Efficacy and Safety of Biosimilar and Originator Etanercept in Rheumatoid Arthritis Patients: Real-Life Data

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ABSTRACT

Background: There is a lack of real-life clinical data for biosimilar etanercept, an anti-TNF blocking fusion protein. We describe the comparable efficacy and safety of originator and biosimilar etanercept in rheumatoid arthritis (RA) patients in a real-life clinical setting. Our data confirm that a biosimilar etanercept can be safely used as first-line treatment as well as in patients switched from a previous originator compound.

Objectives: To compare the efficacy and safety of originator and biosimilar etanercept in a cohort of RA patients attending two Italian hospitals.

Methods: The study involved 81 consecutive adult RA patients treated for at least 6 months with originator or biosimilar etanercept and considered their clinical and laboratory data, concomitant medications, and adverse events at baseline, and after 3 and 6 months of treatment.

Results: Group 1 included 51 patients taking originator etanercept; group 2 included 30 taking biosimilar etanercept, including 19 who had been switched from the reference product. Despite a significant baseline difference in clinical disease activity, one-way analysis of variance showed that the two groups were clinically comparable after 6 months of treatment, and the same was true when only those receiving etanercept as first-line biological treatment were considered. Nine patients discontinued the treatment due to inefficacy or adverse events, which were never serious and were only reported in group 1.

Conclusions: The efficacy and safety profiles of originator and biosimilar etanercept are comparable in RA patients in a real-life clinical setting. Further studies are needed to confirm these preliminary findings.

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KEY WORDS: arthritis, biosimilar, etanercept, rheumatoid efficacy, safety

Rheumatoid arthritis (RA) is a chronic autoimmune disease that is characterized by small peripheral joint synovitis [1] and is more prevalent in middle-aged women. The worldwide prevalence is approximately 0.5–1% of the population [2]. Its pathogenesis of the disease is still debated, but it is fairly clear that environmental triggers such as infections may aberrantly activate the immune system against self-antigens in genetically predisposed patients. Tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and IL-6 are critical cytokines in the inflammatory cascade of RA [3]. High levels are secreted by macrophages in the synovial fluid of inflamed joints, thus stimulating the proliferation of synoviocytes, the recruitment of pro-inflammatory cells from the bloodstream, the release of metalloproteases by polymorphonuclear cells and macrophages, the activation of osteoclasts, and finally joint destruction. Given the central role of TNF-α in the pathogenesis of RA, monoclonal antibodies or fusion proteins targeting it have been developed and successfully used to treat RA and other rheumatic diseases.

One of these is etanercept, a genetically engineered, fully human fusion protein consisting of p78 TNF-α receptor and the crystallisable fragment (Fc) of human immunoglobulin G1 (IgG1) that prevents the interactions of TNF-α and TNF-β with endogenous receptors and their subsequent pro-inflammatory effects by binding both with great avidity [4]. It was the first TNF-blocker licensed for the treatment of moderate to severe RA in the United States by the U.S. Food and Drug Administration (FDA) [5], and has also been approved by the European Medicines Agency (EMA) for use in RA patients failing to respond to conventional therapies, including methotrexate, and as first-line treatment in patients with poor prognostic factors and aggressive disease [6].

Anti-TNF agents have revolutionized the clinical course of RA by allowing good symptomatic control and remission in more than two-thirds of patients, but are burdened by high manufacturing costs. However, the recent expiry of the patents of many biological drugs and the marketing of their biosimilar counterparts has led to considerable cost savings and allowed greater access to treatment.

According to the EMA and FDA, a biosimilar drug is a biological medicine that is highly similar to another already approved biological medicine, and shows no significant differences in terms of efficacy, safety, and biological qualities after highly rigorous comparability testing [7]. Pre-clinical and clinical trials, as well as active drug surveillance, have also helped to define small differences in the efficacy and safety profiles of biosimilars and their reference products due to the slight differences in their molecular structures occurring during the manufacturing process [8].

The physico-chemical characteristics and in vitro biological activity of the biosimilar etanercept Benepali® (Biogen) are comparable with those of its originator [9]. It has recently been licensed by the EMA for the same clinical indications.

