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REVIEW

Clinical and Real-World Evidence on Etanercept Biosimilar Switching: A Narrative Literature Review of Efficacy and Safety

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ABSTRACT

The introduction of biosimilars into global markets has increased utilisation and reduced costs of biological therapies. However, the uptake varies by country because of differences in biosimilar knowledge and concerns about their safety and efficacy. This review examines clinical and real-world data on the effects of switching between reference and biosimilar (SDZ-ETN, SB4, LBEC0101, YLB113) etanercept on treatment efficacy and safety in patients with inflammatory rheumatic and musculoskeletal diseases. To date, all controlled clinical trials and real-world studies indicate that switching between reference and biosimilar etanercept does not affect treatment efficacy and safety. These findings support broader biosimilar adoption to improve patient access and reduce healthcare costs. However, published data on multiple biosimilar switches and patient-reported outcomes remain limited, warranting further research efforts in these areas.

Keywords: Axial spondyloarthritis; Biosimilar switch; Etanercept; Health economics; LBEC0101; Psoriasis; Rheumatoid arthritis; SB4; SDZ-ETN; YLB113

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Key Summary Points

By reducing treatment cost, biosimilars can broaden patient access to biological disease-modifying drugs.

Lack of trust in the safety and efficacy of switching to a biosimilar remains a key barrier that restricts the real-world benefits of biosimilar prescription.

This review of data from 18 trials has found that switching between reference and biosimilar etanercept does not affect clinical outcomes.

However, our searches highlighted that data on multiple switches and the impact of switching on patient-reported outcomes remain limited.

Education of patients and physicians about the current evidence supporting biosimilar switching is paramount.

INTRODUCTION

The treatment of inflammatory rheumatic and musculoskeletal diseases has been revolutionised by the introduction of biological disease-modifying antirheumatic drugs (bDMARDs) [1]. These drugs have the potential to change the clinical course of the disease for many patients, especially those with complicated disease or poor response to treatment [1]. However, high costs can restrict their real-world use. Recently, the patents for some bDMARDs have begun to expire, allowing the introduction of biosimilars into the market. Biosimilars benefit from tailored clinical development programmes and extrapolation of indications, making them more affordable than their reference biologics [2, 3]. This affordability creates price competition for reference bDMARDs, resulting in cost savings to healthcare systems that can be reinvested to broaden patient access to bDMARDs and support novel drug discovery [4].

As a result of these market developments, one bDMARD with available biosimilars is etanercept [2], which is an Fc fusion protein targeted towards tumour necrosis factor alpha (TNFα; Fig. 1). It is approved for treating rheumatoid arthritis (RA), juvenile idiopathic arthritis, psoriatic arthritis (PsA), axial spondyloarthritis (AxSpA) and plaque psoriasis (PsO) [5, 6]. Patents for reference etanercept (Enbrel®; Amgen) expired in Europe in 2015 [7]. That same year, the European Medicines Agency (EMA) adopted a positive opinion on the first etanercept biosimilar, SB4 (Benepali™; Samsung Bioepis), which was granted marketing authorisation in January 2016 [8, 9]. This approval was followed by the European approvals of SDZ-ETN (Erelzi®; Sandoz) in 2017 and YLB113 (Nepexto®; Mylan) in 2020 [10, 11]. As expected, the entry of etanercept biosimilars into the European market has led to increased treatment utilisation and substantial price reductions [12, 13]. In contrast, the extension of Enbrel patents in the USA has prevented any etanercept biosimilars from entering the market to date, despite the approval of SDZ-ETN by the U.S. Food and Drug Administration in 2016 [14]. Consequently, the reported median price of reference etanercept in 2019 was more than three times higher in the USA than in Germany [15].

