoid arthritis

Key Summary Points

Real-world post-marketing data are required to improve the information available on the safety and effectiveness of marketed drugs, including biosimilar medicines.

Etanercept (including biosimilars) is one biologic treatment option for adults with autoimmune arthritis.

The ASQA trial was performed using data from a large number of patients with ankylosing spondylitis, psoriatic arthritis, or rheumatoid arthritis in real-world settings. The biosimilar etanercept was found to be safe and effective in improving quality of life in this study.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13387328.

INTRODUCTION

Rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) are chronic, multisystem inflammatory disorders with articular and extra-articular manifestations. RA primarily affects the joints and is marked by chronic inflammation in the synovial membranes and articular structures. PsA is an inflammatory arthritis linked with psoriasis. It often affects the axial joints and the peripheral terminal interphalangeal joints. AS mainly affects the axial joints such as the sacroiliac joint and other intervertebral or costovertebral joints and is characterized by pain and stiffness of the spine and inflammation at tendon insertions [1]. Progressive articular damage could potentially lead to functional disability [2] and impedes work productivity [3]. Disease progression would likely have psychiatric complications. Depression and anxiety are more common in patients with RA, PsA, and AS than in the general population [4–7]. Moreover, almost all patients report fatigue and pain during their disease course [7, 8]. Collectively, physical disability, productivity loss, psychological complications, fatigue, and pain can seriously impair quality of life in patients with autoimmune rheumatic disorders [9–11]. This highlights the importance of an effective and safe treatment approach to protect patients from symptom deterioration and to improve their quality of life.

For over two decades, tumor necrosis factor (TNF) inhibitors have been the mainstay of the treatment of patients with autoimmune arthritis unresponsive to conventional disease-modifying anti-rheumatic drugs (cDMARDs). TNF is a pro-inflammatory cytokine, which is attributed to the pathogenesis of various inflammatory autoimmune diseases. Etanercept is a human

dimeric fusion protein consisted of the extracellular ligand-binding portion of the 75-kDa (p75) tumor necrosis factor receptor (TNFR) and the Fc portion of IgG1. Etanercept binds to TNF molecules and interferes with TNF-activated signaling pathways. It is approved for the treatment of patients with RA, AS, PsA, polyarticular juvenile idiopathic arthritis (pJIA), and plaque psoriasis (PsO) [12]. Etanercept has established long-term safety and efficacy profiles, evaluated with several clinical trials and after two decades of use in different clinical indications. Etanercept is among the most frequently used biological therapeutic agents in routine clinical practice [13]; however, the administration of biologic drugs is generally constrained by the high cost and low drug availability, especially in low-income regions [14].

Biosimilars are biotechnological medicinal products that are highly similar to the corresponding reference products in terms of quality characteristics, biological activity, safety, and efficacy [15]. Biosimilar products could potentially improve drug accessibility by providing biologic treatments at lower costs [16]. The presence of biosimilars on the market expands physicians' options when making decisions on the treatment plan, hence, alleviating the impact of socioeconomic conditions on the usage of biologic treatments [17]. Several etanercept biosimilar products are manufactured across the globe, including Altebrel (AryoGen Co., Iran) [18]. Throughout the biosimilar drug development program, preclinical and clinical studies have proved the similarity of this biosimilar to the reference etanercept (Enbrel, Pfizer). Primary structure, N-glycan profile, methionine oxidation rate, and in vitro functionality of biosimilar and reference etanercept were found to be highly similar [19]. Moreover, the comparability of the efficacy, safety, and immunogenicity of these products was evaluated in a phase III randomized controlled trial in patients with moderately to severely active RA [20]. This biosimilar etanercept has been available on the local market since 2013, and no safety signals were identified up to now, as all reported adverse drug reactions were consistent with the safety information on the reference product. However, phase IV post-marketing clinical trials are required to evaluate the real-world safety and effectiveness of marketed drugs [21]. In this regard, the ASQA (assessment of treatment safety and quality of life in patients receiving etanercept biosimilar for autoimmune arthritis) trial was designed to collect data on the safety and effectiveness of biosimilar etanercept (Altebrel, AryoGen, Iran) in a naturalistic setting in a large cohort of patients with RA, PsA, and AS.

