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-naive 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-
in the mouth, were observed in single patients. In four
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 Dis-
ease 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 bio-
similar 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, up-
swing 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 biosim-
ilar 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 (dura-
tion 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 condi-
tion. Six patients with RA showed an increase in DAS28
scores by 2.09–4.39 points (mean change 2.87, SD ±1.29).
In two individuals with AS, BASDAI scores increased by
0.9 and 6.0, respectively (mean change 3.45, SD ±3.61).
In one person with PsA, the activity of the disease re-
mained 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 psori-
asis, 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 previ-
ously well controlled arterial hypertension, abdominal
pain, vomiting, diarrhea, night sweats, and metallic taste
in the mouth, were observed in single patients. In four
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Discussion

According to literature, the proportion of patients in
whom etanercept therapy had to be discontinued after
switching from the originator to the biosimilar investig-
ated 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 oc-
currence 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 pa-
tients 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.
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 mono-therapy 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

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

| Authors                        | Emery et al. [20] | Glintborg 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) |
|--------------------------------|-------------------|-----------------------|-----------------------|-------------------|-------------------|---------------------------|--------------------------|--------------------------------|
| Discontinuation due to adverse effects or lack of efficacy | 2 (2%)           | 101 (7%)             | 7 (8%)                | 4 (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.*

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(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 nocebo 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 biologics. 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 nocebo 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.

The authors declare no conflict of interest.

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