Given the cost-saving advantages of biosimilars in patients affected by chronic diseases such as RA, there is growing interest in better defining their long-term effects in biological drug-naïve RA patients and those switched from the originators, but there are still few data concerning the efficacy and safety of the etanercept biosimilar in a real-life clinical setting. The aim of this study was therefore to evaluate the post-marketing comparability of originator and biosimilar etanercept in RA patients attending two Italian hospitals.

We describe the comparable efficacy and safety of originator and biosimilar etanercept in rheumatoid arthritis patients in a real-life clinical setting. Our data are in line with the results of randomized controlled trials and confirm that a biosimilar can be safely used as first-line treatment as well as in patients switched from a previous originator compound.

PATIENTS AND METHODS

In a double-center study, we retrospectively enrolled patients with RA who had been treated with originator or biosimilar etanercept. All RA patients diagnosed on the basis of the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria [10], attending the rheumatology units of two Italian centers between 2018 and 2019 underwent to ETN originator or biosimilar therapy for at least 6 months in accordance with the 2010 ACR /EULAR guidelines [11]. Those patients had been clinically followed from baseline with periodic visits every 3 months. The recorded data were the number of tender and swollen joints, a pain visual analogue scale (VAS), the assessments by patients and their physicians of the disease and global health (GH), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level, CRP 28-joint Disease Activity Score (CRP-DAS28), Clinical Disease Activity Index (CDAI), Simple Disease Activity Index (SDAI), EULAR response [12], anti-citrullinated protein antibody (ACPAs) and rheumatoid factor (RF) positivity, previous and concomitant medications, and adverse events.

The switch from originator to biosimilar was made in all patients who achieved remission or low disease activity based on phamacoeconomic Italian regional reason while from the originator vs. biosimilar due to inefficacy or adverse events.

All of the patients gave their informed consent to participate in the study, which was conducted in accordance with the Declaration of Helsinki and local regulations. Local Ethics Committee approval was not required as the participants underwent the clinical and clinimetric examinations on the basis of routine hospital protocols.

STATISTICAL ANALYSIS

The data recorded were entered into a database (Microsoft Office Excel 2011, version 11.41.1 Microsoft, Redmond, WA, USA). Continuous data were presented as means ± standard deviations or percentage.

The patients were divided into two groups: those assigned to the etanercept originator (Enbrel®, Pfizer) and those to the etanercept biosimilar (Benepali®, Biogen). The clinical and laboratory data were divided into nominal and ordinal variables, and the ordinal data were compared between groups at baseline and after 3 and 6 months of treatment using chi square test to compare categorical variables, while Bonferroni correction for post hoc analysis in one-way ANOVA test was conducted for continuous variables.

A P value of ≤ 0.05 was considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 23 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

BASELINE DEMOGRAPHIC DATA

The mean age of the cohort was 54.0 ± 16.0 years. The mean disease duration was 12 ± 9 years. The mean age at the time of RA diagnosis was 38.0 ± 17.0 years. Sixty-three patients (77.8%) were female; nine (11.1%) were smokers; 37 (45.6%) had ACPAs, and 55 (67.9%) RF. Forty-eight patients (59.2%) had previously been treated with disease-modifying antirheumatic drugs (DMARDs) alone or in combination, and 23 (28.4%) had taken steroids.

All of the 51 patients treated with the etanercept originator (group 1) had received etanercept as their first biological line, whereas 19 (63.3%) of the 30 patients treated with biosimilar etanercept (group 2) had received the drug as second-line treatment after being switched from the originator.

The 51 patients in group 1 included 40 females (78.4%). Their mean age was 52.0 ± 15.5 years; mean age at the time of the diagnosis of RA was 33.1 ± 15.8 years; mean disease duration was 12.6 ± 9.0 years; and mean age at the start of the study treatment was 46.2 ± 15.3 years. Six of the patients (11.7%) were smokers, 22 (43.1%) had ACPAs, and 37 (72.5%) RF. Thirty (58.8%) had been treated with at least one DMARD and 11 (21.5%) had received corticosteroids [Table 1].

