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Comparative Effectiveness and Persistence of SB4 and Reference Etanercept in Patients With Psoriatic Arthritis in Norway

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Objective. We aim to compare drug effectiveness and persistence between the reference etanercept (ETN) and ETN biosimilar SB4 in patients with psoriatic arthritis (PsA) naive to ETN and to investigate drug effectiveness and persistence in those undergoing a mandatory nonmedical switch from ETN to SB4.

Methods. We used a retrospective comparative database study including 1,138 patients with PsA treated with ETN or SB4 (years 1999–2021) in Norway. Disease activity score in 28 joints (DAS28) and drug persistence were compared between unmatched ETN (n = 644) and SB4 (n = 252) cohorts and in matched analyses (n = 144, both cohorts) at baseline using a propensity score (PS) to adjust for confounders. Drug persistence was analyzed with the Kaplan-Meier method.

Results. In unmatched analyses, difference in change from baseline between ETN (n = 140) and SB4 (n = 132) for DAS28 at one year was mean 0.67 (95% confidence interval [CI] 0.38–0.96) in favor of ETN. In PS-matched analyses, the difference in change from baseline between ETN (n = 54) and SB4 (n = 54) was mean 0.09 (95% CI −0.33 to 0.50), and the mean difference assessed with an analysis of covariance model was 0.01 (95% CI −0.38 to 0.40), both within predefined equivalence margin (±0.6). Drug persistence at one year was mean 0.75 (95% CI 0.71–0.78) for ETN, mean 0.58 (95% CI 0.51–0.63) for SB4, hazard ratio (HR) 2.45 (95% CI 2.02–2.97) in unmatched analysis, and mean 0.55 (95% CI 0.46–0.63) for ETN, mean 0.60 (95% CI 0.51–0.67) for SB4, HR 1.29 (95%CI 0.94–1.76) in PS-matched cohorts.

Conclusion. At one year, outcomes for PsA disease activity and drug persistence were comparable for patients treated with either ETN or SB4. In patients undergoing a mandatory nonmedical switch from ETN to SB4, drug effectiveness was maintained during a two-year period.

INTRODUCTION

Biologic originator etanercept (ETN), a tumor necrosis factor alpha inhibitor approved for use in Europe more than two decades ago, was one of the first biologic disease-modifying antirheumatic drugs (bDMARDs) available for treatment of psoriasis and psoriatic arthritis (PsA).[1,2] After expiry of the reference ETN patent in 2015, several biosimilars, including SB4, were developed. Randomized controlled trials (RCTs) demonstrated high comparability of SB4 to ETN in terms of structural and functional properties, pharmacokinetics, efficacy, and safety.[3,4] In 2016, SB4 was approved for treatment of rheumatoid arthritis (RA),[5] and its use for PsA was obtained as an extrapolation of RA indication. Due to the high cost-saving potential of biosimilars, many health care providers in Europe (eg, in Denmark and Norway), initiated the process of a mandatory nonmedical switch from reference to biosimilar bDMARDs and started therapy de novo with biosimilars. This approach raised an intense and ongoing debate on the interchangeability between originator and biosimilar bDMARDs use in routine clinical care.[6,7] It has been recently

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SIGNIFICANCE & INNOVATIONS

- Similarity has previously been demonstrated between SB4 and the reference etanercept (ETN) in biosimilarity exercises including phase III randomized controlled trials in patients with rheumatoid arthritis, and several real-world data articles have been published on SB4 in RA. No real-world data on SB4 in patients with psoriatic arthritis (PsA) is available so far.
- This is the first real-world study on SB4 in PsA to report comparable effectiveness, drug persistence, and safety for patients with PsA who started treatment with either ETN or SB4 for up to two years as a part of routine outpatient clinical care in Norway. In patients with PsA who underwent a mandatory nonmedical switch from ETN to SB4, drug effectiveness was maintained in the two-year period.
- Presented findings indicate that SB4 is an effective and safe treatment for patients with PsA, both for those who are switching from ETN and those who are starting therapy with SB4.

demonstrated that the mandatory nonmedical switch has led to a significant reduction of the average annual costs of treating patients with RA with bDMARDs in Norway,[8] and there is reason to believe that the same applies to PsA.

Real-world data focusing on SB4 in PsA is very limited.[9] To our knowledge, there is no published data specifically comparing the originator ETN and biosimilar ETN SB4 in terms of drug effectiveness and survival in the context of PsA. Thus, there is an emerging, unmet need for such analyses, as also addressed in the latest 2022 Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) guidelines.[10]

The main aim of this study was to compare drug effectiveness and drug persistence between the reference ETN and the ETN biosimilar SB4 in patients with PsA naive to ETN. Secondly, we aimed to investigate drug effectiveness and drug persistence in patients with PsA treated with SB4 after a mandatory nonmedical switch from ETN and thirdly to examine reasons for drug withdrawal among all three treatment subgroups: ETN, SB4, and SB4-switch. We used the framework of an equivalence study for our statistical hypothesis. In essence, the null and alternative (research) hypothesis in testing equivalence are simply those of a traditional comparative study reverse.[11] Therefore, the null hypothesis proposed that the effectiveness and persistence of ETN and SB4 were not equivalent. The alternative hypothesis proposed that ETN and SB4 were equivalent.

MATERIALS AND METHODS

Study design. A retrospective comparative database observational study including ETN-naive patients with PsA who were treated with ETN or SB4 and ETN-treated patients with PsA who were mandatory switched to SB4. To be included, all patients had to have at least one year follow-up. Patients with initial registration less than a year before closing the database were excluded (two patients in the SB4 subgroup identified and excluded). In the one-year period, patients could have stopped treatment.