METHODS

Trial Design

The ASQA trial was a post-market, open-label, multicenter, prospective, longitudinal, observational, phase IV trial evaluating the safety and effectiveness of a biosimilar etanercept product in a cohort of adult patients with rheumatic disorders of RA, PsA, and AS. This was a national study conducted in various clinical settings around Iran between April 2014 and March 2018. The study was approved by the research ethics committee of Tehran University of Medical Sciences (#IR.TUMS.PSRC.REC.1396.3243), and was carried out according to the principles of the Declaration of Helsinki. The trial was retrospectively registered at ClinicalTrials.gov on October 9, 2020 (NCT04582084). Informed consent was obtained from all individuals prior to collecting their medical information.

Study Population

Adult patients with RA, PsA, and AS were eligible for the trial if their physician had prescribed biosimilar etanercept (either 25 mg or 50 mg) for their medical condition. Patients were administered etanercept 25 mg twice weekly or 50 mg once weekly and were followed for a maximum duration of 12 months. Case report forms were provided in four booklets and were to be filled in by physicians and patients. The first booklet contained baseline and months 1, 2, and 3 visits, and each of the subsequent booklets comprised three monthly visits. The

Table 1 Data collected with case report forms in study visits

Baseline visit	Follow-up visits	
	Months 1, 2, 4, 5, 7, 8, 10, 11	**Months 3, 6, 9, 12**
Physical examination	Physical examination	Physical examination
Adverse events	Adverse events	Adverse events
Concomitant medications	Concomitant medications	Concomitant medications
Etanercept treatment details	Etanercept treatment details	Etanercept treatment details
Health assessment questionnaires		Health assessment questionnaires
Pain assessment		Pain assessment
Informed consent		Physician and patient global assessment of disease activity
Eligibility screen		
Clinical indication		
Demographics		
Preceding treatments		
Medical history		

data collected with case report forms is shown in Table 1.

Study Outcomes

The primary objective was to evaluate the safety of biosimilar etanercept in a real-world situation. All adverse events were documented in the case report forms during the study period, regardless of the relationship between the treatment and the adverse event. Adverse events were defined using system organ classes and preferred terms of the Medical Dictionary for Regulatory Activities (MedDRA Desktop Browser 4.0 Beta). The causality assessment of adverse events was performed using the World Health Organization–Uppsala Monitoring Center (WHO-UMC) causality assessment system [22]. Adverse events that resulted in death, a threat-to-life, persistent or significant disability or incapacity, congenital anomalies or birth defects, required or prolonged hospitalization, or any other significant condition that compromised the patient and needed medical or surgical intervention to prevent the preceding outcomes were considered as serious adverse events [23].

The secondary objective was to evaluate the effectiveness of biosimilar etanercept in a real-world situation. A health assessment questionnaire (HAQ) was used to assess the functional status of patients at baseline and at 3, 6, 9, and 12 months. The HAQ-disability index (HAQ-DI) and HAQ-spondyloarthropathies (HAQ-S) were examined in patients with RA/PsA and AS, respectively. Pain assessment was performed on a scale of 0–10, with higher scores indicating greater pain, at 3, 6, 9, and 12 months. To further evaluate the maintenance of treatment effects on the disease activity, physician and patient global assessments of disease activity (PhGA and PGA, respectively) were documented on a scale of 0–10, with higher scores indicating higher disease activity, at 3, 6, 9, and 12 months. A PhGA score of 1.5 or less and a PGA score of 2 or less were considered as low global assessment [24, 25].

After completion of case report forms, data from all booklets were transferred to a web-based electronic database and were used for the final report after cleaning.

