# Non-medical switching from reference to biosimilar etanercept - no evidence for nocebo effect: a retrospective analysis of real-life data

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## Abstract

### Objective

*To evaluate the effectiveness and safety of non-medical switching from reference to biosimilar etanercept in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) or axial spondyloarthritis (axSpA) using different information strategies before switching.*

### Methods

*Data of adult patients with RA, PsA or axSpA who had received reference etanercept were retrospectively analysed. Whether or not patients were informed about the switch from reference to biosimilar etanercept was left to the discretion of the treating rheumatologist. Disease activity and function were regularly assessed in two consecutive visits (week 12 and 24). The scores documented at week 12 week after the switch were defined as primary outcome. Adverse drug events (ADE) were documented.*

### Results

*Data of 84 patients were available (44 RA, 25 axSpA and 15 PsA patients), of whom 24 had been informed about the planned switch (28.5%). The scores at week 12 of disease activity and function remained rather unchanged. Neither outcomes nor frequency of ADE were influenced by information strategy. The retention rate was high (96.4% at week 12, 87.6% at week 24). Seven patients were lost to follow-up, and six patients discontinued due to inefficacy or ADE. 18 ADEs were reported in 10 patients (12%). In 3 patients (3.6%) who had 5 ADEs in the first 12 weeks the reference etanercept was successfully readministered.*

### Conclusion

*Systematic switch from reference to biosimilar etanercept was not associated with changes in disease activity or function in. This was independent of information on the switch transmitted to the patients.*

**Key words**

switching, biosimilar, nocebo, inflammatory disease, anti-TNF

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## Introduction

The recent expiry of patents for several key biologic disease-modifying anti-rheumatic drugs (bDMARDs) including the TNF inhibitors infliximab, etanercept and adalimumab as well as the B-cell depleting agent rituximab has led to the approval of already many biosimilars produced by different companies.

The safety and efficacy of biosimilars has already been studied quite extensively, and there is good evidence that there is almost no difference in comparison to the performance of reference products in the treatment of the most frequent inflammatory rheumatic diseases rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) as well as other chronic inflammatory conditions such as psoriasis, ulcerative colitis and Crohn's disease (1-7). This includes starting and switching of biosimilars, even multiple switches have now been studied (1-4, 8, 9). International and national recommendations on the use of biosimilars have been published (10), and a major German National Authority, the Paul-Ehrlich Institute, has clearly stated that 'biosimilars can be used in the same way as reference products after equivalence has been proven and marketing authorisation has been granted' - 'this implies that they can be administered to both, patients who have not previously been treated with bDMARDs and those who previously have received the originator product' (11).

Thus, following approval by the European Medicines Agency (EMA) biosimilars can and have been used in Germany since 2015 in this way. However, many societies and groups have stressed that post-marketing data generation in real-life patient populations is needed to confirm long-term effectiveness and safety. Also for the etanercept-biosimilar SB4, although already been studied extensively, (1, 2, 12-15), it is crucial to confirm its performance (i) in real life settings and also (ii) in extrapolated indications such as AS, PsA and psoriasis. The EMA regulatory pathway does not require to perform studies to demonstrate the efficacy and safety of switching. Therefore, clinical trials addressing this important clinical issue of switching patients from the reference product to a biosimilars are important to assess and document the outcome of switches in clinical practice in order to confirm the comparability of biosimilars and reference products. Many studies have clearly shown that switching from reference product to the biosimilar did not influence safety and efficacy of the drug (2, 3, 16-18). However, some patients experience therapy failure, resulting in therapy discontinuation.

