ORIGINAL ARTICLES

# Effectiveness and safety of original and biosimilar etanercept (Enbrel® vs Benepali®) in bDMARD-naïve patients in a real-world cohort of Portugal

Pinto AS[1], Cunha MM[2], Pinheiro F[3], Bernardes M[3], Assunção H[4], Martins-Martinho J[5], Tenazinha C[5], Monteiro AM[5], Silva S[6], Martins FR[7], Silva L[8], Couto M[9], Faria M[10], Araújo F[11], Fontes T[12], Santos-Faria D[13], Tavares-Costa J[13]

## ABSTRACT

**Objective:** To compare the effectiveness and safety of original (Enbrel®) and biosimilar (Benepali®) etanercept in Biologic Disease-modifying Antirheumatic Drug (bDMARD)-naïve patients, measured by persistence rates over 36 months of follow-up.

**Methods:** A retrospective multicentre observational study using data collected prospectively from The Rheumatic Diseases Portuguese Registry (Reuma.pt) was performed, including patients with: age ≥ 18 years old; diagnosis of Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA) or Spondyloarthritis (SpA) (axial or peripheral) with active disease and biologic-naïve who initiated treatment with etanercept as the first line biological treatment after 2010. Kaplan-Meyer and Cox regression were used to calculate the persistence rate in treatment. Disease activity at baseline and follow-up data at 6, 12, 18 and 24 months of treatment were compared. Causes for discontinuing therapy were summarized using descriptive statistics. Statistical significance was assumed for 2-sided p-values <0.05.

**Results:** We included 1693 patients (413 on Benepali® and 1280 on Enbrel®): 864 diagnosed with RA, 335 with PsA and 494 with SpA. The 3-year persistence rates were not significantly different between both treatment groups in RA, PsA and SpA patients. In the adjusted Cox model, hazard ratios of discontinuation were not statistically different (p>0.05). The proportion of subjects in remission or low disease activity in each disease was similar in both groups. Overall, 535 (31.6%) patients discontinued etanercept (428 patients on Enbrel® and 107 patients on Benepali®). The major cause of discontinuation was inefficacy (57.8%). No differences for the occurrence of inefficacy or adverse effects were found between treatment groups.

**Conclusions:** Benepali® and Enbrel® demonstrated similar effectiveness and safety in RA, PsA and SpA in our cohort of patients. These data corroborate that the original and biosimilar drugs have similar quality characteristics and biological activity.

**Keywords:** Persistence rate; Drug survival; Etanercept; Biosimilar; Original; Effectiveness; Efficacy; Safety.

## BACKGROUND

Biologic agents are important therapeutic options in the management of patients with rheumatic diseases[1,2,3].

[1]Rheumatology Department, Unidade Local de Saúde da Guarda; Unidade Local de Saúde do Alto Minho; [2]Rheumatology Department, Hospital Garcia da Orta; [3]Rheumatology Department, Centro Hospitalar Universitário de São João; [4]Rheumatology Department, Centro Hospitalar Universitário de Coimbra; [5]Rheumatology Department, Centro Hospitalar Universitário de Lisboa-Norte; [6]Rheumatology Department, Centro Hospitalar Baixo Vouga; [7]Rheumatology Department, Centro Hospitalar Universitário do Algarve; [8]Rheumatology Department, Centro Hospitalar Trás-Os-Montes e Alto Douro; [9]Rheumatology Department, Centro Hospitalar Tondela-Viseu; [10]Rheumatology Department, Hospital Central do Funchal; [11]Rheumatology Department, Hospital de Sant'Ana; [12]Rheumatology Department, Hospital do Divino Espírito Santo; [13]Rheumatology Department, Unidade Local de Saúde do Alto Minho, Ponte de Lima.

**Submitted:** 15/08/2021
**Accepted:** 19/12/2021

**Correspondence to:** Ana Sofia Pinto
E-mail: anapinto1_2@hotmail.com

Etanercept is one of the most widely used biologic disease-modifying anti-rheumatic drugs (bDMARD), with approval in diverse indications, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA)[4,5].

In 2016 Benepali® became the first etanercept biosimilar to obtain marketing authorization in Europe. The similarity to the original product in terms of quality characteristics and biological activity is required by the European Medicines Agency[6] and the Food and Drug Administration[7] for biosimilar drug approval. Furthermore, it must demonstrate comparable safety and effectiveness[8,9,10].

Benepali® approval for indications other than RA was based on data extrapolated from a clinical trial involving RA patients[11]. Non-significant differences in efficacy and safety were noticed in clinical trials which are not expected to influence clinical performance.

Nonetheless, daily practice data should be collected to support the claim for biosimilarity. The ability to extrapolate license indications without data supporting the use of that product in certain indications may raise concerns. Ongoing surveillance by physicians in reporting adverse events (AE) and treatment outcomes is therefore essential[4,8,9].

Regarding this topic, some studies have been published using real-world data. *Cătălin Codreanu, et al*[9] showed that original and biosimilar etanercept are endowed with similar efficacy and safety after the first 6 months of treatment in RA patients based on a national registry, which brings further evidence for biosimilarity in unselected patients in a real-world setting. However, long-term data is missing for the majority of the diseases.