Data extraction at the participating centers was performed between October 26, 2022, and March 28, 2023. The study was designed and conducted in accordance with the recommendations outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE),[12] the EULAR points to consider when analyzing and reporting comparative effectiveness research using observational data in rheumatology,[13] and Good Research for Comparative Effectiveness (GRACE) guidelines.[14]

Study population. The study population included patients with PsA naive to ETN who started treatment with either reference ETN or biosimilar ETN SB4 and patients with PsA who underwent mandatory nonmedical switch from ETN to SB4 between January 1999 and September 2021 at five centers in Norway. In Norway since 2007, a national tender system for bDMARDs has been implemented to reduce drug cost. Since SB4 became available in 2016, it has been less expensive than the reference ETN. As a consequence of the tender system, all patients treated with reference ETN underwent an obligatory nonmedical switch to SB4, and patients naive to ETN started on SB4. In the period before 2016, patients starting on ETN started on the reference ETN. In the present study, starting on ETN took place between January 1, 1999 and November 24, 2015, on biosimilar in SB4-naive subgroup between February 9, 2016 and September 11, 2021, and in SB4-switch subgroup between January 1, 2016 and January 8, 2020.

The participating centers included Haukeland University Hospital, Bergen; Vestre Viken Hospital, Drammen; Haugesund Hospital for Rheumatic Diseases, Haugesund; Sørlandet Hospital, Kristiansand; and University Hospital of North Norway, Tromsø. All patients were followed for up to two years. The study was approved by the regional ethical committee (REC; Regional etisk komite Midt-Norge, study reference number 2010/3078) and complied with the Declaration of Helsinki. Regional Committees for Medical and Health Research Ethics - REC Central (REK; Regionale komiteer for medisinsk og helsefaglig forskningsetikk) waived the need for informed consent from patients, because all data were anonymized and collected as part of routine clinical care. Patients were not involved in the design, conduct, reporting, or dissemination of this study.

Data collection and data variables. Data collection at participating centers was recorded at clinical visits as a part of routine practice with frequency defined by the treating doctor decision. Recommended outcome measures were collected and

followed using the GoTreatIt Rheuma software as part of standard clinical care.[15] All standardized Excel data files obtained from the participating centers were anonymized before they were sent for merging and analysis. Data variables included age, sex, body mass index (BMI), disease duration, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), 28 swollen and tender joint counts (SJC28 and TJC28); patient global assessment (PGA) reported on a 0 to 100 mm visual analog scale; modified health assessment questionnaire (mHAQ), and, among composite scores, disease activity score in 28 joint counts with ESR (DAS28-ESR). The dates of the first doses of ETN and/or SB4 were recorded, as well as previously used DMARDs, both conventional synthetic and bDMARDs, including their line number. Concomitant DMARDs, dates of onset and withdrawal, and main reasons for drug cessation were also collected. Demographic data and patient-reported outcomes (PROs) were self-registered by the patients. Standardized joint counts were performed by doctors or trained nurses and collected along with laboratory and treatment data.

Study objectives. The main objective of this study was to compare drug effectiveness and drug persistence between the reference ETN and SB4 after one year (at week 52) in patients with PsA naive to ETN. Secondary objectives were to investigate drug effectiveness and drug persistence after one-year and two-year follow-up (at week 52 and 104, respectively) in patients with PsA treated with SB4 after a mandatory nonmedical switch from ETN and to examine reasons for drug withdrawal among all three treatment subgroups: ETN, SB4, and SB4-switch.

Study endpoints. Primary outcome measures included DAS28-ESR (continuous variable), and drug persistence measured as time to treatment discontinuation, both assessed after one-year follow-up (at week 52). Primary (unmatched) and supportive (propensity score [PS]-matched) analyses were conducted including a sensitivity analysis of PS-matched samples using all available data. The equivalence of DAS28-ESR was determined based on a predefined equivalence margin of ±0.6.[16] Secondary outcome measures included DAS28-ESR (continuous variable) assessed after two-year follow-up (at week 104) as well as the following variables: CRP, ESR, SJC28, TJC, PGA, and mHAQ, all assessed after one-year and two-year follow-up (at week 52 and 104, respectively). Reasons for drug discontinuation were also recorded.

Statistical analysis. To compare baseline characteristics by treatment subgroup in unmatched analysis, independent samples *t*-test and chi-square tests were used. To compare baseline characteristics in matched data, paired samples *t*-test and McNemar's test were conducted for continuous and categorical variables, respectively.

For the primary (unmatched) analysis of DAS28-ESR outcomes between patients with PsA treated with ETN and patients with PsA treated with SB4, a conventional independent samples *t*-test was used (unmatched model). For the supportive (matched) analyses of DAS28-ESR, PS-matching was conducted and analyzed with a paired samples *t*-test. The rationale behind the choice of potential confounders included in the PS models was based on clinical knowledge, authors' previous experience in this type of analysis, and data availability.

The PS is the probability of assignment to one treatment conditional on a subject. Five logistic regression PS models (M1, M2, M3, M4, and M5) that matched for different sets of confounders at baseline were developed: M1 adjusted for age; M2 adjusted for age and sex; M3 adjusted for age, sex, and baseline DAS28-ESR; M4 adjusted for age, sex, baseline DAS28-ESR, and order of bDMARDs (ie, first, second or third or later order); and M5 adjusted for age, sex, baseline DAS28-ESR, order of bDMARDs, and mHAQ. Finally, M4 was consistent with clinical experience of group differences and possible confounders with acceptable model fit and available data and thus was found to be the most supportive model (main model). We matched one to one on the logit of the propensity score using calipers of width equal to 0.25 of the SD of the logit of the PS. A standardized difference (d) of 0.1 at baseline indicated a good match.

Drug persistence was analyzed with the Kaplan-Meier survival method, and estimates were calculated for one-year (week 52) and two-year (week 104) both in primary (unmatched) and supportive (PS-matched) analyses. We estimated hazard ratios from Cox regression with standard errors that allowed for intragroup correlation after PS matching. Secondary efficacy endpoints were analyzed based on the same approach as for DAS28-ESR and PS models matched for different sets of confounders at baseline. In addition, we used an analysis of covariance model with DAS28-ESR at one year as the dependent variable and group and DAS28-ESR at baseline as the independent variable with matched pairs as random intercepts in a linear mixed model. No imputation of missing data was performed. Statistical analyses were performed using Stata Statistical Software version 18 (StataCorp LLC) with the user-written package psmatch2 for PS matching[17] and SAS Studio (SAS Institute). $P < 0.05$ was considered significant. A statistical plan of the performed analyses had been prepared in advance of this study.