It has been hypothesised that non-objectifiable loss of response, low retention rates or manifestation of adverse drug events (ADEs) upon switching from reference bDMARDs to biosimilar products might be subject to the nocebo effect. This effect does not have a single consensus definition, but it may broadly be described as negative expectations that lead to negative consequences. Social observations, perceived dose, verbal suggestions of symptoms, and baseline symptom expectations are the strongest factors that may increase the risks of experiencing nocebo effects (19). It is well known that the act of informing patients about possible side effects of a treatment alone can significantly increase the numbers of patients who report ADEs and intensify worry and concern (20). An increased incidence of ADEs related to the nocebo effect has previously been reported for several medications (21-23). The nocebo response can also be created by subtler branding cues when patients are switched from a branded to a generic medicine or by limiting patients' choice of funded medications as it is the case in many health care systems to control costs (24, 25). Approximately 20–30% of patients, and a similar percentage of pharmacists and physicians, have negative views of generic drugs, seeing them as being less effective and having poorer quality than their branded equivalents (24).

However, as concluded in a recent meta-analysis on this topic, current evidence is insufficient to confirm a biosimilar nocebo effect, although higher discontinuation rates in infliximab biosimilar open-label studies support this theory (26, 27). Although the nocebo effect is a well-recognised phenomenon in pain studies, evidence is limited

in immune-mediated diseases primarily because it is difficult to quantify. Further studies are needed to evaluate the existence of a biosimilar nocebo effect. Availability of less costly biosimilar products has created a financial incentive for healthcare payers to force the treating physicians to switch without a medical need. By end of 2016, the local self-governing body of physicians in the region Westfalia in Germany directed a mandatory switch from reference biologics to a cheaper biosimilar, the so called "non-medical" switch (28). The recommendation was due to economic reasons and applied to all biosimilars and to all patients in which the physician thought that a switch can be performed without harming the patient. However, systematic substitution for biosimilar is not allowed in Germany according to the regulatory authority Paul-Ehrlich Institute (11, 29).

In this study we retrospectively evaluate the effectiveness and safety of systematic non-medical switching from reference etanercept (Enbrel®) to biosimilar etanercept (SB4 (Benepali®)) in adult patients with RA, PsA or axial spondyloarthritis (axSpA) in a real-life setting based on different information strategies before switching.

## Materials and methods

*Study design*

Restrospective chart review of patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) or axial spondyloarthritis (axSpA) in our tertiary centre for rheumatology.

*Study population*

All adult patients with RA, PsA or axSpA that have already initiated treatment with reference etanercept 50 mg/week and were switched to biosimilar etanercept between January 2017 and December 2017 were analysed. The indication for switching was made due to economic reasons. Patients who received etanercept 25 mg/week were not analysed because this formulation was not available as a biosimilar.

*Setting*

Patients were switched to biosimilar etanercept at the same dose and frequency as reference etanercept. Whether or not patients were informed about that switch was left to the discretion of the treating physician. Content, structure and intention of the information strategy was not prespecified. Patients were evaluated after switch in two consecutive visits at week 12 and 24.

*Clinical data*

The following data were extracted from the hospital electronic records: demographic data, diagnosis of patients, disease activity and physical function, laboratory parameter (rheumatoid factor, HLA-B27, C-reactive protein (CRP)) and current and past medication use.

Disease activity and function were regularly assessed, and any changes were recorded. Disease activity was assessed in RA and PsA patients using the 28-joint Disease Activity Score (DAS28) and in axSpA using the Bath Ankylosing Spondylitis (AS) Disease Activity Index (BASDAI) and the AS Disease Activity Score (ASDAS) (30-32).

Functional disability was assessed in RA and PsA patients by using the Funktionsfragebogen Hannover (FFbH) score, which strongly correlates with the Health Assessment Questionnaire (HAQ) (33). Values of FFbH were converted into HAQ values by the published formula: HAQ score = 3.16 – (0.028 × FFbH score). Physical function was assessed in axSpA patients by using the Bath AS functional index (BASFI) (34). Information about switch and reports about ADEs were extracted from the hospital database for each visit. Any change in disease status was assessed whether it was potentially related to the switch or not.

*Definition of outcome*

As main outcome of the study the disease activity and function at week 12 after switching was defined. Secondary outcomes included the retention rate of biosimilar etanercept and occurrence of ADEs.

The local ethics committee approved the study protocol (ref. no.: 2017-748-f-S).