The persistence rate on treatment with biological therapy (probability of maintaining the treatment over time) provides an index of overall drug effectiveness and safety[12].

In our study, we compared the effectiveness and safety of the original (Enbrel®) and biosimilar (Benepali®) etanercept in bDMARD-naïve patients. This type of study with real-world data can improve confidence when choosing the best option for the patient.

Our primary aim was to compare the effectiveness and safety of original and biosimilar etanercept, in bDMARD-naïve patients, measured by persistence rate (PR) over 36 months of follow-up.

Our secondary aims were to compare disease activity and response rates in bDMARD-naïve patients treated with Enbrel® and Benepali® after 6,12,18 and 24 months of treatment; to investigate the frequency and reasons for treatment discontinuation in both therapeutic arms and to compare the rates of AE in patients treated with Enbrel® and Benepali®.

## METHODS

We performed a retrospective multicentre observational study, using data collected prospectively from Reuma.pt (www.reuma.pt), the Rheumatic Diseases Portuguese Registry. This database became active in 2008 and consists of a national registry of patients with rheumatic diseases, providing an excellent source of prospective real-world data.

Electronic clinical records were reviewed for all patients that fulfilled the study inclusion criteria. Real-world coded patient-level data from the Reuma.pt database was used.

Missing data from the platform was identified and when possible was filled in by each participating centre based on hospital clinical registries.

Patients were included if they fulfilled classification criteria for RA (American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR)'10), PsA (Classification Criteria for Psoriatic Arthritis (CASPAR criteria) or axSpA and pSpA (Assessment of Spondyloarthrtitis International Society (ASAS) classification criteria), were older than 18 years old and biologic-naïve having initiated treatment for an active disease with etanercept as the first line of biological treatment after the year of 2010. Patients not fulfilling the inclusion criteria or who did not have at least one evaluation after commencing etanercept were excluded from the study.

Baseline was set at the starting date of etanercept. Baseline data collected included demographic and clinical characteristics, date of diagnosis, comorbidities and concomitant medication.

Disease activity (tender joint count [TJC] 28, swollen joint count [SJC] 28, patients global/pain visual analogue scale [VAS], physician VAS, erythrocyte sedimentation rate [ESR] and C-reactive protein [CPR]) was registered for the three diseases, as appropriate. Additionally, for each disease, other outcome measures were evaluated: for RA, disease activity score-28 joints [DAS28] CPR 4 variables, Clinical disease activity index [CDAI], Simplified disease activity index [SDAI]) and function (Health assessment questionnaire [HAQ]), ACR response criteria (ACR20, 50 and 70); EULAR response; for PsA, Disease Activity in Psoriatic Arthritis (DAPSA), Psoriatic Arthritis Response Criteria (PsARC), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Physical Function (BASFI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) response; and for SpA patients, BASDAI, BASFI and ASDAS response were collected. Disease activity data were collected at baseline and follow-up (6,12, 18 and 24 months).

Discontinuation date and reasons for discontinuation were detailed. AE were categorized as infections, cancer, allergic reactions and hematologic alterations. Time to AE was defined as months from bDMARD initiation until the first AE occurrence. AE were described according to the available patient information.

## DEFINITIONS

Discontinuation was defined as either one of the following events: end of treatment recorded by the treating physician (regardless of the reason); switch to a different bDMARD; or continuous 90-day treatment gap without a subsequent bDMARD treatment. Temporary discontinuations, corresponding to a period <90 days, regardless of the cause and after which the patient restarted the same biological agent, were considered persistency of treatment.

Response to biologics was measured by composite disease activity/ response scores. Remission for RA was defined as a DAS28 <2.6, a CDAI ≤2.8 and a SDAI ≤3.3. Low disease activity included patients with a <2.6

DAS28 <3.2, 2.8< CDAI ≤10 and 3.3 < SDAI ≤11. Remission in PsA patients was defined as DAPSA ≤4 or ASDAS <1.3 and low disease activity as 4 < DAPSA ≤14 or 1.3 ≤ ASDAS < 2.1. In SpA patients, remission disease was defined as ASDAS <1.3 and low disease activity as 1.3 ≤ ASDAS < 2.1.

## STATISTICAL ANALYSIS

The data was analysed using SPSS version 26.0. Descriptive statistics of continuous variables were reported as mean (standard deviation) if normally distributed or as median and quartiles if non-normally distributed. Descriptive analysis of categorical variables was displayed as frequency or proportions. *P*-value was considered significant at <0.05.

Kaplan-Meyer was used to calculate 36-month PR in biologics since there was no available data for longer use of Benepali®. Univariate analysis with the independent variables (age, gender, disease duration in years, clinical characteristics, comorbidities and baseline disease activity) was performed. To obtain a predictor model of discontinuation we used a Cox model. All the variables considered clinically relevant and all the variables with *p*-value <0.20 from the univariate analysis were considered for the model and selected by stepwise selection method. For RA, we used only the variables resultant from the univariate analysis, for PsA we added gender, age and DAPSA at baseline and for SpA, the variables added were gender, age, tobacco consumption, BASDAI, BASFI and ASDAS at baseline. These variables were added regarding the potential association with more aggressive disease and treatment failure.