Statistical Analysis

Descriptive analysis was carried out for the demographic and baseline clinical characteristics of patients. For the primary endpoint, all the adverse events were reported as incidence per number of patients and frequencies. Subgroup analysis of adverse events was performed by the clinical indication of etanercept (i.e., RA, PsA, or AS) using a proportion test. For the secondary endpoints, longitudinal data were analyzed using generalized estimating equation (GEE) models. All statistical analyses were performed using STATA software, version 14.0 (Stata Corporation, Texas, USA). *P* values less than 0.05 were considered as statistically significant.

RESULTS

Demographic and Baseline Characteristics

A total of 583 patients were included in this study. Table 2 summarizes the demographic and baseline characteristics of the patients. Overall, 65.18% of the participants were female. The study population comprised patients of different adult age groups ranging from 18 to 108 years. The majority of patients included in the study had a diagnosis of RA ($n = 397$, 68.10%), followed by AS ($n = 153$, 26.24%) and PsA ($n = 36$, 6.17%).

Safety

In this study, patients received biosimilar etanercept for an average duration of 8.12 ± 3.96 months. A total of 607 adverse events were reported during the study period, which were mostly at least possibly related to etanercept treatment (88.63%, 538/607). Among the 583 patients of this analysis, adverse events were observed in 172 (29.50%) patients, of whom 166 (28.47%, 166/583) experienced at least one possibly related adverse event. The incidence of adverse events categorized by system organ classes and preferred terms is illustrated in Table 3. The majority of adverse events were classified in the general disorders and administration site conditions class, with injection site reaction as the most incident adverse event (26.42%, 154/583). Most of the patients reported their first injection site reaction in the first 3 months of etanercept administration (90.26%, 139/154); 234 patients were followed for the full duration of 12 months. Among these patients, injection site reaction occurred in 10 (4.27%), the majority of whom (70.00%, 7/10) experienced injection site reaction in the first month of treatment with biosimilar etanercept. Subgroup analysis revealed no statistically significant difference in the incidence of any adverse event between patients with RA, PsA, and AS [28.21% (112/397), 45.67% (15/36), and 30.06% (46/153) respectively, between-group $p > 0.05$]. In this safety study, two serious adverse events were reported in two individuals, including one upper respiratory tract infection and one urosepsis. Both patients were hospitalized and treated with intravenous antibiotics. Following hospitalization and appropriate medical management, both infections resolved successfully, and no further complications arose.

Effectiveness

Figure 1 demonstrates the profiles of functional health questionnaires and pain assessment scores over time. The HAQ-DI score (Fig. 1a) decreased from 1.32 ± 0.77 at baseline to 0.81 ± 0.61 at 12 months, with a statistically significant downward trend ($p < 0.01$). The HAQ-S score (Fig. 1b) decreased from 0.82 ± 0.58 at baseline to 0.66 ± 0.63 at 12 months; however, the trend was not statistically significant ($p = 0.18$). The pain scores (Fig. 1c) show an intense pain in the study patients at baseline with an average score of 6.49 ± 2.41, which decreased significantly to 3.51 ± 2.39 over time ($p < 0.01$). Longitudinal PhGA and PGA scores demonstrate the

Table 2 Patient demographics and baseline clinical characteristics

Demographic and baseline characteristics	
Patients, *n*	583
Gender, *n* (%)	
Female	380 (65.18)
Male	203 (34.82)
Age (years), mean ± SD	44.80 ± 13.09
Weight (kg), mean ± SD	72.72 ± 14.48
Height (cm), mean ± SD	164.56 ± 9.15
Diagnosis, *n* (%)	
Rheumatoid arthritis	396 (67.92)
Ankylosing spondylitis	149 (25.56)
Psoriatic arthritis	33 (5.66)
Ankylosing spondylitis + psoriatic arthritis	3 (0.51)
Ankylosing spondylitis + rheumatoid arthritis	1 (0.17)
Missing data	1 (0.17)
Prior biologic use, *n* (%)	0 (0.00)
Concomitant DMARD use, *n* (%)	179 (30.70)
Concomitant MTX use, *n* (%)	135 (23.16)
HAQ score, mean ± SD	
HAQ-DI	1.32 ± 0.77
HAQ-S	0.82 ± 0.58
Pain score, mean ± SD	6.49 ± 2.41