*Statistics*

All data are expressed as mean values ± standard deviation (SD) or number and percentage (%) for continuous and categorical variables, accordingly. Categorical variables were compared between groups using chi-squared test while quantitative variables were compared using students t-test. Drug survival was estimated according to the Kaplan-Meier survival analysis and further analysed with log-rank statistics. All analyses were made using SPSS v. 26.0, and a $p$-value <0.05 was considered statistically significant.

## Results

In total, 84 patients were on maintenance therapy with reference etanercept 50 mg/week (Table I).

Patients with axSpA were younger compared with RA or PsA patients (both $p<0.001$). Patients with axSpA and PsA were less likely to receive chemic-synthetic DMARDs (csDMARDs) than RA patients (22/44 patients, 50% *vs.* 4/40 patients, 10%, $p=0.029$). Very few patients with axSpA (3/25, 12%) were receiving glucocorticoid treatment compared to RA (26/44, 59.1%) or PsA patients (6/15, 40%), $p<0.001$).

Treatment with reference etanercept prior to the switch was 3.3±2.3 years (range 0–0 years) for the total group, and that was not different between subgroups (RA 3.3±2.3 years, axSpA 3.1±2.3 years, PsA 3.4±2.3 years). None of the patients were on treatment with reference etanercept for less than 24 weeks. A total of 81 patients had a documented visit for week 12 and 71 patients for week 24. Baseline values of the different disease activity und physical function scores are provided in Table II. In patients with RA and PsA, disease activity remains stable during first 12 weeks but in patients with axSpA mean CRP level decreased from baseline to week 12. Function remains stable in all three disease groups. Concomitant medication did not change in the majority of patients. Change in csDMARDs occurred in 2 patients over a period of 24 weeks (increase of methotrexate dosage of 2.5 mg per week in week 12 in one patient, MTX discontinuation in parallel to change to abatacept in the second patient). Change of prednisolone occurred in 22 patients over a period of 24 weeks: 11 patients

**Table I.** Study population at baseline.

| | Global population (n=84) | RA (n=44) | PsA (n=15) | axSpA (n=25) |
|---|---|---|---|---|
| Age (y), mean (SD) | 52 (15) | 57 (14) | 55 (13) | 43 (13) |
| Gender (male), n (%) | 40 (47.6) | 19 (43.2) | 7 (46.7) | 14 (56.0) |
| Disease duration (y), mean (SD) | 8.88 (8.2) | 9.50 (7.276) | 9.20 (10.8) | 7.64 (8.1) |
| Glucocorticoid treatment n (%) | 35 (41.7) | 26 (59.1) | 6 (40,0) | 3 (12,0) |
| Prednisolone equivalent (mg), mean (SD) | 5.38 (3.6) | 5.24 (4.1) | 5.33 (1.1) | 6.7 (2.9) |
| csDMARDs n (%) | 26 (31) | 22 (50) | 2 (13.3) | 2 (8) |
| bDMARDs before etanercept, mean (SD) | 0.5 (0.8) | 0.3 (0.5) | 0.6 (0.9) | 0.8 (0.9) |
| Time on treatment (years) with reference etanercept, mean (SD) | 3.3 (2.3) | 3.3 (2.3) | 3.4 (2.3) | 3.1 (2.3) |

**Table II.** Changes of clinical and biological parameters assessing disease activity between baseline and the last visit.