RESULTS

Baseline characteristics. Baseline clinical data are displayed in Table 1. A total of 1,138 patients with PsA were included in the analysis: 644 in the ETN cohort, 252 in the SB4 cohort, and 242 in the SB4-switch cohort. In unmatched analysis, the

Table 1. Baseline clinical data for unmatched (observed) and propensity (PS)-matched Etanercept (ETN)-naive psoriatic arthritis (PsA) patients treated with ETN or SB4 and in PsA patients switched from ETN to SB4*

	Unmatched					PS-matched			
Clinical data	ETN (n = 644)	SB4 (n = 252)	*P* value	d	SB4-switch (n = 242)	ETN (n = 144)	SB4 (n = 144)	*P* value	d
Age, y	59.8 ± 11.8	55.0 ± 13.4	<0.001	0.38	60.7 ± 11.7	57.6 ± 12.1	57.0 ± 11.9	0.672	0.05
Male, n (%)	343 (53.3)	123 (48.8)	0.230	0.09	138 (57.0)	69 (47.9)	69 (47.9)	1.000	0.00
BMI[a]	30.8 ± 21.2	28.7 ± 11.6	0.198	0.13	29.0 ± 13.3	27.9 ± 13.5	30.1 ± 16.7	0.337	−0.15
Disease duration, y	8.6 ± 9.1	7.8 ± 8.3	0.090	0.21	16.8 ± 10.2	7.5 ± 7.8	8.3 ± 8.3	0.393	−0.10
CRP, mg/L[b]	16.3 ± 30.5	7.4 ± 10.7	<0.001	0.39	4.9 ± 9.6	10.6 ± 14.6	8.2 ± 11.9	0.132	0.18
ESR, mm/hr[c]	23.5 ± 22.0	14.3 ± 13.8	<0.001	0.50	12.5 ± 12.4	17.6 ± 14.4	16.5 ± 14.9	0.475	0.08
SJC28 (range 0–28)[d]	3.0 ± 3.5	1.5 ± 2.1	<0.001	0.51	0.5 ± 1.3	2.1 ± 3.1	1.8 ± 2.3	0.198	0.12
TJC28 (range 0–28)[e]	5.3 ± 5.3	3.1 ± 4.0	<0.001	0.47	1.6 ± 3.0	3.3 ± 3.3	3.6 ± 4.2	0.473	−0.07
PGA (range 0–100mm)[f]	58.0 ± 21.9	52.5 ± 23.9	0.008	0.24	33.7 ± 27.2	55.1 ± 21.6	54.0 ± 25.0	0.653	0.05
DAS28-ESR[g]	4.2 ± 1.3	3.3 ± 1.3	<0.001	0.70	2.5 ± 1.2	3.6 ± 1.2	3.5 ± 1.3	0.199	0.11
mHAQ (range 0–3)[h]	0.7 ± 0.4	0.6 ± 0.4	0.116	0.15	0.4 ± 0.4	0.6 ± 0.4	0.6 ± 0.4	0.821	−0.03
Current MTX, n (%)	283 (43.9)	110 (43.7)	0.937	0.01	122 (50.4)	62 (43.1)	64 (44.4)	0.816	0.03
Current csDMARDs, n (%)	315 (48.9)	140 (55.6)	0.074	0.13	135 (55.8)	74 (51.4)	85 (59.0)	0.179	0.15
Order of bDMARDs, n (%)	–	–	<0.001	0.80	–	–	–	0.482	0.15
1	532 (82.6)	120 (47.6)	–	–	0 (0)	91 (63.2)	82 (57.0)	–	–
2	88 (13.7)	90 (35.7)	–	–	182 (75.2)	39 (27.1)	49 (34.0)	–	–
≥3	24 (3.7)	42 (16.7)	–	–	60 (24.8)	14 (9.7)	13 (9.0)	–	–
Center, n (%)	–	–	<0.001	0.52	–	–	–	<0.001	0.81
Haukeland University Hospital	158 (24.5)	73 (30.2)	–	–	21 (8.3)	28 (19.4)	10 (6.9)	–	–
Vestre Viken Hospital	106 (16.5)	37 (15.3)	–	–	71 (28.2)	10 (6.9)	48 (33.3)	–	–
Haugesund Hospital for Rheumatic Diseases	136 (21.1)	53 (21.9)	–	–	49 (19.4)	36 (25.0)	31 (21.5)	–	–
Sørlandet Hospital	108 (16.8)	31 (12.8)	–	–	36 (14.3)	44 (30.6)	23 (16.0)	–	–
University Hospital of North Norway	136 (21.1)	48 (19.8)	–	–	75 (29.8)	26 (18.1)	32 (22.2)	–	–

* Values are the mean ± SD unless indicated otherwise. For the PS-matched population, the logistic regression model used for the PS matching adjusted for age, sex, DAS28-ESR, and order of bDMARDs. A d of 0.1 indicates a good match. bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; csDMARDs, conventional synthetic DMARDs; CRP, C-reactive protein; d, standardized difference; DAS28-ESR, disease activity score in 28 joints with erythrocyte sedimentation rate; ESR, erythrocyte sedimentation rate; ETN, etanercept; mHAQ, modified Health Assessment Questionnaire; MTX, methotrexate; PGA, patient global assessment; PS, propensity score; PsA, psoriatic arthritis; SB4, ETN biosimilar; SJC28, 28 swollen joint count; TJC28, 28 tender joint count.
[a] Patients for unmatched ETN (n = 175), unmatched SB4 (n = 225), unmatched SB4-switch (n = 205).
[b] Patients for unmatched ETN (n = 248), unmatched SB4 9 (n = 224), unmated SB4-switch (n = 180).
[c] Patients for unmatched ETN (n = 261), unmatched SB4 (n = 214), unmatched SB4-switch (n = 166).
[d] Patients for unmatched ETN (n = 267), unmatched SB4 (n = 226), unmatched SB4-switch (n = 176).
[e] Patients for unmatched ETN (n = 267), unmatched SB4 (n = 226), unmatched SB4-switch (n = 176).
[f] Patients for unmatched ETN (n = 257), unmatched SB4 (n = 225), unmatched SB4-switch (n = 176).
[g] Patients for unmatched ETN (n = 226), unmatched SB4 (n = 199), unmatched SB4-switch (n = 148).
[h] Patients for unmatched ETN (n = 227), unmatched SB4 (n = 227), unmatched SB4-switch (n = 189).