Disease activity at baseline and follow-up data at 6, 12, 18 and 24 months of treatment was compared using the chi-square test for categorical variables and t-student or Mann-Whitney tests for continuous variables. An analysis of missing values was added to this section, and these variables were tested to observe if the missing data were random.

Reasons for discontinuing therapy were summarized using descriptive statistics and stratified by the treatment. The safety analysis was performed by calculating the cumulative incidence of adverse events at the end of the follow-up period.

This study was conducted according to the Declaration of Helsinki and the International Guidelines for

**Table I. Demographic and clinical baseline characteristics**

| | Rheumatoid Arthritis | | Psoriatic Arthritis | | Spondyloarhritis | |
|---|---|---|---|---|---|---|
| | Enbrel® (n=645) | Benepali® (n=219) | Enbrel® (n=267) | Benepali® (n=68) | Enbrel® (n=368) | Benepali® (n=126) |
| Female, n (%) | 532 (82.5) | 168 (76.7) | 151 (56.6) | 34 (50.0) | 176 (47.8) | 58 (47.4) |
| Age (years), mean (SD) | 52.9 (12.5) | 55.0 (12.8) | 48.6 (11.6) | 50.0 (11.0) | 43.8 (12.4) | 45.0 (13.2) |
| Education (years), mean (SD) | 8.2 (4.5) | 8.5 (4.1) | 8.7 (4.2) | 9.3 (4.6) | 9.9 (3.9) | 10.5 (4.6) |
| Smoker, n (%) | 75 (14.5) | 38 (23.0) | 21 (10.4) | 6 (13.3) | 65 (24.8) | 20 (22.0) |
| Alcohol current consumer, n (%) | 27 (5.4) | 15 (9.1) | 27 (13.6) | 5 (11.4) | 20 (7.8) | 9 (10) |
| BMI (Kg/m$^2$), mean (SD) | 27.2 (6.8) | 25.0 (6.5) | 27.9 (4.9) | 27.4 (9.6) | 26,7 (4.5) | 26,1 (5.2) |
| Comorbidities, n (%)<br>Hypertension<br>Dyslipidaemia<br>Diabetes<br>CV disease | 113 (25.1)<br>15 (3.3)<br>42 (9.3)<br>31 (6.9) | 39 (26.9)<br>7 (4.8)<br>14 (9.7)<br>5 (3.4) | 44 (22.4)<br>8 (4.1)<br>16 (8.2)<br>4 (2.0) | 6 (14.3)<br>2 (4.8)<br>3 (7.1)<br>0 (0.0) | 42 (18.7)<br>6 (2.7)<br>13 (5.8)<br>11 (4.9) | 13 (18.8))<br>2 (2.9)<br>4 (5.8)<br>3 (4.3) |
| HLA B27 positivity, n (%) | - | - | 22 (20.8) | 0 (0.0) | 182 (72.8) | 56 (62.9) |
| RF positivity, n (%) | 386 (72.4) | 151 (77.8) | 11 (6.6) | 1 (2.4) | - | - |
| ACPA positivity, n (%) | 342 (69.9) | 144 (77.4) | 5 (3.8) | 0 (0.0) | - | - |
| Erosive disease, n (%) | 295 (57.2) | 104 (55.3) | - | - | - | - |
| Disease duration (years), median (IQR) | 7.9 (111.7) | 7.2 (10.7) | 7.8 (9.7) | 7.4 (8.8) | 9.3 (14.4) | 11.1 (15.0) |
| Treatment<br>csDMARDs, n (%)<br>NSAIDs, n (%)<br>Glucocorticoids, n (%) | 505 (78.7)<br>214 (33.3)<br>426 (66.4) | 186 (84.9)<br>51 (23.3)<br>152 (69.4) | 170 (63.7)<br>72 (27.0)<br>93 (34.8) | 51 (75.0)<br>13 (19.1)<br>27 (39.7) | 133 (36.3)<br>99 (27)<br>73 (19.9) | 40 (31.7)<br>25 (19.8)<br>15 (11.9) |

SD: Standard deviation; BMI: Body Mass Index; CV: Cardiovascular; HLA: Human Leucocyte Antigen; RF: Rheumatoid Factor; ACPA: Anti-Citrullinated Protein Antibodies; csDMARD: conventional synthetic Disease-Modifying Anti Rheumatic Drugs; NSAID: Non-Steroid Anti-Inflammatory Drug

Ethical Review of Epidemiological Studies. The study protocol was approved by the Coordinator and Scientific Board of Reuma.pt and by the Ethics Committee of the Unidade Local de Saúde do Alto Minho.

## RESULTS

We included 1693 patients who started etanercept as the first biologic medication, 864 with RA, 335 with PsA and 494 with SpA. Benepali® was initiated in 413 patients and 1280 were started on Enbrel®.

Demographic and clinical characteristics at baseline are listed in Table I and disease activity at baseline is described in Table II.

