Effectiveness of SB4 transition from originator etanercept in rheumatoid arthritis and axial spondyloarthritis: A subgroup analysis from the BENEFIT study

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Objectives: The pan-European BENEFIT study of patients with stable rheumatoid arthritis (RA) or axial spondyloarthritis (axSpA) who transitioned from reference etanercept to SB4 found no clinically meaningful changes in disease control after transition. The analysis aims to illustrate the peculiarities of the Italian cohort of patients compared with the whole population to provide a more real-life approach to the data for the Italian rheumatologists, ruling out possible local confounding factors.

Methods: A prospective study for up to 6 months following transition was conducted. Outcome measures of interest include clinical characteristics at time of transition and disease activity scores (Disease Activity Score-28 [DAS28] for RA, Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] for axSpA) over time and safety.

Results: One-hundred and eleven subjects (out of the 557 in total enrolled in the study) were derived from 8 Italian sites, including 79 with RA and 32 with axSpA. In both cohorts, the efficacy was maintained at 3 months and 6 months from the transition to the biosimilar with no significant change in mean DAS28 and BASDAI scores: at the end of the 6 months of observation the mean DAS28 and BASDAI was similar to baseline (confidence interval [CI] -0.22, 0.22), while the mean variation of the BASDAI was -0.14. Of note, 100.0% (95% CI 89.1, 100.0) in the axSpA and 90.8% (95% CI 81.5, 95.5) in the RA cohort of patients continued to receive SB4 at month 6 (binary variable with 95% Clopper-Pearson CI).

Conclusions: Italian patients with stable RA or axSpA who transitioned from originator Etanercept to SB4 maintained clinical response at 6 months post-transition. Both the cohorts are representative of typical patients with long-standing established diagnoses. Most of the patients transitioned to the same dose regimen of biosimilar as that received for the originator, and the regimen remained unchanged at 6 months, supporting the effectiveness of the transition.

bioequivalence • biosimilars • efficacy • originator • safety • TNF-alfa

Abstract

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Keywords

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Background

In recent decades, the therapeutic approach to chronic inflammatory joint diseases has progressively changed and has switched from symptomatic therapy, aimed at improving quality of life, to drugs that can change the course of the disease and stop radiographic progression. The current
recommendations for the management of patients with chronic arthritis, taking into account the greater therapeutic possibilities available, aim to help the clinician personalize the therapy, based on both the disease characteristics and any comorbidities or needs of the patient.\textsuperscript{[1, 2]}

The introduction of biotechnological drugs in the 1990s has resulted in a real revolution for patients with chronic arthritis, particularly for cases that are nonresponsive or intolerant to conventional Disease Modifying Anti-Rheumatic Drugs (DMARDs), allowing a clear improvement in prognosis and a consistent reduction in mortality rates.\textsuperscript{[3]}

However, the high costs associated with the use of these innovative drugs have sometimes limited their use, also causing consequent problems of therapy adherence and persistence.\textsuperscript{[4]}

In this scenario, the arrival of biosimilars could represent a step toward overcoming certain prescribed limits, improving treatment standards and controlling costs.\textsuperscript{[5]} As is known, the approval of a biosimilar drug requires studies demonstrating its “comparability” with the reference biological drug (known as an originator) in terms of efficacy and safety; however, to date, there is still a lack of consistent data on the use of these drugs in real-life conditions which are more applicable in clinical practice.

The data from the registers and cohorts of these “real” patients constitute a source of valuable information for clinical practice, also in consideration of the possible concerns of doctors and patients with regard to their use in place of the originator.\textsuperscript{[6, 7]} The BENEFIT study was developed with the aim of evaluating the effects of switching from the originator to the biosimilar SB4 of etanercept, in a subgroup of Italian patients belonging to the broader pan-European cohort of the BENEFIT observational study in rheumatoid arthritis (RA) during the activity phase after inefficacy or intolerance of a conventional DMARD, and of axial spondyloarthritis (axSpA) not responsive to standard treatment. The present sub-analysis was performed to investigate the possible confounding factors that may limit the application of the observed data in the Italian scenario.

