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## Acceptance Rate And Sociological Factors Involved In The Switch From Originator To Biosimilar Etanercept (SB4)

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## **Abstract**

**Objective:** To study acceptance rate and factors influencing acceptance of the switch from originator etanercept (Enbrel©) to biosimilar etanercept (SB4, Bénépali©) in patients with rheumatic disease.

**Methods:** Patients with a well-controlled rheumatic disease consulting in our rheumatology department were offered the switch for SB4. After oral and written information concerning biosimilar, free choice to accept the switch was left to the patients. The main outcome was primary switch acceptance rate defined by switch acceptance during the initial consult. Real switch adherence, socio-cultural factors and beliefs influencing switch acceptance rate were retrieved during a telephonic interview at distance from the consultation.

**Results:** Fifty-two patients were eligible for the switch: 32 (62%) with spondyloarthritis and 20 (38%) with rheumatoid arthritis. The primary acceptance rate was 92% (48/52). Patients refusing the switch were more likely to report a bad opinion on generic drugs (100% vs 11%,  $p < 0.001$ ). Other patient characteristics were roughly identical except for a statistical trend in the refusal group toward older age (61.4 vs 50.7 years,  $p = 0.08$ ) and longer disease duration (26 vs 12.1 years,  $p = 0.05$ ). Despite initial acceptance, two patients did not begin SB4 after receiving negative information by their regular pharmacist. Real SB4 switch rate was 85% (44/52) and 86% (38/44) of patients reported a good experience of the switch.

**Conclusions:** Acceptance rate of the switch from originator to biosimilar etanercept is high. Patient information, physician and pharmacist knowledge on biosimilars should be taken into account in order to improve their diffusion.

## **Introduction**

The economic burden of inflammatory rheumatic diseases is high and biologic treatments represent an important part of rheumatoid arthritis (RA) direct costs [1]. Biosimilar DMARDs (bsDMARDs) offer an opportunity to reduce these costs and to improve the access to biologics in developing countries [2]. The financial issues are substantial. In the UK, the savings following the launch of infliximab and etanercept biosimilars and the price discounts of bio-originators compared to price before launch of biosimilars have been estimated to £38.8 million (€45.9 million) over two years [3].

Regardless of the studies showing biosimilarity between bsDMARDs and their originator products with reassuring data on the switch [4], and despite the consensus-based recommendations recently issued by an international group [5], biosimilars market remains limited in most countries where both originator and biosimilar treatments are available [6]. Among the factors limiting the switch from originator to its biosimilar for a non-medical reason, patient acceptance is of primary importance, as previously demonstrated in rheumatology settings [7,8]. Incomplete acceptance linked to a negative perception of the biosimilar may lead to a re-switch to the originator, often because of subjective complaints without worsening of disease activity scores, highly suggestive of a nocebo effect of the biosimilar [9]. At this time, little is known about factors influencing the acceptance of bsDMARDs, such as socio-cultural parameters, the confusion with generic drugs or even the lack of knowledge among health professionals. A better understanding of these factors could help us to improve the information given to patients in order to maximize the switch acceptance rate, therefore generating important savings.

We conducted a real-life study in the rheumatology department of Bordeaux university hospital by systematically offering a switch from originator etanercept (OE; Enbrel®) to biosimilar SB4 (Benepali®). The main outcome was the primary switch acceptance rate. The secondary outcomes were to evaluate real switch adherence, socio-cultural factors and fears or beliefs influencing the acceptance rate.

## **Patients and methods**

### **Patients**

Patients consulting in the rheumatology department of Bordeaux University Hospital between 1<sup>st</sup> May and 31 October 2017 were screened to participate in the study. They were proposed to participate if: 1) they presented a RA or a spondyloarthritis (SpA) according to the 2010 ACR/EULAR criteria and the 2009 ASAS criteria, respectively [10,11]; 2) they were treated with OE, in monotherapy or in association with conventional synthetic DMARDs (csDMARDs), under stable etanercept treatment regimen for at least 6 months; and 3) their disease was controlled according to the physician opinion.

### **Intervention**

During a regular follow-up consultation, patients were given oral and written information on biosimilars (see translated document in supplementary material 1) and were proposed to switch for SB4 for non-medical reason. The information was provided by two rheumatology residents (MS & VG), who reached agreement before the beginning of the study to communicate homogenous information on: 1) the concept of biosimilars and the scientific evidence supporting their efficacy and their safety; 2) the physician's good opinion on biosimilars; 3) their lower price allowing savings for the health system; 4) the possibility to switch back to OE upon simple request in case of lack of efficacy or intolerance. Five to ten minutes of a thirty minutes consultation were devoted to provide information on biosimilar and to address the patient's questions. When oral consent was given, patients were switched to SB4 at the same regimen than previous OE, without any modification of associated csDMARDs or glucocorticoids.

