

# Observational study of inflammatory arthritis treatment by etanercept originator switched to an etanercept biosimilar

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## Abstract

**Objectives:** The aim of the study was to assess the safety and efficacy of switching an etanercept originator to an etanercept biosimilar in rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, and ankylosing spondylitis patients.

**Material and methods:** In 162 patients etanercept originator treatment had been replaced with the biosimilar (Group 1), and in six patients the biosimilar was initiated as the first biological agent (Group 2). The efficacy and safety of the treatment were monitored at 3–6 months.

**Results:** In the majority of patients in Group 1 ( $n = 138$ ) the etanercept biosimilar was well tolerated, whereas in 24 patients a switch back to the originator was required. The loss of efficacy was confirmed in nine patients using clinical scoring system, and nine patients reported subjective loss of efficacy; 13 patients reported adverse events, most often headache ( $n = 3$ ) and skin lesions ( $n = 3$ ). In four patients injection site reactions were present. The adverse events (AE) and/or the loss of the biosimilar efficacy were more commonly observed in women, patients with rheumatoid arthritis (especially in those who did not receive methotrexate), and in patients with a previous history of any other biological treatment. In patients in Group 2 the therapy was effective and no adverse events were observed.

**Conclusions:** The etanercept biosimilar seems to be effective and well-tolerated in the majority of patients. Nevertheless, in some cases, switching from the originator to the biosimilar was associated with AEs or loss of efficacy.

**Key words:** inflammatory arthritis, biologics switching etanercept, biosimilar.

## Introduction

Etanercept is a biological agent that inhibits proinflammatory cytokine – tumor necrosis factor (TNF). It is a human TNF receptor p75 Fc fusion protein produced by recombinant DNA technique using mammalian-based expression system: Chinese hamster ovary cells. Etanercept is indicated for the treatment of rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), axial spondyloarthritis (both ankylosing spondylitis – AS and

axial spondyloarthritis without radiological abnormalities), and plaque psoriasis [1]. At the time of this study, two etanercept products are available in Poland: the originator etanercept (ENB) and a biosimilar etanercept (SB4).

According to the European Medicines Agency (EMA) definition, a biosimilar is a medicine highly similar to another already marketed biological agent in terms of qualitative characteristics, biological activity, safety, and efficacy. In vitro studies of the biosimilar should verify its receptor binding potential and signal transduction at the target

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site of the originator. The second stage of drug evaluation involves *in vivo* studies in an animal model. The aim of clinical trials is to compare the pharmacokinetics, pharmacodynamics, efficacy, safety, and immunogenicity of both agents. If the novel compound was shown to be similar to the already marketed drug in one therapeutic indication, these data could be extrapolated to other indications without additional trials. However, some additional conditions need to be satisfied: the originator's mechanism of action, efficacy, and safety previously demonstrated should be the same regardless of the indication, and a post-marketing safety surveillance plan should be submitted by the biosimilar's manufacturer to the authorities [2].

The issue of replacing originators with their biosimilars has not been addressed in the EMA guidelines, leaving regulations in this area at the discretion of individual European Union member states [3]. The European Commission distinguishes between substitution, i.e. the practice of dispensing one medicine instead of an equivalent medicine at the pharmacy level without consulting the prescriber, and interchangeability, i.e. the practice of changing one medicine for another on the initiative or with the agreement of the prescriber. Moreover, the term switching exists, defined as the exchange of one medicine for another during treatment [4, 5]. In Poland, no separate regulations exist for biosimilar agents, and distribution of these drugs follows the same rules as in the case of the generic agents, which means that the originator and the biosimilar can be freely replaced with one another [5, 6].

The etanercept biosimilar, with clinical trial code SB4, was approved by the EMA on January 14, 2016 [7]. Registration studies involving healthy volunteers and patients with RA confirmed the similarity of the etanercept originator and SB4 in terms of their pharmacokinetic characteristics, tolerance, and safety profiles. Furthermore, SB4 was shown to be less immunogenic

than the originator [8, 9]. In this paper, we present our experiences with the replacement of the etanercept originator with its biosimilar in patients with rheumatic diseases (RA, PsA, and ankylosing spondylitis) who received TNF inhibitors (TNFi) within the framework of drug programs.

## Material and methods

The analysis included clinical data of patients treated with the etanercept biosimilar (50 mg weekly) within the framework of drug programs at the Biological Therapy Centre (BTC) of the National Institute of Geriatrics, Rheumatology and Rehabilitation in Warsaw (Poland). The study was conducted from November 2016 to May 2017. Because of the selection of the drug's provider based on the result of public bidding, permission from the Ethics Committee was not required.