Materials and Methods

Starting from the BENEFIT multicenter observational study, patients with RA and axSpA belonging to 8 rheumatology sites in Italy enrolled between June 2017 and November 2018 were analyzed and data were compared with the entire study population. The BENEFIT study included patients over the age of 18 with a confirmed diagnosis of RA or axSpA, a disease activity deemed clinically stable in the 2 months prior to participation in the study, and who switched from originator etanercept to SB4 on the indication of their rheumatologist (subject to information being given to the patient and their agreement) after at least 6 months of therapy with originator etanercept at a stable dose (Table 2). Patients were also evaluated with at least 1 clinimetric datum during therapy with originator etanercept (e.g., Disease Activity Score-28 [DAS28] or Bath Ankylosing Spondylitis Disease Activity Index [BASDAI]). The exclusion criteria, on the other hand, included hypersensitivity to the active substance or to excipients of SB4, the existence of contraindications to the continuation of etanercept, the use of other biological or investigational drugs in the 6 months prior to the switch to the biosimilar or during the observation period, and finally the administration of therapies that could influence the disease activity in the previous 2 months.

Each patient signed an informed consent form approved by the ethics committee of each individual site for participation in the study and publication of all data; once the consent of each participant was obtained, the retrospective starting data regarding the 6 months prior to enrolment were collected anonymously. Subsequently, the same clinical, laboratory, and clinimetric data were recorded 3 months and 6 months after the switch to SB4 and entered in an electronic database, together with any adverse events signaled and reported by each patient at follow-up visits.

The primary objective of the study was to evaluate the progress of disease activity indices over time after switching to SB4; in particular, for patients with RA, the DAS28 value calculated by measuring C-reactive protein (CRP) was taken into consideration, or using other clinimetric indices if not available, while for axSpA activity was evaluated using BASDAI. After 3 months and 6 months, patients were then divided into 4 subgroups based on the degree of disease activity estimated with the clinimetric scores; in this way, patients in remission, and those with low, moderate, or high disease activity were differentiated (low [LDA], moderate [MDA], and high [HDA] disease activity respectively).

To evaluate the maintenance of efficacy after the change of therapy, only patients for whom data were available at the time of switching to the biosimilar and at subsequent checks at 3 months and 6 months were included in the analysis.

Statistical Analysis

The 2 cohorts of patients with RA and axSpA were analyzed separately. The results relating to the categorical variables were presented considering the number of patients, the frequency, the percentages, and a confidence interval (CI) of 95%, while for continuous ones, the number of patients, the averages, and a 95% CI were considered. Therapy persistence with SB4 at 3 months and 6 months was measured with Kaplan-Meier curves and the relative 95% CIs. In order to evaluate the course of disease activity, clinimetric indices
at time 0 were used (including the period between the previous 6 months and 1.5 months after starting SB4) at 3 (±1.5) months and 6 (±1.5) months. To further increase the sensitivity of the study, the data were analyzed using the mixed model for repeated measurements (MMRM).

Results

Of 557 patients included in the original BENEFIT study, 111 patients enrolled by the 8 Italian sites were considered in the present sub-analysis; of these, 79 were suffering from RA and 32 from axSpA. The demographic, clinical, and clinimetric characteristics of the patients enrolled at the time of the switch in therapy are summarized in Table 1. The patients were mostly women (79.7% with RA vs 28.1% with axSpA) and with a significantly higher average age in RA patients compared to those with axSpA (59.8 years vs 54.8 years); at the time of enrolment, the average duration of the disease was 14.2 years in the RA cohort and 11.1 years in the axSpA cohort. Based on baseline clinical indices, 69/79 (87.3%) patients with RA were classified as in disease remission, 7/79 (8.9%) with low disease activity, and 3/79 patients (3.8%) with moderate-severe disease activity; the average DAS28 CRP recorded was 1.74. Among patients with axSpA, however, those with moderate/severe disease activity numbered 4/32 (12.9%) and the average starting BASDAI was 1.75 (data not calculable for 1 patient).