## DRUG RETENTION

The 36-month PR was not significantly different between both treatment groups in RA, PsA and SpA (Figure 1). In RA, PR in Benepali® was 72.6%, with a mean time-on-drug (TOD) of 28.3 months; for Enbrel® PR was 63.6%, with a mean TOD of 27.4 months ($p$=0.566). 369 patients with RA were in the original drug after 36 months and 18 patients persisted in biosimilar drug after 36 months. In PsA patients, the PR for Benepali® was 70.6%, with a mean TOD of 27.6 months, and in Enbrel® 67.0%, with a mean TOD of 28.1 months ($p$=0.743). 9 Patients maintained biosimilar treatment in PsA and 162 maintained original treatment after 36 months. In SpA patients, the PR were 78.4% for Benepali® (mean TOD of 27.4 months) and 71.5% for Enbrel® (mean TOD of 28.0 months ($p$=0.816)). 17 patients were on Benepali® after 36 months and 232 patients were on Enbrel®.

## REASONS FOR DRUG DISCONTINUATION

Overall, 535 (31.6%) patients stopped etanercept (428 patients on Enbrel® and 107 patients on Benepali®). Discontinuations due to inefficacy were the most frequent and there were no significant differences between both groups as for AE (Table III).

Due to economic reasons, some patients switched from original to biosimilar etanercept. The proportion of patients who switch to biosimilar was only significantly higher in the RA group ($p$=0.03). Other reasons included pregnancy, patient's option to discontinue the treatment, surgeries, remission, death or loss of follow-up.

## PREDICTORS OF DRUG DISCONTINUATION

A univariate analysis was performed with independent variables, all the variables with $p$-value <0.20 and other

**Table II. Disease activity at baseline**

| | Rheumatoid Arthritis | | Psoriatic Arthritis | | Spondyloarhritis | |
|---|---|---|---|---|---|---|
| | Enbrel® (n=645) | Benepali® (n=219) | Enbrel® (n=267) | Benepali® (n=68) | Enbrel® (n=368) | Benepali® (n=126) |
| CRP, median (IQR) | 1.0 (1.7) | 1.1 (1.8) | 0.9 (1.8) | 1.1 (2.8) | 0.9 (2.2) | 1.1 (1.8) |
| ESR, median (IQR) | 26.0 (32.5) | 31.5 (33.5) | 25.5 (26.8) | 40.5 (30.0) | 24.0 (32.0) | 28.0 (30.0) |
| SJC, median (IQR) | 6.0 (6.0) | 5.0 (4.5) | 4.0 (6.0) | 4.5 (8.5) | 0.0 (1.0) | 0.0 (1.0) |
| TJC, median (IQR) | 7.0 (9.0) | 6.0 (8.0) | 10.0 (13.2) | 4.5 (8.5) | 1.0 (6.0) | 1.0 (3.0) |
| Patient Global Assessment, median (IQR) or mean (SD) | 62.0 (±25.3) | 63.8 (±21.8) | 70.0 (41.3) | 70.0 (31.3) | 65.9 (±24.2) | 65.6 (±23.9) |
| Pain VAS, mean (SD) or median (IQR) | 60.3 (±25.4) | 62.6 (±23.5)) | 70.0 (30.0) | 70.0 (22.8) | 60.4 (±24.7) | 52.9 (±28.7) |
| DAS28, mean (SD) or median (IQR) | 4.8 (±1.2) | 4.6 (±1.1) | 4.6 (2.1) | 4.0 (1.1) | - | - |
| CDAI, median (IQR) | 25.0 (16.1) | 23.0 (15.6) | 20.0 (12.8) | 16.4 (8.3) | - | - |
| SDAI, mean (SD) or median (IQR) | 28.3 (±12.6) | 26.0 (±11.3) | 22.2 (14.7) | 18.6 (9.7) | - | - |
| HAQ, mean (SD) or median (IQR) | 1.3 (±0.6) | 1.3 (±0.7) | 1.3 (1.1) | 1.0 (0.84) | - | - |
| DAPSA, median (IQR) | - | - | 31.9 (21.2) | 26.6 (17.1) | - | - |
| ASDAS, median (IQR) | - | - | 3.7 (1.5) | 3.5 (1.3) | 3.6 (1.3) | 3.6 (1.0) |
| BASDAI, median (IQR) or mean(SD) | - | - | 6.6 (3.0) | 7.5 (2.2) | 6.2 (±2.0) | 5.7 (±2.1) |
| BASFI, median (IQR) or mean (SD) | - | - | 5.4 (4.7) | 6.8 (2.7) | 5.9 (±2.6) | 5.9 (±2.7) |

CRP: C-Reative Protein; IQR: Inter Quartile Range; ESR: Erythrocyte Sedimentation Rate; SJC: Swollen joint count; TJC: Tenderness joint count; SD: Standard deviation; VAS: Visual Analogue Scale; DAS: Disease Activity Score; CDAI: Clinical Disease Activity Index; SDAI: Simplified Disease Activity Index; HAQ: Health Assessment Questionnaire; DAPSA: Disease Activity in Psoriatic Arthritis; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index