Beyond patent considerations, the global cost-saving benefits of biosimilar drugs are influenced by international differences in biosimilar prescription rates [16–21]. Overall, Europe has high rates of biosimilar adoption [16–18]. However, in several other countries, including Canada and the USA, the prescription of biosimilars has been suboptimal [19, 20]. The low uptake in certain countries can be attributed to barriers such as lack of effective policies or guidelines, lack of financial incentives, lack of general knowledge about biosimilars and concerns about biosimilar safety and efficacy [19–21]. Prescriber concern about the safety and efficacy of biosimilars has been identified as one of the most difficult barriers to overcome [22]. These misconceptions arise from the aforementioned knowledge gaps and can contribute to the development of the nocebo effect, whereby patients' negative expectations, and not the pharmacological action of the bDMARD itself, lead to new or worsening perceived symptoms and adverse events that may necessitate a switch back to the reference bDMARD [23]. As such, further investment into

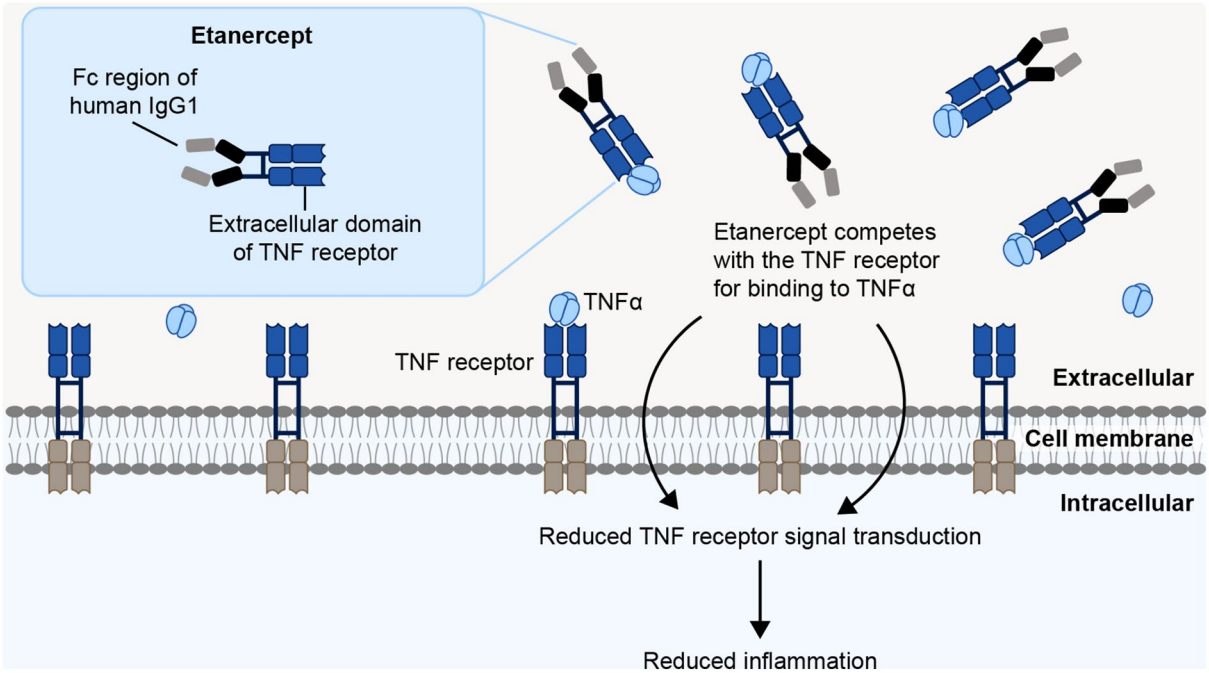

Fig. 1 Mechanism of action of etanercept. *Fc* fragment crystallisable, *IgG* immunoglobulin G, *TNF(α)* tumour necrosis factor (alpha)

schemes to educate about the safety and efficacy of biosimilars is paramount to deepen patients' and physicians' trust in these drugs [24].

Given these challenges, the objective of this article is to review current evidence regarding safety, efficacy and immunogenicity outcomes in patients switching between reference etanercept and its biosimilars. The aims of the article are to help healthcare professionals and patients make informed decisions about switching between reference and biosimilar etanercept; highlight the current profile of patients treated with etanercept, almost 20 years after it first entered the market; and discuss the effects that biosimilar bDMARDs have had on global markets since their introduction.