difference in DAS28-ESR between the ETN and SB4 groups was observed, with a mean ± SD of 4.2 ± 1.3 and 3.3 ± 1.3, respectively, which resulted in a standardized difference (d) of 0.7. At baseline in these two cohorts, differences were also observed in age (d = 0.38), BMI (d = 0.13), CRP levels (d = 0.39), ESR (d = 0.50), SJC28 (d = 0.51), TJC28 (d = 0.47), PGA (d = 0.24), mHAQ (d = 0.15), and order of bDMARDs (d = 0.80). In matched analysis based on the main PS model (M4) adjusting for age, sex, baseline DAS28-ESR, and order of bDMARDs, 144 patients were included in both the ETN and SB4 cohorts. The mean ± SD DAS28-ESR was 3.6 ± 1.2 and 3.5 ± 1.3, respectively (d = 0.11). Baseline characteristics showed a good overlap between the PS-matched cohorts with BMI (d = –0.15), CRP levels (d = 0.18), SJC28 (d = 0.12), TJC28 (d = –0.07), mHAQ (d = –0.03), and order of bDMARDs (d = 0.15). In the SB4-switch cohort, the mean ± SD DAS28-ESR was 2.5 ± 1.2.

Primary outcome measures. *DAS28-ESR at one year (continuous).* Results for primary outcome measures and their change during the subsequent study periods are displayed in Table 2 and Figure 1. In unmatched analysis, the mean DAS28-ESR at one year was 2.8 (95% confidence interval [CI] 2.6–3.0) for the ETN cohort (n = 189) and 2.5 (95% CI 2.3–2.7) for the SB4 cohort (n = 143). In PS-matched analysis the mean DAS28-ESR at one year was 2.7 (95% CI 2.3–3.0) for the ETN cohort (n = 54) and 2.6 (95% CI 2.2–2.9) for the SB4 cohort (n = 54) (results shown in Table 3). For the SB4-switch cohort, DAS28-ESR remained stable, and the mean was 2.4 (95% CI 2.2–2.6) for the 52-week period before the switch

Table 2. Disease status before the start of treatment, at baseline, and up to two-year follow-up (at week 104) in ETN-naive patients with PsA treated with ETN or SB4 in unmatched patient cohorts and in patients switched from ETN to SB4*

Variable and treatment	52 weeks before baseline		Baseline		Baseline to 52 weeks		52–104 weeks	
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)
DAS28-ESR	–	–	–	–	–	–	–	–
ETN	65	3.7 (3.4–4.0)	226	4.2 (4.0–4.3)	189	2.8 (2.6–3.0)	131	2.4 (1.9–2.5)
SB4	139	3.2 (3.0–3.4)	199	3.3 (3.1–3.4)	143	2.5 (2.3–2.7)	57	2.2 (1.9–2.5)
SB4-switch	141	2.4 (2.2–2.6)	148	2.5 (2.3–2.7)	117	2.3 (2.1–2.5)	82	2.2 (1.9–2.4)
CRP, mg/L	–	–	–	–	–	–	–	–
ETN	79	7.6 (5.8–9.4)	248	16.3 (12.5–20.2)	220	6.9 (4.8–9.0)	152	6.1 (4.1–8.1)
SB4	164	8.6 (6.2–10.9)	224	7.4 (6.0–8.8)	185	4.3 (2.9–5.6)	74	4.2 (1.8–6.6)
SB4-switch	176	5.1 (3.6–6.6)	180	4.9 (3.5–6.3)	152	4.9 (2.6–6.2)	109	4.0 (1.8–6.1)
ESR, mm/hr	–	–	–	–	–	–	–	–
ETN	74	19.1 (16.0–22.2)	261	23.5 (20.8–26.2)	212	12.3 (10.7–13.9)	147	12.3 (9.9–14.6)
SB4	154	15.5 (13.2–17.9)	214	14.3 (12.5–16.2)	156	9.7 (8.1–11.3)	60	8.0 (4.8–11.1)
SB4-switch	157	12.0 (10.2–13.8)	166	12.5 (10.6–14.4)	126	12.6 (10.3–14.9)	90	10.7 (7.9–13.4)
SJC28 (range 0–28)	–	–	–	–	–	–	–	–
ETN	82	2.0 (1.4–2.5)	267	3.0 (2.6–3.4)	235	1.2 (0.9–1.5)	165	0.7 (0.4–1.0)
SB4	159	1.0 (0.8–1.3)	226	1.5 (1.2–1.8)	189	0.7 (0.5–0.9)	79	0.4 (0.2–0.6)
SB4-switch	174	0.3 (0.2–0.5)	176	0.5 (0.3–0.7)	148	0.3 (0.2–0.4)	112	0.4 (0.3–0.6)
TJC28 (range 0–28)	–	–	–	–	–	–	–	–
ETN	82	3.6 (2.7–4.6)	267	5.3 (4.7–6.0)	235	3.0 (2.4–3.6)	165	1.9 (1.4–2.5)
SB4	159	2.9 (2.2–3.5)	226	3.1 (2.6–3.6)	189	2.0 (1.5–2.5)	79	1.8 (1.0–2.5)
SB4-switch	174	1.4 (1.0–1.8)	176	1.6 (1.2–2.1)	148	0.9 (0.6–1.2)	112	0.9 (0.6–1.3)
PGA (0–100 mm)	–	–	–	–	–	–	–	–
ETN	80	51.0 (45.9–56.1)	257	58.0 (55.3–60.7)	229	37.1 (33.8–40.4)	166	33.8 (29.7–37.8)
SB4	161	48.2 (44.3–52.1)	225	52.5 (49.3–55.6)	189	42.5 (38.5–46.5)	77	43.5 (36.8–50.3)
SB4-switch	179	31.6 (27.9–35.2)	187	33.7 (29.8–37.6)	156	33.3 (29.1–37.6)	118	33.6 (28.8–38.4)
mHAQ (range 0–3)	–	–	–	–	–	–	–	–
ETN	76	0.6 (0.5–0.6)	227	0.7 (0.6–0.8)	207	0.5 (0.4–0.5)	147	0.4 (0.4–0.5)
SB4	154	0.6 (0.5–0.7)	227	0.6 (0.6–0.7)	188	0.5 (0.5–0.6)	75	0.6 (0.4–0.7)
SB4-switch	176	0.4 (0.4–0.5)	189	0.4 (0.4–0.5)	154	0.4 (0.4–0.5)	118	0.4 (0.3–0.5)

* CI, confidence interval; CRP, C-reactive protein; DAS28-ESR, disease activity score in 28 joints with ESR; ESR, erythrocyte sedimentation rate; ETN, etanercept; mHAQ, modified Health Assessment Questionnaire; PGA, patient global assessment; PsA, psoriatic arthritis; SB4, ETN biosimilar; SJC28, 28 swollen joint count; TJC28, 28 tender joint count.