Patients with RA had been taking etanercept for an average of 68.3 months in total, with an average duration of the last cycle of therapy before switching to a biosimilar of 49.7 months, and an average interval from the last dose of originator of 0.5 months. The majority of patients were in therapy with a dose of 50 mg/week (n = 75, 94.9%) and of these 98.6% (n = 69) had switched to the same weekly dosage of SB4. 59.3% of patients with RA and 40.6% of patients with axSpA took the drug in combination with conventional Disease Modifying Anti-Rheumatic Drugs (DMARDs), 27.8% and 6.3% with steroids, and 13.9% and 15.6% with NSAIDs respectively (Table 1). The cohort of patients with axSpA had an average duration of therapy with originator etanercept of 62.2 months at baseline, an interval from the last dose before switching to a biosimilar of 0.0 months, and an average duration of the last cycle of therapy with originator etanercept of 56.9 months. In this case as well, all enrolled patients (n = 32, 100%) were on therapy with 50 mg/week and 84.4% (n = 27) switched to the same dose of biosimilar SB4 (Figure 1). Furthermore, in half of the cases, patients took the drug alone (37.5%), or in combination with NSAIDs (15.6%) and csDMARDs (40.6%) conventional synthetic DMARDs (csDMARDs) (Table 1).

After 3 months of switching to the biosimilar, the mean variations from baseline were -0.01 (95% CI -0.20, 0.22) for DAS28 and -0.01 (-0.45, 0.43) for BASDAI (Figure 2). Six months after the switch the mean DAS28 was the same as the baseline (CI -0.22, 0.22), while the mean variation of the calculated BASDAI was -0.14 (-0.54, 0.25) (Figure 3).

Safety and Therapy Persistence

In the Italian cohort, no serious adverse events were recorded in the 2 study groups. An episode of uveitis is reported among the adverse events in the axSpA group. At the end of the 6-month observation period, 90.8% (CI 95%, 81.5%, 95.5%) of patients with RA persisted with the therapy, with 3 discontinuations due to non-serious adverse events (gastrointestinal intolerance and headache), and 4 due to loss of efficacy. Among patients with axial SpA, no patient discontinued therapy before completing the observation period and, as can be seen from the Kaplan-Meier curve in Figure 4, persistence in therapy in this population was 100% at 6 months.

Comparison of the Italian Subgroup with the BENEFIT Total Cohort

No significant differences were observed in terms of SB4 efficacy and safety following the switch from originator Etanercept. In particular, Figure 1 illustrates the individual average variations in disease activity indices from baseline.

Figure 1: Etanercept dosing regimens at the time of the transition to the biosimilar and after 6 months in the total population enrolled and in the Italian cohort. RA, rheumatoid arthritis; axSpA, axial spondyloarthritis.
Table 1: Characteristics of patients at baseline assessment.

|                         | Rheumatoid arthritis (n = 79) | Axial spondyloarthritis (n = 32) |
|-------------------------|-------------------------------|----------------------------------|
| Age, years, average (SD)| 59.8 (11.04)                  | 54.8 (13.16)                     |
| Women, no. (%)          | 63 (79.7)                     | 9 (28.1)                         |
| BMI, no.                |                               |                                  |
| Average (SD)            | 18                            | 6                                |
| Duration of disease, years | 14.2 (8.96)                  | 11.1 (6.66)                     |
| Median (IQR)            | 12.1 (7.6, 19.9)              | 9.6 (6.7, 13.5)                 |
| Smokers, no. (%)        |                               |                                  |
| Smoker                  | 10 (12.7)                     | 4 (12.5)                         |
| Ex-smoker               | 3 (3.8)                       | 4 (12.5)                         |
| Non-smoker              | 66 (83.5)                     | 24 (75.0)                        |
| Disease activity, no. (%)|                              |                                  |
| Remission               | 69 (87.3)                     | N/A                              |
| Low disease activity    | 7 (8.9)                       | 27 (87.1)                        |
| Active disease          | 3 (3.8)                       | 4 (12.9)                         |
| Concomitant therapies, no. (%) |                   |                                  |
| csDMARDs                | 47 (59.3)                     | 13 (40.6)                        |
| NSAIDs                  | 11 (13.9)                     | 5 (15.6)                         |
| Steroids                | 22 (27.8)                     | 2 (6.3)                          |

BMI, body mass index; csDMARD, conventional synthetic DMARDs; IQR, interquartile interval; NSAIDs, non-steroidal anti-inflammatory drugs; SD, standard deviation; remission = DAS-28 ≤2.8; low disease activity = DAS-28 ≤3.2 for RA = rheumatoid arthritis or BASDAI <4 for axSpA = axial spondyloarthritis; active disease = DAS-28 >3.2 or BASDAI ≥4 for axSpA.