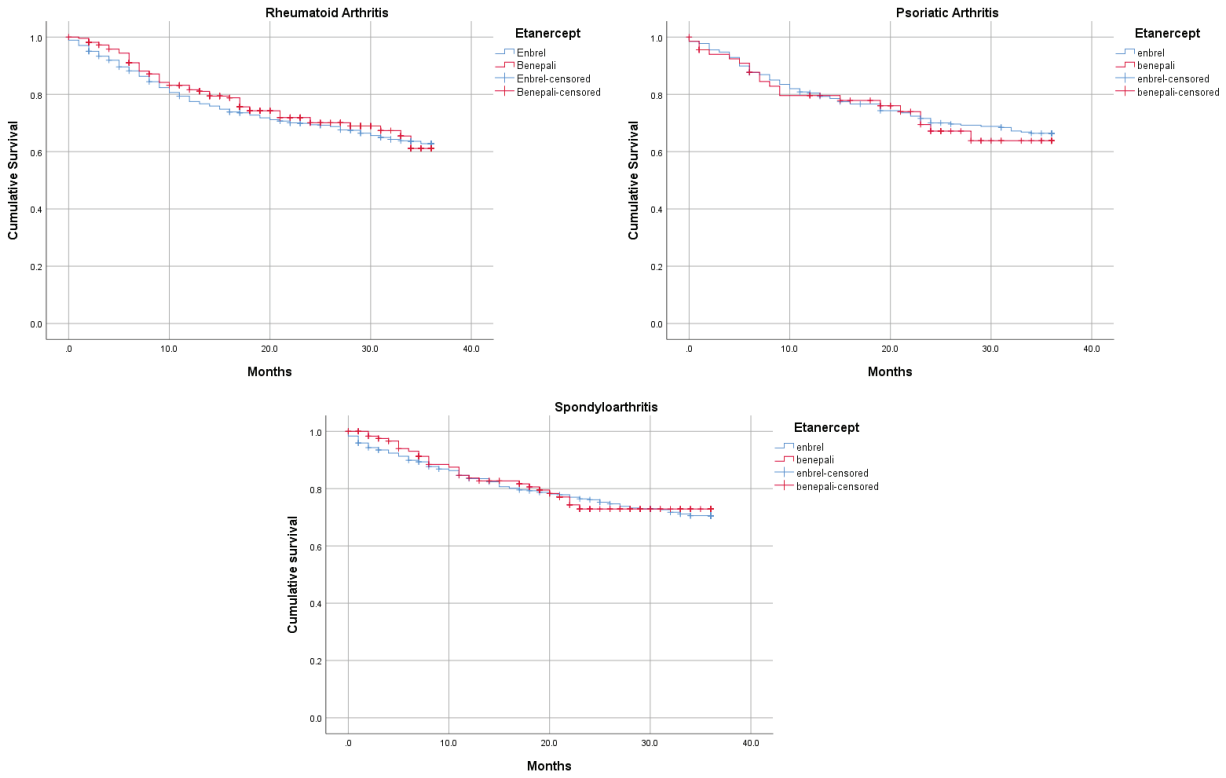


**Figure 1.** Drug survival with Benepali® and Enbrel® for the 3 diseases studied: Rheumatoid Arthritis, Psoriatic Arthritis and Spondyloarthritis

clinically relevant were included in the cox model. The proportional hazard analyses showed no statistically significant difference ($p$>0.05) in treatment retention when comparing the biosimilars with their respective originator products for the 3 diseases. There were no identified associations of clinical characteristics or disease activity scores and discontinuation for both drugs.

## ADVERSE EVENTS ANALYSIS

In Table III, we described the number of patients with AE per diagnostic group. The most common AE reported were infections, malignancies, heart failure, skin or systemic reaction and liver or hematologic toxicity. As the number of AE for each disease was small, the analysis was done for the drug regardless of the diagnosis. The cumulative risk of AE, adjusted for other comorbidities and clinical characteristics (alcohol or tobacco consumption), was higher with Enbrel® (Figure 2) however, without a statistical significance ($p$=0.643).

## RESPONSE TO TREATMENT

In this section, we had a higher rate of missing data, so all the variables are presented with a different denominator, indicating the number of patients with information available. We asked all centres to fill in the missing information however, some data was not available. The missing information is similar between both drugs and diseases. We confirmed that it was missing completely at random (p>0.05). In RA patients, we did not find differences between the two treatment groups for the proportion of patients in remission or low disease activity according to CDAI, SDAI or DAS28 at 6, 12, 18 and 24 months of treatment (Table IV). The ΔDAS after 24 months of treatment, the proportion of patients with a good EULAR response or ACR response >50% were not significantly different. In terms of function, there were no statistically significant differences for ΔHAQ among both groups. In PsA, no differences were found in the same timelines for DAPSA, DAS28, BASDAI, ASDAS or PsARC response (Table V). Also, in SpA patients (Table 6), no differences were found for BASDAI, BASFI, ASDAS, ASDAS response and BASDAI response in all the timelines with exception of BASDAI response at 18 months, which was achieved in fewer patients in biosimilar therapy (p=0.02), although this difference wasn't reproduced at 24 months.