DMARD disease-modifying anti-rheumatic drugs, *HAQ* health assessment questionnaire, *HAQ-DI* HAQ-disability index, *HAQ-S* HAQ-spondyloarthropathies, *MTX* methotrexate

maintenance of low disease activity with etanercept treatment over time. The proportion of patients reporting a PhGA score of 1.5 or less was 70.31%, 70.87%, 69.90%, and 80.40% at 3, 6, 9, and 12 months, respectively ($p = 0.06$). The proportion of patients reporting a PGA score of 2 or less was 72.85%, 77.20%, 73.22%, and 81.12% at 3, 6, 9, and 12 months, respectively ($p = 0.17$).

DISCUSSION

Throughout the life of a medicinal product, safety monitoring is required to assess the nature and frequency of adverse drug events and to detect any safety signals. Spontaneous adverse drug reaction reporting systems and phase IV non-interventional studies are the main sources of data for the safety evaluation of pharmaceuticals in the post-marketing phase [21]. ASQA was the nationwide post-marketing surveillance

Table 3 Incidence of adverse events classified by system organ classes and preferred terms

Incidence of adverse events, *n* (%)			
System organ class		**Preferred term**	
Blood and lymphatic system disorders	2 (0.34)	Leukopenia	2 (0.34)
		Thrombocytopenia	1 (0.17)
Gastrointestinal disorders	31 (5.32)	Abdominal pain	24 (4.12)
		Diarrhea	15 (2.57)
		Vomiting	10 (1.72)
General disorders and administration site conditions	154 (26.42)	Flushing	1 (0.17)
		Injection site reaction	154 (26.42)
Immune system disorders	2 (0.34)	Hypersensitivity	1 (0.17)
		Skin reaction	1 (0.17)
Infections and infestations	23 (3.95)	Lower respiratory tract infection	9 (1.54)
		Rhinitis	6 (1.03)
		Upper respiratory tract infection	16 (2.74)
		Urosepsis	1 (0.17)
Investigations	16 (2.74)	Antinuclear antibody increased	11 (1.89)
		Hepatic enzyme increased	5 (0.86)
Musculoskeletal and connective tissue disorders	1 (0.17)	Arthritis	1 (0.17)
Nervous system disorders	2 (0.34)	Headache	1 (0.17)
		Paraesthesia	1 (0.17)
Respiratory, thoracic, and mediastinal disorders	3 (0.51)	Cough	1 (0.17)
		Dyspnea	2 (0.34)
Skin and subcutaneous tissue disorders	7 (1.20)	Contusion	2 (0.34)
		Pruritus	3 (0.51)
		Skin lesion	2 (0.34)
Vascular disorders	1 (0.17)	Hypertension	1 (0.17)

of the biosimilar etanercept Altebrel (AryoGen Co., Iran). The main objective of this multicenter, prospective study was to evaluate the safety profile of biosimilar etanercept in real-world settings in a mixed cohort of patients with RA, PsA, and AS, the approved rheumatologic indications of etanercept in adults. The results of this safety analysis involving 583 patients demonstrate biosimilar etanercept to be a safe and generally tolerable treatment option, with no meaningful differences in the risk of adverse events between the three patient groups (i.e., patients with RA, PsA, and AS). All adverse events documented through the study period were within the expected spectrum of etanercept adverse events. Injection site