After the initial consultation, a telephone interview was proposed to all patients, regardless of initial acceptance or refusal of the switch. All telephonic interviews were conducted by the same investigator (MS). The patients were asked a standardized set of open and closed questions concerning their socio-cultural background, their fears and beliefs, their adherence to treatments and other medical interventions (supplementary data 2). Patient experience about the switch was determined as well as the factors influencing their decision.

### **Outcome and follow-up**

The main outcome was to assess the primary switch acceptance rate, defined by the proportion of patients accepting to switch from OE to SB4 during the initial consultation. The secondary outcomes were to evaluate the socio-cultural determinants and fears or beliefs influencing the acceptance rate, as well as the real adherence to the switch determined by reported biosimilar use. After the consultation, patients were followed prospectively until December 31<sup>st</sup>, 2017.

### **Statistical analysis**

Quantitative variables, expressed as mean with standard deviation or median with range, were compared using a non-parametric Mann-Whitney analysis. Qualitative variables, expressed as proportions, were compared using Fisher's exact test. A p-value of less than 0.05 was considered as statistically significant.

### **Ethical statement**

The study conforms with French ethical recommendations. For this type of sociological study, French legislation requires neither informed consent of the participant, nor independent validation of this work by an independent ethics committee.

**Role of the funding source**

No external funding to report for this study.



## **Results**

### **Population characteristics**

Fifty-two patients were included in the study between 1<sup>st</sup> May and 31<sup>st</sup> October 2017. Mean age was  $51.7 \pm 14.4$  years and 23 (44%) were male. Twenty (38%) patients had RA and 32 (62%) had SpA including 24 axial spondyloarthritis, 4 psoriatic arthritis, 4 SAPHO syndromes and 2 reactive arthritis. Mean disease duration was  $13.1 \pm 11$  years. At inclusion, mean DAS28-VS was  $2.1 (\pm 0.6)$  and mean BASDAI was  $2.7 (\pm 1.8)$ . The patients were treated with OE for mean duration of  $4.5 \pm 3.3$  years, and OE was the first line of biological therapy in 40 (77%) patients. Half of the patients were followed exclusively in the hospital, the other half concomitantly with a private practice rheumatologist. Other patient, disease and treatment characteristics are detailed in table 1.

### **Patient reaction during the consultation**

All patient accepted to receive information about biosimilars. The main questions raised by patients regarded the drug similarity in term of efficacy and safety. Many patients asked about the experience of the switch with other patients and were reassured by the existing data provided by the NOR-SWITCH and DANBIO studies [12,13].

In the subgroup of patients refusing the switch ( $n = 4$ ), suspicious and defensive behavior was noted when the prospect of switching to a biosimilar was raised. These patients tended to have lower interest in biosimilar and to ask less questions on this subject (not objectively quantified).

### **Switch acceptance rate and outcomes**

The primary switch acceptance rate (defined by switch acceptance during the initial consultation) was 92% (48/52; figure 1).

After the consultation, 50 patients were successfully contacted and all agreed to participate in the survey. The telephone interview was not possible for two patients because of missing contact information. The telephonic survey occurred after a median of 16 weeks following the initial consultation (range 3-28 weeks).

Two patients did not begin SB4 despite their initial acceptance of the switch: for both patients, contradictory and negative information had been given by their regular pharmacist. One pharmacy continued to deliver OE although the medical prescription mentioned SB4.

After the switch, two patients developed a flare-up. One patient with RA reported increased arthralgia with moderate signs of disease activity assessed by musculoskeletal ultrasound (before switch DAS28-VS = 2.1; after switch DAS28-VS = 4.2), and was therefore switched back to OE. Two months after reswitching to OE, arthralgia and patient global assessment decreased to baseline but same level of objective signs of activity persisted (after OE resumption DAS28-VS = 3.0); OE was continued following the patient's wish. One patient with AS reported increased axial pain with a morning stiffness lasting two hour after the switch. The BASDAI index was largely unchanged (6.0 before switch and 6.2 after switch) without C-reactive protein or erythrocyte

sedimentation rate increase. In accordance to the patient wish, she was switched back to OE with good reported outcomes during a follow-up telephonic interview.

A third patient, treated with fluindione for cardiac arrhythmia requested to resume OE because of an asymptomatic increased INR above 4 which happened 10 weeks after the switch and that she attributed to SB4. Switching back to OE did not result in an improvement of the anticoagulant pharmacologic stability.