The 30 patients in group 2 included 23 females (76.7%). Their mean age was 58.20 ± 16.8 years; mean age at the time of the diagnosis of RA was 46.77 ± 17.1 years; mean disease duration was 11.0 ± 9.80 years; and mean age at the start of the study treatment was 57.70 ± 17.0 years. Three (10%) were smokers, 15 (50%) had ACPAs, and 18 (60 %) RF. Twelve (40%) had been treated with at least one DMARD, and 18 (60%) had received corticosteroids [Table 1].

Table 1. Patient demographic and clinical data at baseline (T0)

	Group 1 n=51	Group 2 n=30	Significance
Mean age ± SD, years	52.2 ±15.5	58.2 ± 16.8	NS
Females, n (%)	40 (78.4)	23 (76.7)	NS
Smokers, n (%)	6 (11.7)	3 (10)	NS
Mean age at diagnosis ± SD, years	33.1 ± 15.8	46.7 ± 17.1	**P = 0.008**
ACPAs, n (%)	22 (43.1)	15 (50)	NS
RF, n (%)	37 (72.5)	18 (60)	NS
Mean age at the start of ETN ± SD, years	46.2 ± 15.3	57.70 ± 17.0	**P = 0.005**
Mean disease duration at the start of ETN ± SD	12.6 ± 9.0	10.60 ± 9.80	NS
Corticosteroids, n (%)	11 (21.5)	12 (40)	**P > 0.03**
DMARDs, n (%)	30 (58.8)	18 (60)	NS
Mean swollen joint count ± SD	4.49 ± 3.7	2.37 ± 2.6	**P = 0.006**
Mean tender joint count ± SD	9.10 ± 6.4	3.50 ± 3.6	**P < 0.001**
Mean GH score ± SD	7.41 ± 1.5	5.93 ± 2.1	**P = 0.002**
Mean patient VAS score ± SD	7.37 ± 1.5	5.00 ± 2.3	**P < 0.004**
Mean evaluator VAS score ± SD	7.39 ± 1.4	4.43 ± 2.5	**P < 0.001**
Mean ESR ± SD, mm at end of first hour	34.31 ± 16.3	25.03 ±19.7	**P = 0.032**
Mean CRP ± SD, mg/L	3.90 ± 8.2	1.12 ± 1.4	P > 0.046
Mean ESR-DAS28 ± SD	5.48 ± 1.1	3.98 ± 1.3	**P < 0.004**
Mean CRP-DAS28 ± SD	4.98 ± 1.2	3.23 ± 1.4	**P < 0.015**
Mean CDAI ± SD	28.35 ± 10.3	15.30 ± 8.6	**P < 0.001**
Mean SDAI ± SD	32.25 ± 14.9	16.42 ±9.4	**P < 0.001**

Bold signifies significance
ACPAs = anti-citrullinated protein antibodies, CDAI = Clinical Disease Activity Index, CRP = C-reactive protein, DAS28 = 28-joint Disease Activity Score, DMARDs = disease-modifying anti-rheumatic drugs, ESR = erythrocyte sedimentation rate, ETN = etanercept, GH = global health, RF = rheumatoid factor, SD = standard deviation, SDAI = Simple Disease Activity Index, VAS = visual analogue scale

ORIGINATOR VS. BIOSIMILAR ETANERCEPT

At baseline, the patients in the group 1 had a mean CRP-DAS28 of 4.9 ± 1.2, a mean CDAI of 28.3 ± 10.3, and a mean SDAI ± SD of 32.2 ± 14.9. The patients in group 2 had a mean CRP-DAS28 of 3.2 ± 1.4, a mean CDAI of 15.3 ± 8.6, and a mean SDAI of 16.4 ± 9.4. One-way ANOVA of all three indices showed that disease severity was significantly greater in group 1 ($P < 0.00$) [Table 1].