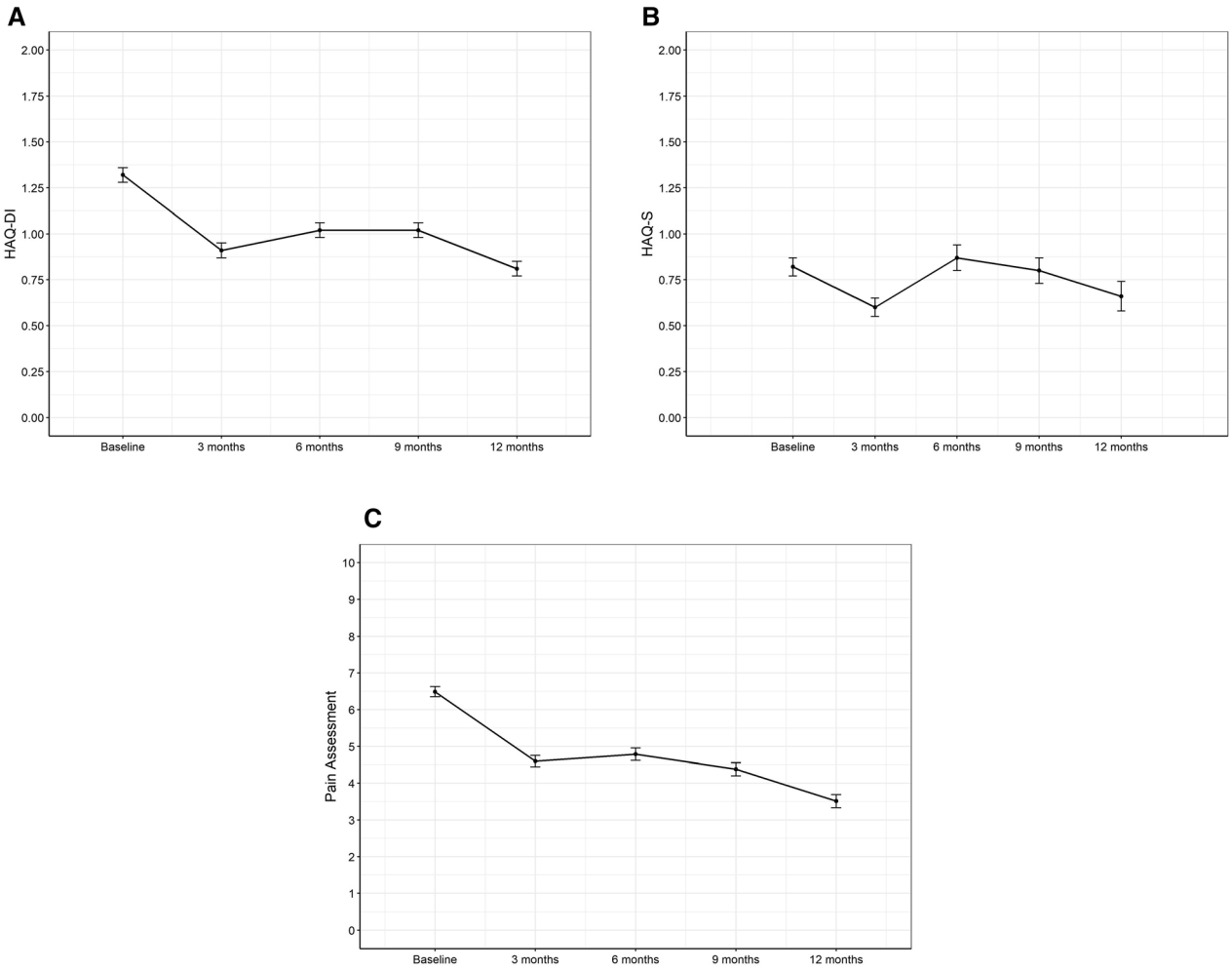

Fig. 1 Longitudinal changes in the patient-reported effectiveness outcomes during the study: **a** HAQ-DI scores; **b** HAQ-S scores; **c** pain assessment scores. HAQ-DI health assessment questionnaire-disability index, HAQ-S health assessment questionnaire-spondyloarthropathies