METHODS

Literature Search

We conducted a literature search via the PubMed database in November 2024. PubMed is a database containing primarily peer-reviewed literature, which allowed for the selection of a scientifically rigorous dataset for this review. To identify articles of potential interest, the following search string was used: ("etanercept" AND "biosimilar") AND ("switch" OR "switching"). Other keywords and phrases searched in the context of the above search included: "efficacy" OR "safety" OR "immunogenicity"; "real-world data"; "health economics" OR "cost-effectiveness"; "rheumatoid arthritis" OR "psoriatic arthritis" OR "ankylosing spondylitis" OR "plaque psoriasis" OR "juvenile idiopathic arthritis"; "non-medical switch" OR "medical switch" OR "treatment transition"; "patient perspective" OR "physician perspective" OR "patient satisfaction" OR "treatment adherence" OR "patient benefits"; "biosimilar uptake" OR "biosimilar adoption" OR "biosimilar interchangeability" OR "interchangeability" OR "bioequivalence".

Selection Criteria

No restrictions were applied regarding publication date or article type. Relevant articles were manually selected. Full-text, original articles assessing efficacy, safety and immunogenicity data in patients switching between reference etanercept and at least one biosimilar were of interest. Additional articles fulfilling these criteria recommended by authors on the basis of their awareness of the literature were also considered for inclusion.

Articles were excluded if they described studies involving healthy volunteers, did not specify the etanercept biosimilar used or were congress abstracts.

Data Extraction and Quality Assessment

Relevant articles were assessed for data quality and content. Data extraction involved identification of key information related to efficacy, safety and immunogenicity outcomes in patients switching between reference and biosimilar etanercept. The quality of the included studies was evaluated on the basis of study design and patient characteristics.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

LITERATURE SEARCH RESULTS

In total, 182 articles of interest were identified. After removing duplicates and screening for relevance, we reviewed 18 original peer-reviewed articles. These included four reporting data from controlled clinical trials and 14 reporting data from real-world studies (Tables 1 and 2).

Evidence from Controlled Clinical Trials

Four phase 3, randomised, double-blind clinical trials assessed the effects of switching between reference and biosimilar etanercept on treatment efficacy, safety and immunogenicity (Table 1; Fig. 2) [25–28]. Of these, only one, the EGALITY clinical trial of SDZ-ETN in patients with PsO [26], assessed the effects of multiple switches. In total, 1091 patients were included in the switching populations across these phase 3 trials: 769 with RA and 531 with PsO. Across the four trials, 698 patients were exposed to SDZ-ETN, 148 patients were exposed to LBEC0101 (Eucept®; LG Chem; approved in South Korea) and 245 patients were exposed to SB4.

Efficacy

The comparable efficacy of reference etanercept and SDZ-ETN was shown in two large switching clinical trials involving patients with moderate-to-severe PsO (EGALITY [26]) or moderate-to-severe RA (EQUIRA [25]; Fig. 2; Table 1). In the EGALITY clinical trial ($N=531$), multiple switches between reference etanercept and SDZ-ETN did not impact efficacy in patients with PsO. Changes in Psoriasis Area and Severity Index (PASI) score and PASI response rate from baseline to week 52 were similar for patients who received continuous treatment and those who experienced three switches (Table 1) [26]. Likewise, in the EQUIRA clinical trial ($N=376$), a single switch from reference etanercept to SDZ-ETN did not impact efficacy in patients with RA (Table 1) [25]. Changes in DAS 28-joint count (DAS28) with C-reactive protein (CRP) and Functional Assessment of Chronic Illness Therapy – Fatigue scores from baseline to week 48 were comparable for the continuous treatment and switched groups [25]. Consistently, similar proportions of patients in the continuous treatment and switched groups achieved good or moderate European Alliance of Associations for Rheumatology (EULAR) responses and improvements in American College of Rheumatology (ACR) responses of ≥ 20%, ≥ 50% or ≥ 70% [25].

Table 1 Summary of clinical data on switching between reference and biosimilar etanercept

#	Trial name/ identifier	Trial design	Trial length	Trial population	Efficacy outcomes	Safety profile	Immunogenicity
SDZ-ETN							
1	EQUIRA/ NCT02638259 [25]	Phase 3, randomised, double-blind Single switch	48 weeks	Switched from ref-ETN to SDZ-ETN: 190 RA pts Continued SDZ-ETN: 186 RA pts Switch at week 24	DAS28-CRP, LSM (SE) change from baseline to week 48 Continued SDZ-ETN: − 2.9 (0.12) Switched to SDZ-ETN: − 2.8 (0.13) FACIT-fatigue score, mean (SD) change from baseline to week 48 Continued SDZ-ETN: 11.6 (9.7) Switched to SDZ-ETN: 10.6 (9.7) Percentage of pts achieving EULAR good/ moderate response Continued SDZ-ETN: 54/42 Switched to SDZ-ETN: 52/44 Percentage of pts achieving ACR20/ACR50/ ACR70 at week 48 Continued SDZ-ETN: 89/63/37 Switched to SDZ-ETN: 82/66/42	Percentage of pts with ≥ 1 TEAE Continued SDZ-ETN: 43 ($n = 75$) Switched to SDZ-ETN: 38 ($n = 63$) Percentage of pts with ≥ 1 SAE Continued SDZ-ETN: 2 ($n = 4$) Switched to SDZ-ETN: 2 ($n = 4$)	ADA positive after switching Continued SDZ-ETN: $n = 4$ Switched to SDZ-ETN: $n = 0$