## DISCUSSION

Our real-world data shows that original and biosimilar Etanercept are similar when comparing effectiveness

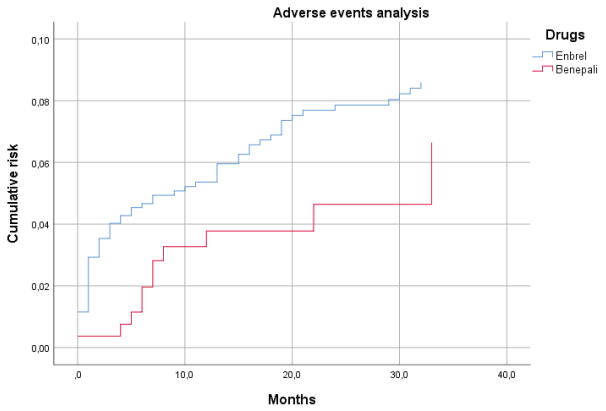


**Figure 2.** Adverse events cumulative risk during the follow-up for Enbrel® and Benepali®

(measured by persistence rates) and safety (comparable rates of adverse events) during the 36 months of follow-up in patients with RA, PsA and SpA. Other authors have published research with comparable outcomes for RA patients, during a shorter follow-up (6 months)[9,10,11,13,14]. A study from Lindström Ulf, *et al.* showed similar results for original and biosimilar infliximab and etanercept in 2334 bDMARD-naïve patients with SpA[15].

Drug retention (time to treatment discontinuation or change) was not significantly different between biosimilar and original etanercept. 44 patients (9 with PsA, 17 with SpA and 18 with RA) persisted in the biosimilar drug during 36 months. This number is small when compared to the number of patients that persisted in Enbrel® however, we have to mind that Benepali® is

**Table III. Reasons for discontinuation of both drugs, in the three diseases**

| | Rheumatoid Arthritis | | | Psoriatic Arthritis | | | Spondyloarthritis | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Reasons for discontinuation** | **Enbrel® (n=645)** | **Benepali® (n=219)** | **p-value** | **Enbrel® (n=267)** | **Benepali® (n=68)** | **p-value** | **Enbrel® (n=368)** | **Benepali® (n=126)** | **p-value** | **Total** |
| Inefficacy, n (%) | 129 (20.0) | 43 (19.6) | 0.91 | 51 (19.1) | 13 (19.1) | 1.00 | 53 (14.4) | 20 (16.0) | 0.66 | 309 (57.8) |
| Adverse events, n (%) | 59 (9.1) | 12 (5.5) | 0.09 | 11 (4.1) | 3 (4.4) | 1.00 | 19 (5.1) | 3 (2.4) | 0.20 | 107 (20) |
| Other reasons, n (%) | 34 (6.0) | 5 (1.8) | 0.07 | 22 (7.5) | 4 (4.4) | 0.52 | 21 (5.7) | 3 (2.4) | 0.14 | 89 (16.6) |
| Etanercept switch, n (%) | 13 (2.0) | 0 (0.0) | 0.03 | 4 (1.5) | 0 (0.0) | 0.59 | 12 (3.3) | 1 (0.8) | 0.20 | 30 (5.6) |
| Total, n | 235 | 60 | | 88 | 20 | | 105 | 27 | | 535 (100) |

**Table IV. Disease activity in Rheumatoid arthritis at 6, 12, 18 and 24 months**

| Rheumatoid Arthritis | Enbrel® N=572 | Benepali® N=198 | p | Enbrel® N=504 | Benepali® N=159 | p | Enbrel® N=462 | Benepali® N=110 | p | Enbrel® N=431 | Benepali® N=78 | p |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 6 Months | 6 Months | | 12 Months | 12 Months | | 18 Months | 18 Months | | 24 Months | 24 Months | |
| CDAI≤10, n (%) | 199/317 (62.8) | 69/124 (55.6) | 0.17 | 193/276 (69.9) | 72/101 (71.3) | 0.80 | 175/232 (75.4) | 40/53 (75.5) | 1.00 | 161/212 (75.9) | 28/40 (70.0) | 0.43 |
| DAS28 <3.2, n (%) | 219/343 (63.8) | 78/125 (62.4) | 0.77 | 200/285 (70.2) | 73/97 (75.3) | 0.34 | 187/250 (74.8) | 41/55 (74.5) | 0.97 | 165/217 (76.0) | 27/39 (69.2) | 0.37 |
| SDAI ≤11, n (%) | 192/307 (62.5) | 67/119 (56.3) | 0.24 | 181/258 (70.2) | 70/95 (73.7) | 0.52 | 167/220 (75.9) | 38/49 (77.6) | 0.81 | 151/203 (74.4) | 23/36 (63.9) | 0.19 |
| Δ HAQ, (±SD) | - 0.5 (0.6) | -0.4 (0.67) | 0.66 | - 0.5 (0.6) | -0.5 (0.6) | 0.86 | -0.5 (0.6) | - 0.4 (0.4) | 0.21 | - 0.5 (-0.5) | - 0.8 (0.7) | 0.42 |
| Δ DAS, (±SD) | - 2.0 (1.3) | - 1.8 (1.4) | 0.33 | - 2.1 (1.3) | -2.0 (-1.4) | 0.59 | -2.3 (1.3) | - 2.0 (1.4) | 0.33 | - 2.3 (1.4) | - 2.3 (1.1) | 0.44 |
| EULAR good responder, n (%) | 138/301 (45.8) | 40/105 (38.1) | 0.07 | 127/249 (51.0) | 37/77 (48.1) | 0.81 | 103/193 (53.3) | 19/38 (50.0) | 0.75 | 96/182 (52.7) | 16/31 (51.6) | 0.38 |
| ACR response >50%, n (%) | 91/146 (62.3) | 27/41 (65.9) | 0.28 | 80/120 (66.7) | 27/41 (65.9) | 0.92 | 79/116 (68.1) | 13/19 (68.4) | 0.98 | 60/86 (69.8) | 9/12 (75) | 0.72 |