reaction was the most frequently documented adverse event in the present study, as it was reported in more than a quarter of patients. In all three randomized controlled trials of etanercept in a total of 955 patients with active RA [26–28], one in 205 patients with active PsA [29], and one in 277 patients with active AS [30], the incidence rate of injection site reaction was significantly higher with etanercept compared to control. As with our study, the most common infection reported in all these five clinical studies was upper respiratory tract infection. Although the types of common adverse events observed in our post-marketing observational study were similar to those in the randomized controlled trials of etanercept, the incidence rates were somewhat lower in our study. The risk of underreporting of adverse events is obviously higher in observational studies than in controlled clinical trials, which could potentially lead to the lower incidence rates of adverse events in the phase IV post-marketing studies [31, 32]. Along with the similar spectrum of the types of adverse events, our data on the incidence rates of adverse events is similar to the previous post-marketing surveillance of etanercept. Incidence rates in the non-interventional studies by Gladman et al. [33] and Gaubitz et al. [34] were lower than the randomized controlled trials, which is

similar to our results. In a 6-month phase IV post-marketing trial in a large cohort of Japanese patients with RA receiving etanercept treatment, Koike et al. [35] reported a total incidence of any adverse event of 31.21%, which is very close to the total incidence of 29.50% in our patients.

Patient-reported outcome measures are valuable tools for the evaluation of treatment efficacy in patients with rheumatic disorders and are being widely used in clinical trials [36]. Strand et al. [37] compared the reliability of patient- and physician-reported outcomes in patients with RA by analyzing the results of two randomized controlled trials. According to this study, patient-reported pain, physical function status, and global assessment of disease activity were superior to physician-reported outcomes in determining the benefits of treatment in patients with RA. In the present study, patient-reported outcomes were mainly considered for the effectiveness evaluation. Our data demonstrates the positive impacts of etanercept treatment on the patient-reported functional status and pain, based on the significantly improved HAQ-DI and pain scores, respectively, during the 1-year study period. Kekow et al. [38], in a randomized controlled trial, compared the longitudinal changes in patient-reported outcomes in patients with RA receiving methotrexate or the combination of etanercept and methotrexate during 52 weeks. Consistent with our findings, they found significantly improved functional status (HAQ scores) and pain assessment scores with etanercept treatment. Similarly, Gaubitz et al. [39], in the subanalysis of an observational trial, found improved patient-reported pain and HAQ scores after 52 weeks of treatment with either etanercept or etanercept plus methotrexate.

Limitations of this safety analysis include the observational, uncontrolled nature of the study and the existence of missing data. Moreover, only adult patients with rheumatic disorders were enrolled in this post-marketing study, and other clinically approved indications of etanercept, PsO and pJIA, were not considered. A larger and wider study population could certainly enhance the power of this safety analysis; however, the number of patients receiving biosimilar etanercept in this phase IV study is large enough to broaden our understanding of the safety of this etanercept biosimilar product.

CONCLUSIONS

Our findings in this open-label, multicenter, observational, phase IV, post-marketing surveillance on the safety and effectiveness of biosimilar etanercept (Altebrel, AryoGen Co., Iran) in patients with RA, PsA, and AS demonstrated that this biosimilar etanercept should be considered as a viable treatment option. The safety profile of biosimilar etanercept was consistent with the large body of clinical evidence in support of the safety and tolerability of etanercept in the approved clinical indications.

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Disclosures. Nassim Anjidani is the head of the medical department of Orchid Pharmed company, which is in collaboration with Aryo-Gen Pharmed company with respect to conducting clinical trials. Farhad Gharibdoost, Amir-Hossein Salari, Mansour Salesi, Faegheh Ebrahimi Chaharom, Peyman Mottaghi, Mansour Hosseini, Maryam Sahebari, Mohammadali Nazarinia, Zahra Mirfeizi, Mohammadreza Shakibi, Hamidreza Moussavi, Mansour Karimifar, Karim Mowla, Hadi Karimzadeh, and Ahmadreza Jamshidi have nothing to disclose.

Compliance with Ethics Guidelines. The study was approved by the research ethics committee of Tehran University of Medical Sciences (#IR.TUMS.PSRC.REC.1396.3243), and was carried out according to the principles of the Declaration of Helsinki. Informed consent was obtained from all individuals prior to collecting their medical information.

Data Availability. The data that support the findings of this study are available from the corresponding author, A.J., upon reasonable request.

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