(n = 141), with a mean of 2.5 (95% CI 2.3–2.7) at time point of the switch (n = 148) and a mean of 2.3 (95% CI 2.1–2.5) for the 52-week period after switch (n = 117).

In Figure 2, disease status in patients with PsA in both the ETN and the SB4 cohort at one year is displayed. In unmatched analyses, the difference in change from baseline between ETN

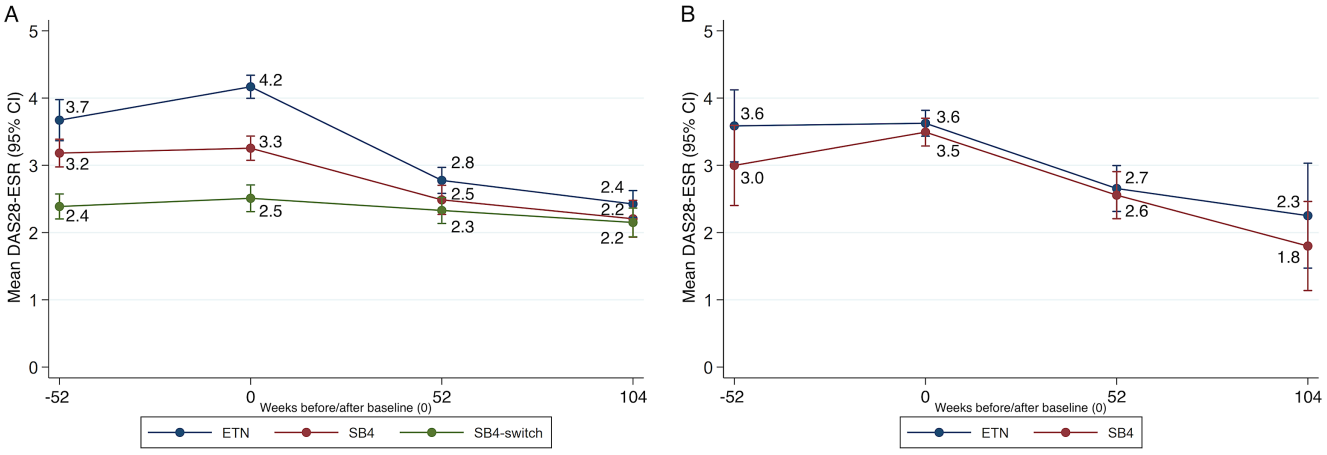

Figure 1. Disease activity expressed as DAS28-ESR over two years of treatment in (A) unmatched and (B) propensity score–matched patients with psoriatic arthritis. Numbers represent the numbers of patients in the unmatched and matched cohorts. Data are shown as the mean with 95% CI. CI, confidence interval; DAS28-ESR, disease activity score in 28 joints with erythrocyte sedimentation rate; ETN, etanercept; SB4, ETN biosimilar.

Table 3. Disease status before the start of treatment, at baseline, and up to two-year follow-up (at week 104) in ETN-naïve patients with PsA treated with ETN or SB4 in PS-matched cohorts*

Variable/ treatment	52 weeks before baseline		Baseline		Baseline to 52 weeks		52 to 104 weeks	
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)
DAS28-ESR	–	–	–	–	–	–	–	–
ETN	24	3.6 (3.0–4.1)	144	3.6 (3.4–3.8)	54	2.7 (2.3–3.0)	10	2.3 (1.5–3.0)
SB4	24	3.0 (2.4–3.6)	144	3.5 (3.3–3.7)	54	2.6 (2.2–2.9)	10	1.8 (1.1–2.5)
CRP, mg/L	–	–	–	–	–	–	–	–
ETN	29	7.3 (4.2–10.5)	130	10.6 (8.1–13.1)	72	5.4 (3.2–7.6)	16	3.0 (1.1–5.0)
SB4	29	9.6 (3.8–15.5)	130	8.2 (6.1–10.3)	72	3.6 (2.5–4.6)	16	2.4 (0.8–4.1)
ESR, mm/hr	–	–	–	–	–	–	–	–
ETN	27	18.5 (13.6–23.4)	144	17.6 (15.2–20.0)	58	10.5 (7.9–13.1)	10	7.7 (3.6–11.8)
SB4	27	15.7 (10.4–20.9)	144	16.5 (14.0–18.9)	58	10.1 (7.6–12.6)	10	7.4 (1.3–13.5)
SJC28 (range 0–28)	–	–	–	–	–	–	–	–
ETN	29	2.1 (1.1–3.0)	144	2.1 (1.6–2.6)	81	1.1 (0.6–1.5)	18	0.4 (0.0–0.7)
SB4	29	1.1 (0.5–1.7)	144	1.8 (1.4–2.2)	81	0.6 (0.4–0.9)	18	0.2 (0.0–0.4)
sTJC28 (range 0–28)	–	–	–	–	–	–	–	–
ETN	29	3.2 (1.7–4.8)	144	3.3 (2.7–3.8)	81	2.7 (1.9–3.6)	18	2.0 (0.2–3.7)
SB4	29	2.4 (0.8–4.1)	144	3.6 (2.9–4.2)	81	1.6 (1.0–2.2)	18	0.9 (0.4–1.4)
PGA (0–100 mm)	–	–	–	–	–	–	–	–
ETN	30	51.2 (42.4–60.0)	144	55.1 (51.6–58.7)	88	36.9 (31.5–42.3)	17	29.8 (16.9–42.6)
SB4	30	47.8 (38.1–57.6)	144	54.0 (49.9–58.1)	88	42.9 (36.7–49.1)	17	42.4 (25.5–58.9)
mHAQ (range 0–3)	–	–	–	–	–	–	–	–
ETN	28	0.6 (0.4–0.7)	123	0.6 (0.6–0.7)	81	0.5 (0.4–0.6)	14	0.4 (0.2–0.5)
SB4	28	0.5 (0.4–0.7)	123	0.6 (0.6–0.7)	81	0.6 (0.5–0.7)	14	0.6 (0.3–1.0)