However, as shown in Table 2, except for the ESR and the evaluator's VAS, the clinimetric scores in the two groups were comparable after 6 months of treatment. In terms of 6-month EULAR responses, dividing the patients into moderate/good responders vs. non-responders showed that those treated with originator etanercept were more likely to respond than those assigned to the biosimilar (chi square test 12.2; $P = 0.0004$).

A second analysis comparing the 11 group 2 patients receiving first-line biosimilar etanercept with the patients in group 1 showed that the two cohorts did not significantly differ at baseline in terms of age, age at the time diagnosis or age at the start of etanercept treatment, gender, smoking habits, auto-antibody levels, DMARD or steroid intake, swollen joint counts, GH, ESR, or CRP, and had more homogenous clinimetric scores with the difference in CRP-DAS28 not reaching statistical sig-

Table 2. Clinical and laboratory data after 6 months

	Group 1 n=51	Group 2 n=30	Significance
Mean swollen joint count ± SD	0.8 ± 1.4	0.6 ±1.0	NS
Mean tender joint count ± SD	3.0 ± 4.8	1.5 ± 2.0	P > 0.0041
Mean GH ± SD	3.9 ± 2.0	4.7 ± 2.5	NS
Mean patient VAS score ± SD	4.0 ± 2.0	3.6 ± 2.1	NS
Mean evaluator VAS score ± SD	3.9 ± 1.9	2.9 ± 2.1	**P = 0.025**
Mean ESR ± SD, mm at end of first hour	22.8 ±17.8	15.4 ± 9.7	**P = 0.033**
Mean CRP ± SD, mg/L	3.2 ± 14.8	0.5 ± 1.2	P = 0.012
Mean ESR-DAS28 ± SD	2.8 ± 1.1	2.4 ±0.9	NS
Mean CRP-DAS28 ± SD	2.7 ± 1.3	2.5 ± 1.0	NS
Mean CDAI ± SD	11.7 ±7.9	8.7 ±5.9	NS
Mean SDAI ± SD	15.0 ± 18.2	9.2 ±6.4	P = 0.041

Bold signifies significance
CDAI = Clinical Disease Activity Index, CRP = C-reactive protein, DAS28 = 28-joint Disease Activity Scale, ESR = erythrocyte sedimentation rate, GH = global health, SDAI = Simple Disease Activity Index, VAS = visual analogue scale

Table 3. Patients treated with etanercept originator and biosimilar as first line compared

	Baseline			After 6 months		
	Originator n=51	Biosimilar n=11	Significance	Originator n=51	Biosimilar n=11	Significance
Mean ESR-DAS28 ± SD	5.4 ± 1.1	4.7 ± 1.0	P = 0.037	2.87 ± 1.1	2.4 ± 0.9	NS
Mean CRP-DAS28 ± SD	4.9 ± 1.2	4.2 ± 1.0	NS	2.74 ± 1.3	2.3 ± 1.2	P > 0.05
Mean CDAI ± SD	28.3 ± 10.3	20 ± 8.2	P = 0.033	11.7 ±7.9	7.3 ± 6.4	NS
Mean SDAI ± SD	32.2 ± 14.9	21.9 ± 9.3	P = 0.021	15.0 ± 18.2	8.1 ± 7.8	P = 0.034

CDAI = clinical disease activity index, CRP = C-reactive protein, DAS28 = 28-joint Disease Activity Score, ESR = erythrocyte sedimentation rate, SDAI = simple disease activity index

nificance [Table 3]. Despite the disproportion in the numbers (11 vs. 51), ANOVA showed that there was no between-group difference in their 6-month clinimetric scores, and the chi square test that there was no significant difference in terms of EULAR responses ($P > 0.05$).

In brief, despite the significant difference in baseline disease activity between the two groups the efficacy profiles of originator and biosimilar etanercept were comparable after 6 months, and there was no significant difference in the clinical responses of the patients receiving either drug as first-line biological treatment [Figure 1].