Table 2: Disease activity indices at the time of switching to the biosimilar and after 6 months

|                         | Rheumatoid arthritis (n = 79) | Axial spondyloarthritis (n = 32) |
|-------------------------|-------------------------------|----------------------------------|
| Transition to SB4       |                               |                                  |
| • No.                   | 79                            | 31                               |
| • Average (CI 95%)      | 1.74 (1.59, 1.89)             | 1.75 (1.12, 2.37)               |
| After 6 months          |                               |                                  |
| • No.                   | 60                            | 23                               |
| • Average (CI 95%)      | 1.77 (1.61, 1.94)             | 1.45 (0.78, 2.13)               |

CI, confidence interval.

Discussion

The evolution of the treatment of chronic arthritis has allowed a gradual transition from symptomatic therapy to an increasingly personalized therapy aimed at achieving the optimal objectives of remission or low disease activity using the treat to target strategy.[1]

While new drugs known as “targeted synthetic DMARDs” are a welcome addition to the available therapeutic arsenal, biosimilar drugs have entered common use. Considering the high costs associated with biological drug treatment and with the most innovative “small molecules,” there may be situations where prescribing is limited. The advent of biosimilars makes treatment possible with quality and effective products at a lower cost and, at the same time, gives access to second-line therapies to more patients, eliminating any disparities in treatment.

As noted, for approval as a “biosimilar” by the European Medicine Agency (EMA), a drug undergoes a comparability test aimed at demonstrating similar efficacy and safety characteristics compared with the reference drug; based on evidence supporting this comparability, in 2018 the Italian Medicines Agency (AIFA) approved a document that confirms the interchangeability of biosimilars with respect to

Figure 2: Individual variations in the indices of disease activity recorded 3 and 6 months after switching to the biosimilar in the Italian cohort of patients from the BENEFIT study. CI, confidence interval.
originators, for both naive patients and those already being treated with the originator drug, supporting the switch to contain healthcare expenditure and the sustainability of the Servizio Sanitario Nazionale (SSN) (Italian National Healthcare Service).\[8\]

However, the need emerged to further confirm the bioequivalence of these drugs from their marketing with real-life data. In fact, the latter provide the clinician with the most solid tools to make therapeutic changes with greater safety and allow for at least a partial reduction of the possible “nocebo” effect that can in turn affect therapy adherence and persistence.\[9, 10\]

In our study, we evaluated the efficacy and safety of the etanercept biosimilar SB4, taking into consideration a cohort of Italian patients previously in good control with originator etanercept. The analysis is part of a more extensive European study including 557 real-life patients (BENEFIT study) in low disease activity or long-term remission.\[11\]

A recent systematic review conducted by Ebbers et al.\[12\] collected data on the use of SB4 showing excellent efficacy data both in naive patients and in populations of patients already treated with originators.

Our data confirm this encouraging evidence and demonstrate a maintenance of clinical response at 6 months in most patients after switching to the biosimilar, both in the RA and axSpA cohorts; in particular, the variations in the disease activity indices recorded at 3 months and 6 months of observation were not significant and the average DAS28 and BASDAI values at the end of the study were substantially comparable to the starting values. The percentages of patients in remission and low disease activity remained similar during the study and in almost all cases there were no disease exacerbations that justified the suspension of the drug; these outcomes are in line with those that emerged from recent real-life studies.\[13–15, 16\]

The dosage regimens also remained unchanged in the 2 populations: most patients in fact maintained the same dose of the drug over the following 6 months without the need for therapeutic adjustments or additions of other therapies.

The confirmation of the efficacy data was associated with excellent safety data, with only 1 significant adverse event of uveitis reported. Consequently, the therapy persistence at 6 months was satisfactory overall, with values above.
90% in the RA cohort and 100% in patients with axSpA, in line with what was previously observed in other real-life cohorts. [17]

This study has some limitations: the number of patients considered is in fact too small to reach statistically relevant conclusions. Furthermore, for some patients it was not possible to retrieve all the data at follow-up visits, in particular those relating to the clinimetric indices. However, the results are encouraging because they derive from a real population regularly monitored at the respective sites and not from selected cohorts of a clinical trial.

In conclusion, the switch from originator etanercept to biosimilar SB4 allowed the maintenance of good disease control in the 2 cohorts of patients with RA and axSpA. No reports of serious adverse events associated with the drug emerged in our patient population.

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