* For the PS-matched population, the logistic regression model used for the PS matching adjusted for age, sex, DAS28-ESR, and order of bDMARDs. bDMARD, biologic disease-modifying antirheumatic drug; CI, confidence interval; CRP, C-reactive protein; DAS28-ESR, disease activity score in 28 joints with ESR; ESR, erythrocyte sedimentation rate; ETN, etanercept; mHAQ, modified Health Assessment Questionnaire; PGA, patient global assessment; PsA, psoriatic arthritis; PS, propensity score; SB4, ETN biosimilar; SJC28, 28 swollen joint count; TJC28, 28 tender joint count.

(n = 140) and SB4 (n = 132) for DAS28-ESR at one year was mean 0.67 (95% CI 0.38–0.96) in favor of ETN. In PS-matched analyses (M4), the difference between ETN (n = 54) and SB4 (n = 54) was 0.09 (95% CI –0.33 to 0.50), which lays within the predefined equivalence margin of ±0.6.

DAS28-ESR at two years (continuous). In unmatched analysis, the mean DAS28-ESR at two years was 2.4 (95% CI 1.2–2.6) for ETN cohort (n = 131) and 2.2 (95% CI 1.9–2.5) for SB4 cohort (n = 57). In PS-matched analysis, the mean DAS28-ESR at two years was 2.3 (95% CI 1.5–3.0) for the ETN cohort (n = 10), and 1.8 (95% CI 1.1–2.5) for the SB4 cohort (n = 10) (results shown in Table 3). For the same period, DAS28-ESR in the SB4-switch cohort (n = 82) was mean 2.2 (95% CI 1.9–2.4). In both the unmatched and PS-matched analyses, reduction in disease activity assessed by DAS28-ESR was observed at two years of treatment with either ETN or SB4 (Figure 1).

Drug persistence. In unmatched analysis, the estimated drug persistence at one year was 0.75 (95% CI 0.71–0.78) for ETN and 0.58 (95% CI 0.51–0.63) for SB4 (Figure 3A). In PS-matched analysis, the estimated drug persistence at one year was 0.55 (95% CI 0.46–0.63) for ETN and 0.60 (95% CI 0.51–0.67) for SB4 (Figure 3B). For the cohort of patients switching to SB4, the estimated drug persistence at one year was 0.83 (95% CI 0.78–0.87).

In unmatched analysis, the estimated drug persistence at two years was 0.63 (95% CI 0.59–0.66) for ETN and 0.27 (95% CI 0.22–0.33) for SB4 (Figure 3A). In PS-matched analysis, the estimated drug persistence at two years was 0.45 (95% CI 0.37–0.53) for ETN and 0.28 (95% CI 0.21–0.35) for SB4 (Figure 3B). For the cohort of patients switching to SB4, the estimated drug persistence at two years was 0.74 (95% CI 0.68–0.79). At the time of data extraction, no patients who had switched back from SB4 to ETN were identified.

Secondary outcome measures. In Tables 2 and 3, secondary outcomes for the unmatched and PS-matched analyses are displayed, respectively. In both types of analyses and for all analyzed cohorts, improvement from baseline to year 1 and 2 were observed in measures reflecting PsA disease activity and PROs (PGA, mHAQ).

Safety. After two years, 37.3% (n = 240) of ETN, 73.4% (n = 185) of SB4, and 26.5% (n = 64) of SB4-switch patients discontinued treatment. The most reported reasons for drug cessation were lack of or no effect, occurring in 27.9%, 22.7%, and 43.8%, and adverse events (AEs), occurring in 21.7%, 13.5%,