SAFETY PROFILE OF ORIGINATOR AND BIOSIMILAR ETANERCEPT

Nine patients discontinued the study treatment because of inefficacy or adverse events during the follow-up. Among those treated with originator etanercept, three (5.8%) experienced skin rashes, one (1.9%) severe headache, and three (5.8%) showed no clinical response. In group 2, two patients (6.6%) stopped the treatment because of inefficacy but there were no adverse events.

DISCUSSION

Our data collected in a real-life clinical setting show that the efficacy and safety of biosimilar etanercept after 6 months of treatment was comparable with those of the reference product in a cohort of RA patients. These findings are in line with those of randomized controlled trials [13-15], even though our patients had significantly different clinimetric scores at baseline because of the study's consecutive recruitment and real-life setting. The patients taking originator etanercept had more severe disease at baseline than those taking the biosimilar compound, possibly because the latter included patients previously treated with the originator and therefore showing milder disease activity. Consequently, our second analysis only considered the group 2 patients receiving first-line treatment as these were less different from those in group 1 at

baseline. However, both analyses showed that clinimetric scores improved during the period of observation, and that there were no significant between-group differences after 6 months of treatment, and no differences in 6-month response among the patients receiving their first biological line.

In addition to the baseline differences between the groups, the limitations include the small number of patients, the short period of observation, and the lack of instrumental (including radiographic) and immunogenicity data.

Immunogenicity may explain the lack of efficacy and onset of adverse events during treatment with biological agents. One phase III randomised controlled trial comparing biosimilar to reference etanercept in methotrexate-resistant RA patients highlighted a similar efficacy and safety profile but a lower percentage of anti-drug antibodies in the biosimilar arm (0.7% vs. 13.1% after 24 weeks, and 1.0% vs. 13.2% after 52 weeks of treatment) [13,14]. Other randomized controlled trials have not found any difference in immunogenicity between RA patients receiving biosimilar or branded etanercept [16]. After extensive similarity testing of biosimilar and branded etanercept, no significant difference was found in their structural, physicochemical and biological characteristics, but there were fewer high-molecular-weight aggregates and lower alpha-1,3-galactose levels in the biosimilar drug [17]. Given that differences in glyco-patterns may affect immunogenicity and impair efficacy, this finding led to another N-glyco-characterization study of Enbrel® and Benepali®, which led to the conclusion that the biosimilar compound had some differences in sialylated, core-fucosylated, and galactosylated structures over the tolerance window, although these did not affect its mechanism of action [18].

The reduced immunogenicity of biosimilar etanercept emerging from these studies may also explain the high treatment retention rate in the case of a previous switch from the originator drug. None of the patients in our cohort who switched from originator to biosimilar etanercept developed inefficacy or adverse events, thus indicating that such a switch may be safe. It is also worth noting that only our group 1 patients reported

Figure 1. Histograms on the efficacy of the drugs used
DAS = Disease Activity Score
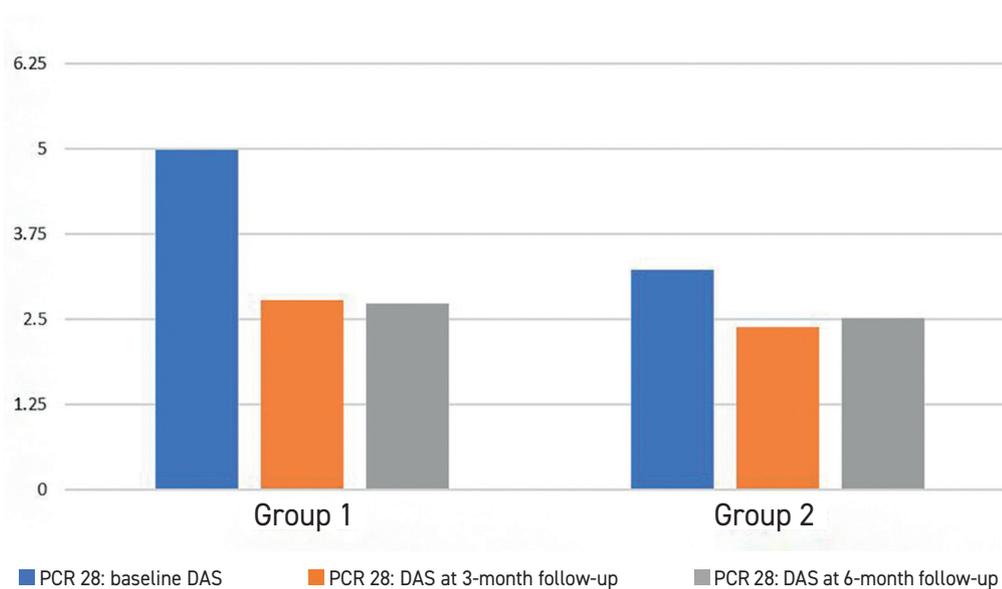
adverse events, although this may have been due to the small number of patients and the short period of observation.