| | Assessment | Baseline* (n=84) | Follow-up 12 weeks (n=81) | Follow-up 24 weeks (n=71) | *p*-value** |
|---|---|---|---|---|---|
| RA | DAS28 | 3.1 (1.4) | 2.8 (1.0) | 3.1 (1.3) | 0.74 |
| | HAQ | 1.2 (0.7) | 1.3 (0.7) | 1.3 (0.7) | 0.41 |
| | CRP (mg/dl) | 0.5 (0.6) | 0.6 (0.8) | 0.7 (0.9) | 0.46 |
| PsA | DAS28 | 2.8 (1.0) | 2.4 (1.1) | 2.8 (1.3) | 0.95 |
| | HAQ | 0.8 (0.5)) | 0.9 (0.9) | 0.9 (0.9) | 0.96 |
| | CRP (mg/dl) | 0.4 (0.5) | 0.6 (0.6) | 0.6 (0.5) | 0.19 |
| axSpA | BASDAI, 0-10 | 4.8 (2.5) | 5.0 (2.5) | 4.7 (2.4) | 0.70 |
| | ASDAS, 0-10 | 2.6 (1.3) | 2.7 (0.9) | 2.7 (0.8) | 0.53 |
| | CRP (mg/dl) | 0.6 (0.6) | 0.3 (0.5) | 0.4 (0.4) | 0.02 |
| | BASFI, 0-10 | 5.3 (2.7) | 5.5 (2.7) | 4.9 (2.8 | 0.41 |

Values are mean ± standard deviation. *Visit at which biosimilar etanercept was started.
**Comparison between values from 12-week post-switch and baseline (switch) visit.

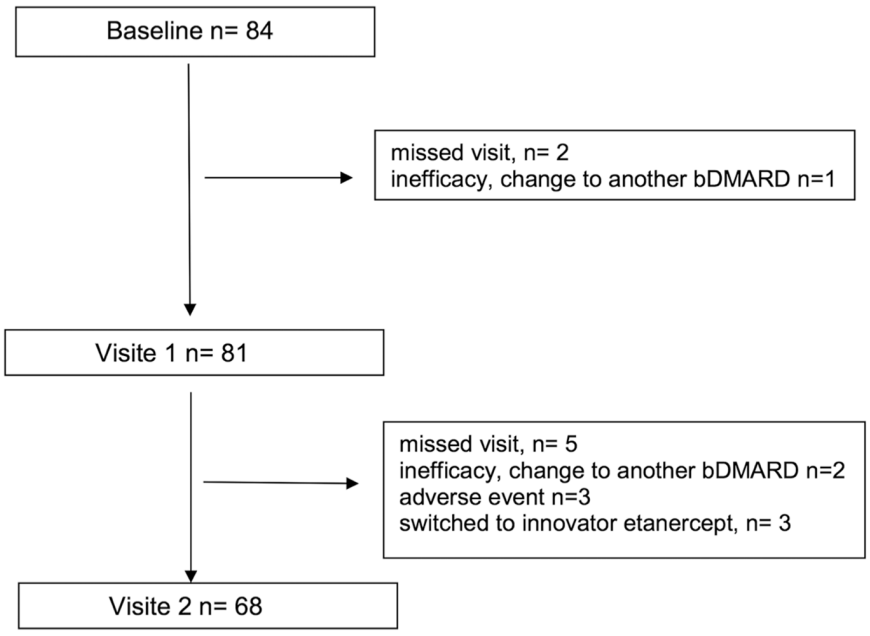


**Fig. 1.** Patient disposition.

were able to reduce the dosage, and the other 11 patients have to increase the dosage. Increase were small to moderate with a mean increase of 7.3±6.6 mg/d for less than than 12 weeks. Dose were increased in 4 of 11 patients in parallel with a change in cs- or bDMARD therapy (see details below for switch to abatacept and rituximab) or occurrence of ADEs (see details below for melanoma and erythema nodosum). The retention rate of the biosimilar was 96.4% (81/84 patients) at week 12 and 83.9% (68/81 patients) at week 24. While 7 patients were lost to follow-up (V1 n=2, V2 n=5), 1 patient discontinued the biosimilar due to inefficacy at week 12 and 8 patients discontinued the biosimilar at week 24 [inefficacy (n=5) or ADE (n=3)]. All three patients who experienced a loss of efficacy suffered from RA and were changed to abatacept, baricitinib or rituximab, respectively (Fig. 1).