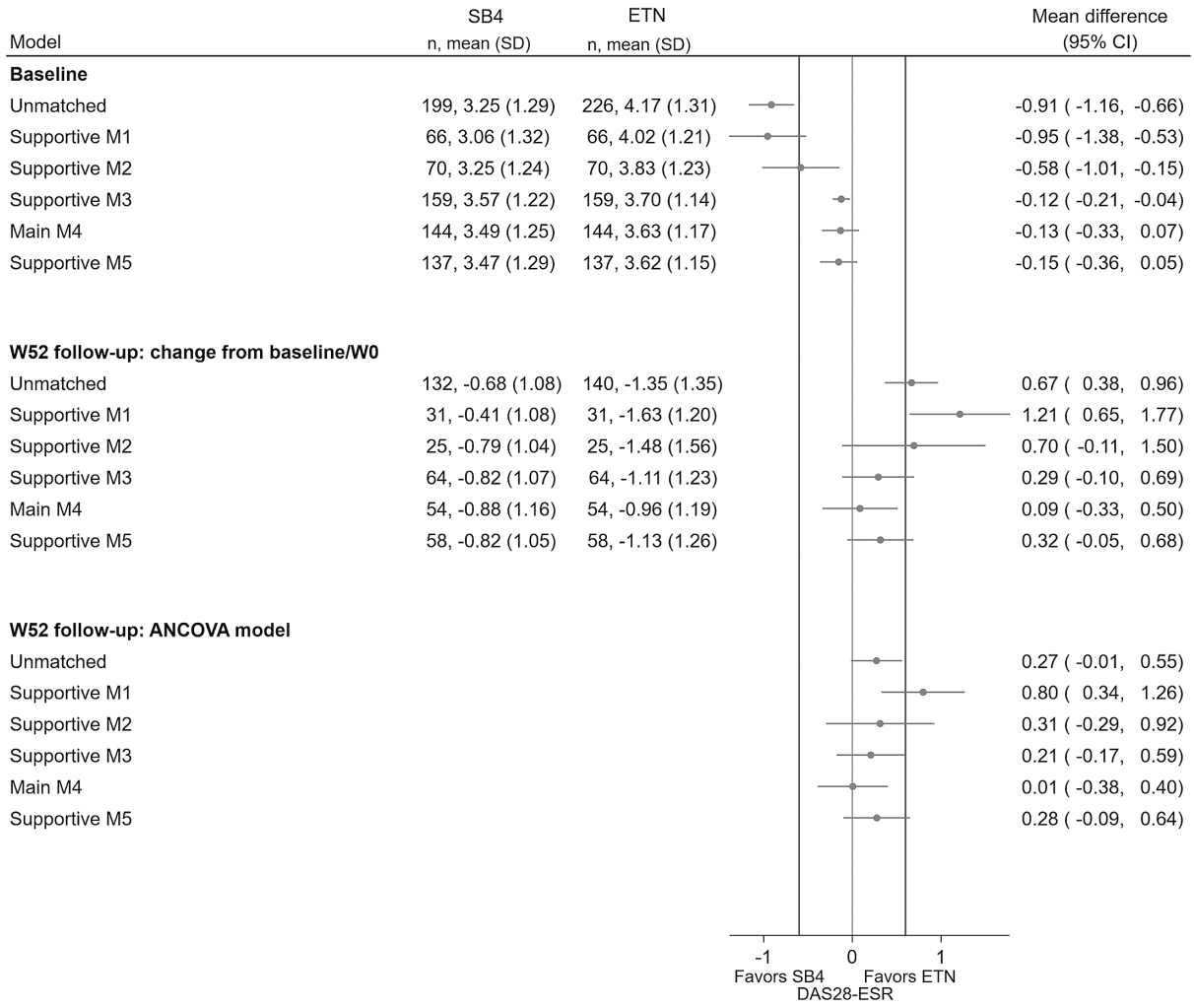

Figure 2. The comparison of effectiveness between ETN and SB4 in patients with psoriatic arthritis. The disease activity is expressed as the DAS28-ESR at baseline and at the 1-year follow-up (W52). This is shown for both unmatched and PS-matched cohorts. The baseline data represent absolute values and the one-year follow-up data represent the mean difference for change from baseline. The additional ANCOVA results are derived from a statistical model, with only the mean difference and 95% CI of DAS28-ESR at W52 reported. The area between the red lines represents the equivalence margin of ±0.6. ANCOVA, analysis of covariance; CI, confidence interval; DAS28-ESR, disease activity score in 28 joints with erythrocyte sedimentation rate; ETN, etanercept; PS, propensity score; SB4, ETN biosimilar; W0, week 0 or baseline; W52, week 52 or 1 year.

and 12.5% of patients in the ETN, SB4, and SB4-switch subgroups, respectively. The most frequent AEs leading to drug discontinuation were skin involvement and infections (more details are available in Supplementary Table 1).

DISCUSSION

The main finding in this study is that, after one-year follow-up, outcomes for PsA disease activity and drug persistence were similar for patients treated with either reference ETN or ETN biosimilar SB4. Further, drug effectiveness was maintained in patients with PsA who underwent the mandatory switch from ETN to SB4.

Real-world data focusing particularly on SB4 in patients with PsA is very limited,[9] because it is usually a part of a pooled analysis of patients with other inflammatory joint disorders and therefore concerns only a small group of patients with PsA. To our best knowledge, this is the first study aiming to directly compare originator ETN and biosimilar ETN SB4 in terms of drug effectiveness and survival in accordance with EULAR recommendations for comparative effectiveness research in rheumatology.[13]

In the current study, the primary outcome measure of DAS28-ESR after one year was similar between patients treated with ETN (2.8, 95% CI 2.6–3.0) or SB4 (2.5, 95% CI 2.3–2.7), and consistent results were confirmed in PS-matched analyses. During the two-year follow-up, further improvement in DAS28-ESR was noted among all PsA cohorts, and observed between-group differences in DAS28-ESR decreased over time. These results stay in line with previously published data reporting

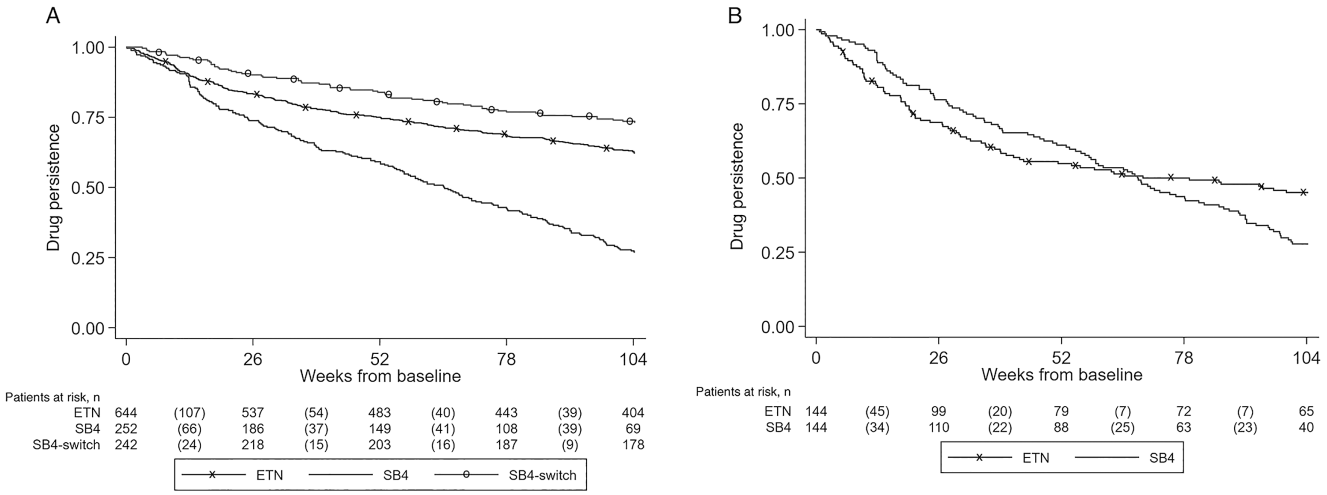

Figure 3. Kaplan-Meier plots of treatment retention rates among patients with psoriatic arthritis (A) treated with ETN or the SB4 or mandatory switched from ETN to SB4 (unmatched cohorts), and (B) treated with ETN or SB4 after PS matching based on the main PS model. CI, confidence interval; ETN, etanercept; PS, propensity score; SB4, ETN biosimilar.