ACR: American College of Rheumatology; CDAI: Clinical Disease Activity Index; DAS: Disease Activity Score; EULAR: European Alliance of Associations for Rheumatology; HAQ: Health Assessment Questionnaire; SDAI: Simplified Disease Activity Index

**Table V. Disease activity in Psoriatic arthritis at 6, 12, 18 and 24 months**

| Psoriatic Arthritis | Enbrel® N=240 | Benepali® N=58 | p | Enbrel® N=210 | Benepali® N=49 | p | Enbrel® N=195 | Benepali® N=43 | p | Enbrel® N=180 | Benepali® N=30 | p |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 6 Months | 6 Months | | 12 Months | 12 Months | | 18 Months | 18 Months | | 24 Months | 24 Months | |
| DAPSA ≤14, n (%) | 74/112 (66.1) | 25/34 (73.5) | 0.42 | 77/105 (73.3) | 17/24 (70.8) | 0.80 | 66/90 (73.3) | 15/21 (71.4) | 0.86 | 61/84 (72.6) | 10/14 (71.4) | 1.00 |
| DAS28 <3.2, n (%) | 82/113 (72.6) | 28/34 (82.4) | 0.25 | 78/99 (78.8) | 23/25 (92) | 0.16 | 77/91 (84.6) | 17/22 (77.3) | 0.52 | 66/82 (80.5) | 14/15 (93.3) | 0.46 |
| BASDAI <4, n (%) | 27/59 (45.8) | 11/19 (57.9) | 0.36 | 26/48 (54.2) | 5/14 (35.7) | 0.22 | 24/46 (52.2) | 7/12 (58.3) | 0.70 | 20/34 (58.8) | 4/8 (50) | 0.71 |
| ASDAS < 2.1, n (%) | 20/57 (35.1) | 10/19 (52.6) | 0.39 | 22/47 (46.8) | 4/14 (28.6) | 0.46 | 24/45 (53.3) | 5/12 (41.7) | 0.77 | 17/32 (53.1) | 3/7 (42.9) | 0.52 |
| PsARC response, n (%) | 72/100 (72.0) | 22/32 (68.8) | 0.73 | 62/82 (75.6) | 18/22 (81.8) | 0.54 | 65/80 (81.3) | 13/19 (68.4) | 0.23 | 46/61 (75.4) | 9/12 (75) | 0.98 |

ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; DAPSA: Disease Activity in Psoriatic Arthritis; DAS: Disease Activity Score; PsARC: Psoriatic Arthritis Response Criteria

**Table VI. Disease activity in Spondyloarthritis at 6, 12, 18 and 24 months**

| Spondyloarthritis | Enbrel® N=330 | Benepali® N=106 | p | Enbrel® N=210 | Benepali® N=49 | p | Enbrel® N=195 | Benepali® N=43 | p | Enbrel® N=180 | Benepali® N=30 | p |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 6 Months | 6 Months | | 12 Months | 12 Months | | 18 Months | 18 Months | | 24 Months | 24 Months | |
| BASDAI <4, n (%) | 115/172 (66.9) | 49/78 (62.8) | 0.53 | 115/170 (67.6) | 48/65 (73.8) | 0.36 | 115/153 (75.2) | 39/51 (76.5) | 0.85 | 102/145 (70.3) | 25/33 (75.8) | 0.54 |
| BASFI <4, n (%) | 92/137 (67.2) | 32/59 (54.2) | 0.09 | 85/138 (61.6) | 32/50 (64) | 0.76 | 86/125 (68.8) | 26/41 (63.4) | 0.52 | 85/126 (67.5) | 13/25 (52) | 0.14 |
| ASDAS < 2.1, n (%) | 92/150 (61.3) | 41/73 (56.2) | 0.41 | 91/153 (59.5) | 35/57 (61.4) | 0.85 | 84/139 (60.4) | 29/44 (65.9) | 0.73 | 76/124 (61.3) | 24/33 (72.7) | 0.36 |
| ASDAS Δ ≥1.1, n (%) | 87/130 (66.9) | 40/62 (64.5) | 0.74 | 105/134 (78.4) | 32/49 (65.3) | 0.07 | 86/115 (74.8) | 24/37 (64.9) | 0.24 | 79/99 (79.8) | 19/26 (73.1) | 0.46 |
| BASDAI Δ ≥2, n (%) | 97/149 (65.1 | 46/70 (65.7) | 0.93 | 106/146 (72.6 | 39/57 (68.4) | 0.55 | 101/131 (77.1 | 25/43 (58.1) | 0.02 | 92/116 (79.3) | 20/27 (74.1) | 0.55 |

ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index

only available since 2016, so many patients included in this study started the treatment more recently and they are still doing the treatment.