Male and female patients fulfilling the following criteria were enrolled for treatment: RA meeting European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) classification criteria [10], AS diagnosed according to modified New York criteria with sacroiliitis in X-ray radiography [11], PsA meeting Classification for Psoriatic Arthritis (CASPAR) criteria [12] and high disease activity despite first-step treatment according to EULAR recommendations for RA [13], EULAR/ASAS (Assessment of Spondyloarthritis International Society) for AS [14], and EULAR/ASAS/GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) for PsA [14–16]. In this study patients already treated with etanercept originator were eligible for enrolment as well as biologic-naïve patients.

All 168 analyzed patients characterized in Table I were enrolled into the study. In 162 cases the etanercept originator was replaced with its biosimilar (Group 1) regardless of the disease activity and duration of the orig-

**Table I.** Patient characteristics

Characteristic	Group 1 (n = 162)	Group 2 (n = 6)
Female, n (%)	88 (54.3)	3 (50)
Age, mean ±SD	49.5 ±14.3	41.5 ±11.6
Diagnosis of inflammatory arthritis, n (%)		
Rheumatoid arthritis	65 (40.1)	3 (50)
concomitant methotrexate therapy	43 (66.2)	3 (50)
monotherapy	22 (33.8)	0
Ankylosing spondylitis	84 (51.9)	3 (50)
Psoriatic arthritis	13 (8)	0
Etanercept as a first biologic agent, n (%)	140 (86.4)	6 (100)
History of previous biologic therapy, n (%)	22 (13.6)	0

inator treatment. In six cases, due to high disease activity in biologic-naïve patients, the biosimilar etanercept was implemented as the first biological agent (Group 2). Efficacy and safety of the treatment were monitored for six months after biosimilar treatment was initiated. Patients who were switched back to the originator were observed until recovery. Control visits were scheduled monthly. The RA, AS, and PsA were scored with the Disease Activity Score (DAS28), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and Psoriatic Arthritis Response Criteria (PsARC), respectively [17–19].

The main focus of this study were reasons for biosimilar treatment discontinuation: loss of efficacy (LoE) or adverse events (AEs). Loss of efficacy was defined as aggravation in disease activity level or constantly high disease activity level measured with DAS28 for RA, upswing or constant BASDAI score > 4 for AS, and lack of response according to PsARC for PsA [17–19]. Subjective loss of efficacy (sLoE) was defined as aggravation of disease activity perceptible only by the patient without objective measurements. An adverse event was defined as a new health disorder that occurred during biosimilar treatment, confirmed by physical examination or medical history.

## Results

In the vast majority of patients in Group 1 ( $n = 138$ , 85.2%) the etanercept biosimilar was well tolerated, whereas in 24 (14.8%) switching back to the originator was required due to the occurrence of AEs or LoE (duration of the originator treatment 3–90 months, mean 46.5 months). In nine patients (37.5%), LoE was confirmed in a clinical scoring system specific to their primary condition. Six patients with RA showed an increase in DAS28 scores by 2.09–4.39 points (mean change 2.87, SD  $\pm 1.29$ ). In two individuals with AS, BASDAI scores increased by 0.9 and 6.0, respectively (mean change 3.45, SD  $\pm 3.61$ ). In one person with PsA, the activity of the disease remained at a high level. Another nine patients (37.5%) reported subjective LoE and worsening of general health condition (back pain, arthralgia in previously non-painful joints, malaise, anxiety, fatigue). Moreover, 13 patients (54.2%) reported AEs, most often headache ( $n = 3$ ) and skin lesions ( $n = 3$ , itchy rash, exacerbation of skin psoriasis, or flare of pustular psoriasis). Other less frequent AEs, such as fatigue, anxiety, lower limb edema, elevated blood glucose (> 400 mg/dl), increase in arterial blood pressure up to 195/90 mm Hg in a patient with previously well controlled arterial hypertension, abdominal pain, vomiting, diarrhea, night sweats, and metallic taste in the mouth, were observed in single patients. In four patients (16.7%) injection site reactions were present. In

five patients, AEs co-existed with the LoE (assessed by physician), and in another two with a subjective lack of improvement (Table II). 23/24 patients showed a therapeutic response and/or resolution of AEs after switching back to the originator. In one person, switching back to the originator due to the lack of treatment effect of the biosimilar was associated with AE in the form of a massive allergic skin reaction that required inpatient treatment in a dermatology unit. Eventually, this patient received another TNF inhibitor.