In total after the intervention, when considering missing data as failure to switch, 44 patients switched to SB4: 92% (44/48) of the patients with primary acceptance and 85% (44/52) of the total population (figure 1). At the end of the follow-up, 41 patients were still treated with SB4 representing 85% (41/48) of the patients with primary acceptance, and 79% (41/52) of the total population (Figure 1).

### **Factors influencing switch acceptance rate**

Patients primary refusing the switch were more likely to report a bad opinion on generics: 100% (4/4) in the group refusing the switch versus 11% (5/46,  $p = 0.001$ ; Fisher's exact test). Other beliefs including bad opinions about vaccines or pharmaceutical industry were not associated with switch acceptance (Table 2). Patients refusing the switch had a statistical tendency to be older (61.4 vs 50.7 years,  $p = 0.08$ ; non-parametric Mann-Whitney test), to have a longer disease duration (26 vs 12.1 years,  $p = 0.05$ ) and to be treated with OE for a longer time (7.1 vs 4.3 years,  $p = 0.24$ ). These patients also presented non-significant trend toward a lower influenza and pneumococcal vaccines adherence (25% (1/4) vs 75% (36/48),  $p = 0.07$ ), as well as a lower adherence to the mandatory dermatologist and dentist annual screenings (50% (2/4) vs 81% (39/48),  $p = 0.19$ ).

The major concerns reported in the group primarily refusing to switch were: fear to lose efficacy of an effective and well tolerated treatment (100%, 4/4), lack of confidence in SB4 biosimilarity (100%, 4/4), fear of an adverse event related to SB4 (75%, 3/4), the will to keep control of their treatment (75%, 3/4; figure 1). None reported a lack of confidence in the attending physician as a cause of refusal. All these patients claimed that during the initial consult, no other argument could have convinced them to accept the switch.

In the primary acceptance group, two subgroups of patients could be identified. A first subgroup including 70% (32/46) of patients, for which the physician good opinion on biosimilars and patient confidence in their physician were the major determinants of switch acceptance. Another subgroup including 30% (14/46) of patients, for which the bsDMARD lower price was the major determinant of switch acceptance.

### **Patient perception of the switch**

Concerning patient perception, 86% (38/44) reported a good experience of the switch.

Seven patients (15%) reported feeling pressured to accept the switch.

Three patients reported a positive effect of the switch on their pain index whereas four others reported a negative effect, two of them reswitching to OE with good outcomes.

## **Discussion**

In this study involving 52 patients with a well-controlled rheumatic disease and consulting in outpatient settings of a tertiary center, we reported a 92% primary acceptance rate of the switch from originator to biosimilar etanercept.

A 92% acceptance rate seems very high for a switch for a non-medical reason, but is close to previous studies investigating biosimilar infliximab switch (86 to 89%) [7,8]. Biosimilar acceptance rate is however higher than the one of generic drugs, including in patients with chronic diseases. For example, a work investigating generic anti-retroviral medications in French HIV patients reported an acceptance rate as low as 44% [14].

The higher acceptance rate reported in our study can be explained by several factors. First, the switch was proposed by physicians used to offering the switch and giving a positive information on biosimilars, which has been shown to increase acceptance [14]. Moreover, written information was systematically provided (supplementary material 1), which has been described to increase patient acceptance of generics drugs [14]. To note, both investigators in charge of recruiting patients and offering the switch were rheumatology residents, suggesting that senior or professorial physician status are not mandatory to reach high acceptance rate. Patients have an ambivalent view of medications: drugs symbolize the power of science and technique in their efficacy but also represent a potential toxic compound capable of inducing severe adverse effects

[15]. Because generics main object is costs limitation, they are apprehended only on the toxic side, explaining their negative perception [15]. Other common explanation of generics' negative perception are a belief of counterfeit drugs (poor quality due to lower cost), a mistrust of foreign manufacturer, and a global skepticism due for example of a history of adverse effect with generics [16]. Differences between generics and biosimilars were underlined by the investigators, thus decreasing the bad representation associated with generics. Although biosimilar follow the same cost-reduction logic than generics, the physician must emphasize that a lesser price does not translate into a lesser quality drug. Moreover, due to the frequent change in manufacturing processes of originator biologics, patients have been treated with equivalent of biosimilars for years. Educating patients on these points seem crucial to promote switch acceptance [17]. Finally, patients were informed of the possibility of a switch back to OE upon request if they considered that tolerance or efficacy was not deemed equivalent, probably improving the acceptance rate.