Overall, 18 ADEs were reported in 10 patients (12%). In three patients (diagnosis of malignant melanoma (RA), presence of spondylodiscitis (axSpA), and generalised itching (PsA) biosimilar was permanently withdrawn due to the ADE. Because of presence of plantar fasciitis (one patient with PsA), presence of erythema nodosum (one patient with RA), and development of skin reactions in four patients (one patient with axSpA and PsA, respectively, and two patients with RA) skip of biosimilar injection (up to 4 weeks) was necessary. The reference etanercept was successfully re-administered in 3/84 patients (3.6%) in the first 24 weeks. No further ADEs were noted for patients back-switched to reference etanercept. Presence of nausea and partial loss of hair (two patients with RA) was potentially linked to concomitant medication with methotrexate and did not cause change in biosimilar medication.

A group of 24 patients (28.5%) had received information about switching from reference to biosimilar etanercept. Patients with information did not deviate from patients without information in respect to demographic (data not shown) and clinical characteristics (Table III, Fig. 2).

## Discussion

This is one of the first studies on a systematic switch from reference etanercept to SB4 biosimilar (Benepali®) in patients with RA, PsA or axSpA in a single tertiary centre. Our retrospective study confirmed the good retention rates of anti-TNF biosimilars recently

**Table III.** Comparison of outcomes between patients with and without information.

| | Patients with information (n=24) | Patients without information (n=60) | *p*-value |
|---|---|---|---|
| Change in disease activity, DAS-28 | 0.01 (1.18) | - 0.13 (0.80) | 0.55 |
| Change in disease activity, ASDAS | 0.30 (0.56) | - 0.23 (0.89) | 0.37 |
| Change in function, HAQ | - 0.04 (0.24) | 0.10 (0.18) | 0.55 |
| Change in function, BASFI | 0.80 (1.13) | 0.19 (1.30) | 0.41 |
| Retention of biosimilar, in weeks | 22.1 (4.1) | 21.8 (4.9) | 0.91 |
| Number of ADEs, n (%) | 5 (20.8) | 13 (21.6) | 0.8 |

Values are mean ± standard deviation if not indicated otherwise.

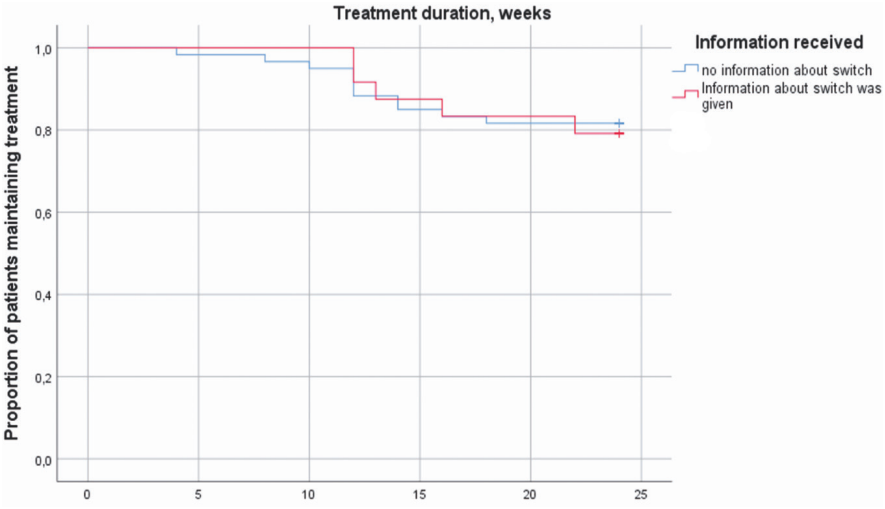


**Fig. 2.** Retention of biosimilar stratified for patients with and without information.

reported (35, 36). More importantly, our study did not show a difference in any outcome parameter within a follow-up period of 24 weeks related to the fact that patients were or were not informed about switching to a biosimilar. We conclude that informed patients did not have negative expectations toward the therapy change resulting in non-adherence to biosimilar. The lack of difference in major outcomes clearly argues against a major nocebo effect and encourages informing patients about the switch. In our opinions, the most important argument is that because of the production process of biopharmaceutical products different charges of reference drugs are also biosimilars, and thus, we have always used biosimilars in the last 20 years. In that regard, multiple changes in the production process had been announced to the authorities in this time period (37, 38).