The AEs or LoE after switching from the etanercept originator to the biosimilar were more common in women than in men (75%, 18/24 vs. 50.7%, 70/138), and were more common in patients with RA than in other indications (50%, 12/24 vs. 38.4%, 53/138), among RA patients who did not receive methotrexate (MTX) (50%, 6/12 vs. 30.2%, 16/53), and in patients with a previous history of biological treatment with other agents (25%, 6/24 vs. 11.6%, 16/138).

In Group 2, for six patients who received etanercept biosimilar as the first biological agent, the therapy was effective, and no AEs were observed.

## Discussion

According to literature, the proportion of patients in whom etanercept therapy had to be discontinued after switching from the originator to the biosimilar investigated in the presented study varies considerably [20–26]. In this study, we focused solely on persons in whom the etanercept biosimilar was withdrawn due to the occurrence of AEs or LoE. The patients who discontinued the treatment due to other reasons, such as remission, pregnancy, or elective surgery, were not included in the analysis.

The registration study of SB4 included adult patients with moderate to high activity of RA, who were

**Table II.** Causes of discontinuation of biosimilar in Group 1

Characteristic	Value
All patients	24/162 (14.8)
Loss of efficacy	9/24 (37.5)*
Subjective lack of effect	9/24 (37.5)*
Adverse effects	13/24 (54.2)*
Headache	3/24 (12.5)
Skin lesions	3/24 (12.5)
Injection site reaction	4/24 (16.7)

\* Numbers do not sum to 100% – in 5 patients adverse effects co-existed with the lack of objectively assessed treatment effect, and in another 2 with a subjective lack of improvement.

**Table III.** Studies concerning the switch from etanercept originator to etanercept biosimilar

Authors	Emery et al. [20]	Glntborg et al. [21]	Hendricks et al. [22]	De Cock et al. [23]	Holroyd et al. [24]	Sigurdardottir et al. [25]	Tweehuysen et al. [26]	Felis-Giemza et al. (own study)
No. of patients switched from etanercept originator to etanercept biosimilar	119	1548	85	29	110	147	636	162
Rheumatoid arthritis	119 (100% concomitant MTX)	891 (60% concomitant MTX)	No data	29	58	76	No data	65 (66% concomitant MTX)
Psoriatic arthritis	0	335 (49% concomitant MTX)	No data	0	16	28	No data	13 (46% concomitant MTX)
Spondyloarthropathy	0	322 (15% concomitant MTX)	No data	0	15	25	No data	84 (0 concomitant MTX)
Other**	0	0	No data	0	4	18	No data	0
Discontinuation due to adverse effects or lack of efficacy	2 (2%)	101 (7%)	7 (8%)	4 (14%)	15 (14%)	12 (8%)	35 (6%)	24 (15%)*
Discontinuation due to lack of efficacy	No data	59 (4%)	No data	No data	14 (13%)	12 (8%)	19 (3%)	18 (11%)*
Discontinuation due to adverse effects	2 (2%)	42 (3%)	No data	No data	1 (1%)	0	15 (2%)	13 (8%)*

\* Numbers do not sum to 100% – in some patients adverse effects co-existed with the lack of objectively assessed treatment effect or subjective lack of improvement, \*\* unclassified arthritis, enteropathic arthritis, juvenile idiopathic arthritis; MTX – methotrexate.

treated with MTX at a minimal dose of 10 mg per week for at least six months before the randomization. Previous therapy with a biological agent was an exclusion criterion. The study patients were randomized into two groups, receiving SB4 or original drug for 52 weeks [9]. Then, patients from both groups were given SB4 up to week 100. Switching from the etanercept originator to the biosimilar compound was not associated with any clinically relevant events, such as an increase in AE rate, higher immunogenicity, or LoE. The therapy was discontinued in only 2% of the patients, in all cases due to AEs [20].

The Danish observational study included patients with various profiles of rheumatic diseases, who switched from etanercept originator to SB4. Among them were patients treated with etanercept in monotherapy and previously treated with biologics. This was the largest analyzed group so far ( $n = 1548$ ). The biosimilar compound was discontinued in 6.5% of the patients. In individuals with RA, the discontinuation of therapy turned out to be associated with the lack of concomitant

MTX treatment [21]. In another study, including a smaller group of Danish patients with an unknown profile of rheumatic diseases and MTX treatment, the etanercept biosimilar was withdrawn in 8% of the subjects. Six percent of patients who were switched back to the originator due to the lack of biosimilar's effect eventually achieved remission [22].