Health professionals' knowledge and acceptance of bsDMARDs are also crucial. During the initial consultation, information was delivered by a physician convinced of the importance of biosimilars as well as their good efficacy and safety. Physician's good opinion on biosimilar was the main reason of acceptance for 70% of patients, which is concordant with a Belgian survey involving patients with inflammatory rheumatic disease [18]. However, physician knowledge on biosimilars is sometimes scarce, thus limiting their use [18]. In two American surveys, only 40% of rheumatologists recognized that biosimilar matched efficacy and safety of the originator product. In the French BRIO study, only 64% of French rheumatologists felt capable of explaining the concept of biosimilar [19]. Finally, roughly 60% of French or American rheumatologists

don't consider to switch patients receiving originator biologics, suggesting mistrust or at least, cautiousness in their use [19,20].

In our study, two patients initially accepted the switch but later reported to have continued OE despite initial acceptance after receiving negative information regarding biosimilars from their regular pharmacist. In one case, the pharmacy continued to deliver OE although the prescription mentioned SB4 which is normally not allowed in France. The data suggest that providing physicians and pharmacists with a better knowledge of bsDMARDs might increase their acceptance, both in health care professionals and in patients, by allowing the delivery of adequate and positive information.

In patients refusing the switch, there was a statistical trend toward older age, longer disease duration and longer etanercept use, characteristics often found in case of generics refusal [21,22]. Patient-physician relationship is characterized by an implicit contract concerning treatment efficacy in their condition. In patient perception, the switch might be felt as the introduction of a new (different) drug, therefore introducing uncertainty in their treatment. Uncertainty takes a major toll on RA patient's daily burden [23], and the relevance of this assumption is supported by the fact that all patients refusing the switch reported that the fear of a loss of efficacy was one of the main reason for their choice. Moreover, the switch might also introduce uncertainty in patient-physician relationship with the idea that the prescriber is taking into account treatment costs over its efficacy and patient's own benefit. In fact, costs are often secondary when considering patient's decision to accept a drug [24]. Interestingly, prescribers are able to overcome these fears and doubts by providing positive and reassuring information: in our study, 70% patients reported that physician's good

opinion of the biosimilar was the main reason for their acceptance. Finally, although thorough information on biosimilar was given, all patients refusing biosimilar had a negative opinion of generics which is therefore an important prognostic factor of switch acceptance. These results suggest that providing patient with positive and reassuring information on biosimilars and underlining differences between generics and bsDMARDs are likely to increase patient acceptance.

After switching, 7% (3/43) of patients switched back to OE. Although long term maintenance rate was not the object of this study and in harmony with previously published data [7,8,13,25], a small proportion (between 5 to 15%) of patients discontinued the biosimilar in the months following the switch. After the switch, 3 patients reported a lower pain index whereas 4 reported increased pain, possibly linked to the natural process of rheumatic diseases with alternation of more and less painful periods, and once more suggesting that the nocebo effect or the incorrect causal attribution bias are at play. Almost 9 out of 10 patients reported a good switch experience irrespective of switch outcome, confirming that when properly exposed, the switch is not a traumatic event for the vast majority of patients. In the recently published Dutch BIO-SPAN study, patients with rheumatic disease accepting the switch from OE to SB4 (99% of patients accepted the switch) were followed prospectively to assess SB4 persistence rate [26]. Compared to an historical cohort of patients treated with OE, the authors found a statistically but not clinically significant lower persistence rate (90% vs 92%) and an increased incidence of subjective adverse events which are likely to be related to a nocebo effect. Interestingly, patients were randomized to receive questionnaires on expectations and beliefs in order to assess if those primed or prevented a nocebo effect, which they did not.



Biosimilar penetrance remains moderate in most developed countries where the switch has not been imposed by health authorities [6]. Yet, a 100% biosimilar market coverage is not necessarily the target to reach, which is for several reasons. First, pharmaceutical competition is one of the main driver of price reduction [27]. Secondly, a subset of refractory patient is likely to never accept the switch, irrelevant of any intervention reinforcing acceptance. Forcing the switch on these patients could be counterproductive, leading to the appearance of subjective complaints mandating a switch to another potentially still patented biologic. In France, health authorities have recently set a goal of 70% bsDMARDs use, a goal which appears to be reasonable and accessible.

This study should help to reach the target of at least 70% bsDMARDs use by highlighting the key factors improving their acceptance, specifically: improving health professionals' knowledge of bsDMARDs, delivering a thorough oral and written information on bsDMARDs to the patients, underlining the differences between biosimilars and generic drugs, and informing them of the possibility of a re-switch to the originator biologic if requested. Considering that the 2015 annual cost of Enbrel® was £408 million/year (€482 million) in the UK [28], and that the discount of the biosimilar is roughly 20%, achievement of 70% use of biosimilar etanercept would correspond to an annual cost saving of £81.6 million/year (€96.4 million).