Switching from originator to biosimilar etanercept has proven to be well tolerated and effective in randomized controlled trials involving RA patients [19]. Our national guidelines (Agenzia Italiana del Farmaco, AIFA) consider biosimilar drugs interchangeable with the original biological agents, without distinguishing treatment-naive and previously treated patients [20]. One large Norwegian non-inferiority study (NOR-SWITCH) of patients with different diseases for which infliximab is indicated found no significant differences after switching from the originator to the biosimilar drug [21].

The reasons for switching from an originator to a biosimilar product may include pharmaco-economics and patient preference for a more intuitive and easy to handle auto-injector [22], but translating data from randomized controlled trials to real-life conditions may be difficult because of differences in patient cohorts, co-morbidities, and the nocebo effect [23]. Only two studies of psoriatic patients have so far evaluated the real-life effectiveness and safety of biosimilar etanercept. They first extrapolated the clinimetric and safety data of 197 patients in the Psobiosimilars registry, 31.4% of whom were affected by psoriatic arthritis, and found no significant differences in Psoriasis Area Severity Index (PASI) scores and adverse events after six months' treatment [24]. The second analysed real-life data from the DERMBIO registry and did not find any difference in the efficacy and safety profiles of originator and biosimilar etanercept after switching psori-

atic patients from the first to the second [25]. Our own data confirmed the efficacy of Benepali® in treatment-naïve and switched RA patients. However, given the slight differences in molecular structure, the heterogeneity of disease indications (characterized by various immunological backgrounds), inconsistency of the findings concerning the immunogenicity of biosimilar etanercept, the diversity in the positions of national and international guidelines, and the still limited post-marketing experience, more information is required before licensing routine switching in any clinical situation.

Conclusions

Our findings indicate the comparable real-life efficacy and safety profile of originator and biosimilar etanercept in RA patients, and show that switching from originator to biosimilar etanercept is safe and did not lead to any drug discontinuations due to inefficacy or adverse events. However, further studies of larger and more homogeneous cohorts are needed to confirm these preliminary data.

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Capsule

TIM-3 restrains anti-tumor immunity by regulating inflammasome activation

T cell immunoglobulin and mucin-containing molecule 3 (TIM-3), first identified as a molecule expressed on interferon-γ producing T cells1, is emerging as an important immune-checkpoint molecule, with therapeutic blockade of TIM-3 being investigated in multiple human malignancies. Using conditional knockouts of TIM-3 together with single-cell RNA sequencing, **Dixon** and colleagues demonstrated the singular importance of TIM-3 on dendritic cells (DCs) in which the loss of TIM-3 on DCs, but not on CD4+ or CD8+ T cells, promotes strong anti-tumor immunity. Loss of TIM-3 prevented DCs from expressing a regulatory program and facilitated the maintenance of CD8+ effector and stem-like T cells. Conditional deletion of TIM-3 in DCs led to increased accumulation of reactive oxygen species resulting in NLRP3 inflammasome activation. Inhibition of inflammasome activation, or downstream effector cytokines interleukin-1β (IL-1β) and IL-18, completely abrogated the protective anti-tumor immunity observed with TIM-3 deletion in DCs. Together, these findings reveal an important role for TIM-3 in regulating DC function and underscore the potential of TIM-3 blockade in promoting anti-tumor immunity by regulating inflammasome activation.

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