Our population reflects the situation of patients in routine care and deviates from that in clinical trials while patients had received bDMARDs for a long time prior to switch and while patients suffered from RA, PsA and axSpA. Reports about retention rates vary between different disease, healthcare systems and countries and are reported to vary between 75 and 95% (39, 40). However, the retention rate must be discussed in the light of the switch acceptance rate which is influenced by the fact whether the patients had a choice to switch or whether it is a mandatory and cost-driven process without having the opportunity to deny the switch. Due to difference in local recommendations the uptake of biosimilar based on defined daily doses vary substantially between German counties and is the highest in our region (41). This causes the fact that in reality every single patient who received etanercept 50 mg/week had to be switched to SB4 and none of the patient receiving etanercept 25 mg/week were switched to SB4 because SB4 was not available in this dosage. Thus, in this retrospective chart review no control group could be implemented. The strength of our study is the fact that we report a large number of real-life patients who are treated based on recommendations of their treating physician. But this treating physician is subject to the treatment standard of the outpatient clinic including training via a standardised assessment and the transfer of information to patients. Thus, having data from one centre gives the opportunity to analyse the physician role from a monocentre perspective without introducing different settings which might deviate in their reporting styles. The main limitation of our study is the retrospective study design in which variations in documenting disease activity measures, treatment changes and/or ADEs might exist due to different reporting styles of different physicians. However, the billing system of the Association of Statutory Health Insurance Physicians required that patients can only be billed if scores for disease activity and function has been collected regularly. Thus, all physicians were trained on a standardised documentation system leading to low number of missing outcome scores. However, the ascertainment of ADEs is likely influenced by different reporting styles of different physicians in terms of number and severity of items to document. Due to the retrospective design, we were not able to analyse different mechanisms of the nocebo effect. Only drug features can be identified as one possible factor to induce a nocebo response. Physician, pharmacists and patient factors as well as influence of the health care setting cannot be identified in our setting and thus, reducing the complexity of the nocebo mechanisms (42). For our study, this means that the appearance of the package of the drug with a different branding alone may have given patients an indication of the switch, regardless of the information strategy applied by the treating physician and thus recognising the switch without being formally informed by the treating physician. Furthermore, in the absence of data we did not perform a formal sample size calculation. We defined a priori that a difference between informed and non-informed patients must exceed 20%

to become clinically meaningful (43). The difference we found was clearly less. However, we cannot exclude that significant differences could arise with much higher patient numbers included. Another limitation is the fact that patients' awareness and the role of the physician in the process of information cannot be analysed due to the retrospective design of the study. Nevertheless, in our study out of 36 patients who had been informed about the switch to the biosimilar only three patients had lost response to etanercept after switching, one had ADEs and two patients had missed a visit. A total of four patients were switched to another biologic. The reference product had to be switched back in 4 cases whereof 75% of the back switches were due to ADEs. Overall, there was no difference in major outcome nor in the number of switches due to ADE or inefficiency. Thus, we found no evidence for a major nocebo-effect in the study. Although many patients maintain treatment response after the switch, some patients experience therapy failure, which implies that we need to take a closer look at this patient population in clinical practice to learn about strategies to reduce a possible nocebo effect (44). Therefore, early identification by rheumatologists and allied health-care professionals of nocebo effects and their risk factors is important to increase awareness and strategies to prevent the nocebo effect.

## Conclusion

This study adds relevant information in addition to previously published RCTs since we could here focus on a population treated in daily care. As it was independent of the information given to the patients whether their medication was switched to a biosimilar, we conclude that we did not find major nocebo-effect in the study. Overall, more robust and well-designed non-medical switching studies are needed to evaluate the impact of the nocebo effect.

## Key messages

- Switching patients from reference to biosimilar product is known to be safe and effective;
- Loss of response or adverse drug events after switching might be subject to the nocebo effect;
- systematic switch was not associated with changes in disease activity or function irrespective of information given to the patient.

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