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**Table 1: Patient, disease and treatment characteristics.**

| Characteristics at inclusion                          | Study Cohort (n = 52) |
|---|-----------------------|
| <b>Patient characteristics</b>                        |                       |
| Age, years, mean (S.D.)                               | 51.7 ( $\pm$ 14.4)    |
| Male Sex  | 44% (23/52)           |
| <b>Disease characteristics</b>                        |                       |
| Disease duration, years                               | 13.1 ( $\pm$ 11.0)    |
| Spondyloarthritis                                     | 62% (32/52)           |
| Axial spondyloarthritis                               | 69% (22/32)           |
| BASDAI, mean  | 2.7 ( $\pm$ 1.8)      |
| Psoriatic arthritis                                   | 12.5% (4/32)          |
| Reactive arthritis                                    | 6% (2/32)             |
| SAPHO   | 12.5% (4/32)          |
| Rheumatoid arthritis                                  | 38% (20/52)           |
| DAS28-VS  | 2.1 ( $\pm$ 0.6)      |
| <b>Treatment characteristics</b>                      |                       |
| Number of lines of biotherapy, median (range)         | 1 (1-3)               |
| Originator etanercept use, years, mean (S.D.)         | 4.5 ( $\pm$ 3.3)      |
| Associated csDMARD                                    | 54% (28/52)           |
| Shared follow-up (private practice & public hospital) | 50% (26/52)           |

**Table 2: Differences between acceptance and refusal cohort.**

| Characteristics at inclusion                  | Acceptance cohort<br>(n = 48) | Refusal cohort<br>(n = 4) | p-value |
|---|-------------------------------|---------------------------|---------|
| <b>Patient characteristics</b>                |                               |                           |         |
| Age, years, mean (S.D.)                       | 50.7 ( $\pm$ 14.3)            | 61.4 ( $\pm$ 10.3)        | 0.08    |
| Male Sex                                      | 44% (21/48)                   | 50% (2/4)                 | 1       |
| <b>Disease characteristics</b>                |                               |                           |         |
| Disease duration, years                       | 12.1 ( $\pm$ 1.4)             | 26 ( $\pm$ 9.1)           | 0.05    |
| Spondyloarthritis                             | 62.5%<br>(30/48)              | 50% (2/4)                 | 0.634   |
| Axial spondyloarthritis                       | 70% (21/30)                   | 50% (1/2)                 |         |
| BASDAI  | 2.83 ( $\pm$ 0.40)            | 2 (NA)                    | 0.55    |
| Psoriatic arthritis                           | 10% (3/30)                    | 50% (1/2)                 |         |
| Reactive arthritis                            | 7% (2/30)                     | 0%                        |         |
| SAPHO   | 13% (4/30)                    | 0%                        |         |
| Rheumatoid arthritis                          | 37.5%<br>(18/48)              | 50% (2/4)                 | 0.634   |
| DAS28-VS                                      | 2.13 ( $\pm$ 0.64)            | 1.91 ( $\pm$ 0.26)        | 0.44    |
| <b>Treatment characteristics</b>              |                               |                           |         |
| Number of lines of biotherapy, median (range) | 1 (1-3)                       | 1 (1-2)                   | 0.94    |
| Originator etanercept use, years, mean (S.D.) | 4.3 ( $\pm$ 3.0)              | 7.1 ( $\pm$ 5.1)          | 0.24    |
| Associated csDMARD                            | 54% (26/48)                   | 50% (2)                   | 1       |
| Alternate follow-up (liberal & hospital)      | 48% (23/48)                   | 75% (3)                   | 0.61    |
| <b>Observance</b>                             |                               |                           |         |
| Vaccines adherence                            | 75% (36/48)                   | 25% (1/4)                 | 0.07    |
| Dermatologist/dentist follow-up adherence     | 81% (39/48)                   | 50% (2/4)                 | 0.19    |
| <b>Beliefs</b>                                |                               |                           |         |
| Bad opinion about generics                    | 11% (5/46)                    | 100% (4/4)                | 0.001   |

|   |             |           |      |
|---|-------------|-----------|------|
| Bad opinion about pharmaceutical industry | 24% (11/46) | 50% (2/4) | 0.28 |
| Bad opinion about vaccines                | 24% (11/46) | 25% (1/4) | 1    |