Concerning efficacy and disease activity, both groups showed comparable activity after 6, 12, 18 and 24 months of treatment. These results match the ones from previous studies[11,15]. Treatment changes due to inefficacy and AE occurred at equivalent rates between both groups. The AE reported in our study were similar to others described in the literature, with no unexpected adverse event reported[4,16]. Drug discontinuation due to adverse events and inefficacy were similar between biosimilar and original etanercept, but a difference was found in RA patients, a higher number of changes from original to biosimilar drug due to economic reasons in most participating centres.

To our knowledge, this is the first study comparing original and biosimilar Etanercept in the 3 diseases (RA, PsA and SpA) during a longer follow-up (36 months). These data provide further support to the claim of similarity between biosimilar and original etanercept and contribute to the totality-of-evidence of Benepali® as a safe and effective version of etanercept.

Although this study was conducted in a real-world cohort, some limitations can be pointed, such as the absence of randomization that can produce a selection

bias. As this work is a retrospective study with data collected prospectively, some information was missing. To minimize these potential biases, each centre was asked to fill in the missing information in Reuma.pt; the availability of other drugs in the first years when bDMARDs started to be commercialized was limited, the reason why we included patients who started etanercept after 2010, to reduce potential confounders. Another limitation was the fact that recently some patients switched for biosimilar due to economic reasons, counting for discontinuations. Some missing information about minor AE and few events were reported to examine specific AE by drug or disease. This study has also some strengths, as the higher number of patients with a longer follow up than other studies published before.

## CONCLUSION

Benepali® and Enbrel® showed similar effectiveness and safety during a follow-up of 36 months in RA, PsA and SpA in our cohort of patients. Disease activity was controlled similarly in both drugs in the three diseases studied. This study corroborated the general notion of biosimilarity between the original and biosimilar etanercept.

### REFERENCES

1. Gossec L, Baraliakos X, Kerschbaumer A, de Wit M, McInnes I, Dougados M, *et al*. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis. 2020 Jun;79(6):700-712.
2 Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis. 2020 Jun;79(6):685-699
3 van der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A, et al. Braun J. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017 Jun;76(6):978-991.
4 Chadwick L, Zhao S, Mysler E, Moots RJ. Review of Biosimilar Trials and Data on Etanercept in Rheumatoid Arthritis. Curr Rheumatol Rep. 2018 Nov 9;20(12):84
5 Deeks ED. GP2015: An Etanercept Biosimilar. BioDrugs. 2017 Dec;31(6):555-558
6 European Medicines Agency (2014) Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.
7 U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) C for BE and R (CBER). (2015) Scientific Considerations in Demonstrating Biosimilarity to a Reference Product Guidance for Industry.
8 Ebbers HC, Pieper B, Issa A, Addison J, Freudensprung U, Rezk MF. Real-World Evidence on Etanercept Biosimilar SB4 in Etanercept-Naïve or Switching Patients: A Systematic Review. Rheumatol Ther. 2019 Sep;6(3):317-338.
9 Codreanu C, Popescu CC, Mogoșan C, Enache L, Daia S, Ionescu R, *et al*. Efficacy and safety of original and biosimilar etanercept (SB4) in active rheumatoid arthritis - A comparison in a real-world national cohort. Biologicals. 2019 Nov;62:27-32. Norman P. Enbrel and etanercept biosimilars: a tale of two patent systems. Pharm Pat Anal. 2017;6:5–7.
10 .Emery P, Vencovský J, Sylwestrzak A, Leszczyński P, Porawska W, Baranauskaite A, *et al*. A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis. 2017 Jan;76(1):51-57.
11. Emery P, Vencovský J, Sylwestrzak A, Leszczyński P, Porawska W, Stasiuk B, et al. Long-term efficacy and safety in patients with rheumatoid arthritis continuing on SB4 or switching from reference etanercept to SB4. Ann Rheum Dis. 2017 Aug 9;76(12):1986–91.
12. Wolfe F. The epidemiology of drug treatment failure in rheumatoid arthritis. Baillieres Clin Rheumatol. 1995 Nov;9(4):619-32.
13. Moots RJ, Curiale C, Petersel D, Rolland C, Jones H, Mysler E. Efficacy and Safety Outcomes for Originator TNF Inhibitors and Biosimilars in Rheumatoid Arthritis and Psoriasis Trials: A Systematic Literature Review. BioDrugs. 2018 Jun;32(3):193-199
14. Emery P, Vencovský J, Sylwestrzak A, Leszczynski P, Porawska W, Baranauskaite A, et al. 52-week results of the phase 3 randomized study comparing SB4 with reference etanercept in patients with active rheumatoid arthritis. Rheumatology (Oxford). 2017 Dec 1;56(12):2093-2101.
15. Lindström U, Glintborg B, Di Giuseppe D, Nordström D, Aarrestad Provan S, Gudbjornsson B, *et al*. Treatment retention of infliximab and etanercept originators versus their corresponding biosimilars: Nordic collaborative observational study of 2334 biologics naïve patients with spondyloarthritis. RMD Open. 2019 Oct 23;5(2):e001079
16. Girolomoni G, Feldman SR, Emery P, Ghil J, Keum JW, Cheong SY, et al. Comparison of injection-site reactions between the etanercept biosimilar SB4 and the reference etanercept in patients with rheumatoid arthritis from a phase III study. Br J Dermatol 2018;178(3):e215–6.