In a study conducted in the UK, including patients with RA, the described biosimilar was withdrawn in 14% of the cases; the authors did not provide any information about MTX status in their patients. Three percent of patients were switched back to the originator, but no information about the outcome was provided [23]. In another British study of patients with various rheumatic diseases, therapy with an etanercept biosimilar was discontinued in 9% of the cases, primarily due to LoE; patients were switched back to the originator or with an unknown effect [24].

In a Swedish study, 8% of patients discontinued the treatment with a biosimilar compound and were switched back to the originator, due to either objective

(3%) or subjective LoE (5%). None of those patients showed a therapeutic response after switching back to the originator, and all of them required a change to another biological agent [25].

The aim of a Dutch study including a group of patients with various rheumatic diseases was to analyze the impact of different communication strategies on the acceptance of a biosimilar agent. The comparative analysis included patients who had been switched from infliximab originator to a biosimilar infliximab (CT-P13) and from etanercept originator to an etanercept biosimilar (SB4). Patients treated with etanercept were provided with more comprehensive information about the planned switch than were those receiving infliximab. Treatment discontinuation rates after switching to etanercept biosimilar and infliximab biosimilar were 6% and 24%, respectively [26]. The authors of both studies mentioned above did not specify if any of their participants had a history of other biological therapies.

In all the studies mentioned above, etanercept biosimilar was discontinued in 8.4% of the patients on average (2–14%), more often due to the LoE (in 7% of the cases on average) than because of AEs (in 2% on average). Compared with other studies, the extension study of etanercept biosimilar as SB4 had the lowest treatment discontinuation rate [20]. However, it should be emphasized that unlike clinical trials conducted in selected groups of patients, observational studies may include individuals with highly variable clinical profiles that occur in real-life practice [27]. This refers in particular to patients who had been previously treated with other biological agents, did not receive MTX, presented with coexisting diseases, or received the drug due to indications other than those covered by the regulatory trial (Table III). Moreover, it should be remembered that the causes of biosimilar therapy discontinuation among patients participating in previous studies differed substantially, from solely the presence of AEs in one to solely the LoE in another two.

Some studies documented the role of a placebo effect in negative perception of biosimilar agents [28]. However, published data from independent centers suggest that switching to the etanercept biosimilar may be associated with the risk of AEs or LoE [21–26].

The emergence of biosimilar drugs is a natural consequence of the termination of patents on originator biologicals. Although biosimilars can be cheaper and thus accessible for more patients than the originators, the benefit-to-risk ratio is still a matter of debate. Furthermore, multiple switching due to non-medical causes cannot be excluded. In recent years EULAR and national experts, including Polish, have recommend the use of biosimilars in rheumatology [29, 30]. In 2017 Moorkens

et al. [31] presented an article about policies for biosimilar uptake across European countries, which is particularly interesting from the point of view of drug policy, legal aspects, and therapy costs.

The need for an evaluation of multiple switching between originators and biosimilars and the patient's role in decision-making are emphasized. Biosimilars are approved as safe and efficacious agents. No additional trials are required for their use in indications other than those covered by the regulatory trial [29].

The presented study has some limitations, such as: a relatively small number of patients in Group 2 and the fact that some patients in Group 1 who reported a sLoE did not confirm this the disease activity scores. The potential possibility for a placebo effect in Group 2 should also be considered. Contrarily, classification of some symptoms is very difficult – for example, malaise, fatigue, and anxiety could be AEs/sLoE; however, they could also be caused by an increase in disease activity. Furthermore, the disease activity at the moment of switching differed between patients, and the drug was switched regardless of the status of disease activity and duration of the originator treatment.

## Conclusions

In our study, the etanercept biosimilar (SB4) turned out to be effective and well-tolerated in most patients, although in some of them the switching was associated with AEs or LoE, which eventually resulted in treatment discontinuation. In most of these cases, switching back to the originator resulted in control of the disease and the same switching tolerance as before the therapy. There is still a need for further investigation of results of switching between bio-originators and biosimilars. Also, in the situation of increasing access to novel biosimilars, switching between them requires further clinical observation and research.

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*The authors declare no conflict of interest.*

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