no clinically relevant differences in terms of efficacy of ETN and SB4 in inflammatory rheumatic diseases (RA, PsA, and ankylosing spondylitis).[18–20] However, none of those studies focused particularly on comparative effectiveness of ETN and its biosimilar in the PsA population. We have recently documented the similarity of ETN and SB4 outcomes in patients with RA using a similar methodologic approach as in the currently reported analyses.[21]

In our study, after one-year follow-up, the estimated drug persistence rates were slightly higher for ETN (0.75) than for SB4 (0.58). After PS-matching, the estimated drug persistence rates were similar for ETN (0.55) and SB4 (0.60). These numbers are lower than rates reported in the available literature, which range from 0.75 to 0.90.[18,20,22,23] For the cohort of patients who were mandatory switched to SB4, the estimated drug persistence at one year was 0.83 (95% CI 0.78–0.87), which is concordant with existing data.[18,24] By contrast, at the two-year follow-up, a higher discontinuation rate in the SB4 subgroup compared to ETN was observed, which could possibly be related to the higher number of patients in the SB4 subgroup receiving second and third lines of treatment as well as to the significantly lower disease activity, lower level of acute phase reactants, and the lower number of tender and swollen joint counts in those patients (all $P < 0.001$). In addition, despite generally low DAS28-ESR scores, which reflects good joint response, at least part of the discontinuation might have been related to insufficient effect on the skin involvement, which we could not evaluate due to the lack of assessment of the skin in our study. Furthermore, also in the PS-matched analysis, the estimated drug persistence was significantly higher for ETN (0.45) than for SB4 (0.28), with no overlapping 95% CI (0.37–0.53 for ETN and 0.21–0.35 for SB4), which may indicate that, in a longer time perspective, the SB4 biosimilar may be less effective than the reference ETN, and this finding requires further evaluation in real-world evidence studies.

The mandatory switch model for biosimilars as, for example, implemented in Denmark and Norway,[25] has been shown to be effective in implementing the use of, for example, infliximab and etanercept biosimilars. Countries with no national implementation strategies for biosimilars in comparison with those where mandatory switch strategies were implemented have shown a lower rate of both switch and use of biosimilars. The use of biosimilars has led to large cost savings for the payers, and the cost-saving potential is significant. The shift from reference adalimumab to biosimilar adalimumab in the last quarter of 2018 resulted in a cost reduction of as much as 83%.[26]

To some extent, the mandatory switch model may appear to contrast with the 2018 consensus-based recommendations for the use of biosimilars to treat rheumatologic diseases because the mandatory switch model puts less emphasis on the patients' perspective.[27] In these recommendations, the authors state that "the treating clinician must be the only one to decide whether to prescribe a biosimilar in place of a bio-originator on a case-by-case basis with full awareness of the patient."

According to the approval process, the biosimilar only requires similarity to the reference drug in one RCT for one of the indications approved for the reference drug. After proving similarity in one RCT, the biosimilar automatically gets approval for all indications of the reference drug. In the rheumatology field, this is mostly tested in RA as was done for SB4.[3,4] It is unlikely that costly RCTs will be performed for a biosimilar tested for other indications of the reference drug. Real-world data may fill this knowledge gap and provide insights into indications not investigated in RCTs. Although the use of real-world data will not achieve the same evidence level of study design as RCTs, the use of sophisticated statistical analyses may partly compensate for the lower methodologic validity.

Our study should be viewed in the context of its limitations. As for all observational studies, there are issues related to a

certain level of missing data, measured and unmeasured confounding factors, and selection and attrition bias. In our analysis, reasons for missing data were, among others, a lack of or incorrect data registration, a different set of variables recorded in participating centers, a certain number of patients not meeting to medical appointment as well as those lost to follow-up. Because the PS-matching method used in our analysis adjusts for confounders but does not directly handle missing data and only the patients with complete data were analyzed, this kind of approach may have reduced the robustness of our results. Moreover, we have not been able to report PsA-specific outcomes, ie, Disease Activity in Psoriatic Arthritis, or skin involvement because of the lack of such data in databases obtained from clinical centers participating in the current study. Additionally, because we evaluated patients who continued with the medication and that the major cause of discontinuation in our cohort was a lack of effect, improvement on the DAS28-ESR reported in our study is somewhat expected because most of the patients who continued the treatment were better. We used the PS method, which mitigates the risk of selection bias, and thus simulates the conditions of conducting RCTs. However, due to data unavailability, we have not been able to include all variables of interest in the models, ie, the cycling versus switching mechanism in patients previously treated with bDMARDs, and this could be one of the reasons why we did not manage to achieve the complete overlap between cohorts. These drawbacks are somewhat balanced by our approach to analyze and report the results in accordance with current EULAR recommendations (Supplementary Table 2), as well as by a high overall patient number and the multicenter character of the study.

In conclusion, our real-world study provides evidence that disease outcomes for biosimilar ETN SB4 and reference ETN are equivalent in both naive and mandatory switching patients with PsA cohorts. Effectiveness was maintained in patients with PsA who underwent the mandatory switch from ETN to SB4. However, drug persistence rates at the end of the two-year follow-up were lower for biosimilar ETN SB4 than for reference ETN, which requires further research and evaluation. The clinical implications of this study support the view that the SB4 ETN biosimilar is as effective and safe as the reference ETN for treatment of patients with PsA who are naive to ETN or switching from the originator drug.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr Łosińska had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Łosińska, Pripp, Bakland, Fevang, Brekke, Wierød, Korkosz, Haugeberg.

Acquisition of data. Bakland, Fevang, Brekke, Wierød, Haugeberg.

Analysis and interpretation of data. Łosińska, Pripp, Haugeberg.

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