Table 1 continued

#	Trial name/ identifier	Trial design	Trial length	Trial population	Efficacy outcomes	Safety profile	Immunogenicity
2	EGALITY/ NCT01891864 [26]	Phase 3, randomised, multicentre, double-blind Multiple switch	52 weeks	Continued ref-ETN: 151 PsO pts Continued SDZ-ETN: 150 PsO pts Switched ref-ETN: 96 PsO pts Switched SDZ-ETN: 100 PsO pts Switches at weeks 12, 18 and 24	From baseline to week 52, the mean PASI scores, percentage changes from baseline in PASI score and adjusted PASI 50, 75 and 90 response rates were similar in the pooled continued ($n = 240$) and pooled switched ($n = 168$) treatment groups	Percentage of pts with ≥ 1 TEAE Continued SDZ-ETN: 60 ($n = 98$) Continued ref-ETN: 57 ($n = 98$) Switched SDZ-ETN: 61 ($n = 61$) Switched ref-ETN groups: 59 ($n = 57$) Percentage of pts with ≥ 1 treatment-related TEAE Continued SDZ-ETN: 21 ($n = 34$) Continued ref-ETN: 19 ($n = 33$) Switched to SDZ-ETN: 22 ($n = 22$) Switched to ref-ETN: 21 ($n = 20$)	ADA positive before switching: Ref-ETN: $n = 5$ SDZ-ETN: $n = 0$ ADA positive after switching: Continued SDZ-ETN: $n = 0$ Continued ref-ETN: $n = 0$ Switched to SDZ-ETN: $n = 0$ Switched to ref-ETN: $n = 1$

Table 1 continued

#	Trial name/ identifier	Trial design	Trial length	Trial population	Efficacy outcomes	Safety profile	Immunogenicity
SB4							
3	NCT01895309 [28]	Randomised double-blind Part 1 Open-label Part 2 Single switch	100 weeks	Continued SB4: 126 RA pts Switched from ref-ETN to SB4: 119 RA pts Switch at week 52	Percentage of pts achieving ACR20/ACR50/ACR70 at week 100 Continued SB4: 78/60/43 Switched to SB4: 79/61/42 Mean (SD) improvement from baseline in DAS28/SDAI/CDAI scores at week 100 Continued on SB4: 3 (2)/27 (16)/27 (15) Switched to SB4: 3 (2)/29 (15)/28 (14)	Percentage of pts with ≥ 1 TEAE Continued on SB4: 48 ($n = 60$) Switched to SB4: 49 ($n = 58$)	1 pt in each treatment group developed non-neutralising ADAs after week 52

Table 1 continued

#	Trial name/ identifier	Trial design	Trial length	Trial population	Efficacy outcomes	Safety profile	Immunogenicity
LBEC0101							
4	NCT02715908 [27]	Phase 3, randomised, double-blind Part 1 Multicentre, single-arm, open-label Part 2 Single switch	100 weeks	Continued LBEC0101: 70 RA pts Switched to LBEC0101: 78 RA pts Switch at week 52	DAS28-ESR score, LSM (95% CI) change from week 52 to week 100 Continued LBEC0101: −0.05 (−0.31 to 0.21) Switched to LBEC0101: −0.15 (−0.42 to 0.12) DAS28-CRP score, LSM change from week 52 to week 100 Continued LBEC0101: 0.24 Switched to LBEC0101: 0.14 Percentage of pts achieving ACR20/ACR50/ACR70 at week 100 Continued LBEC0101: 80/65/45 Switched to LBEC0101: 83/67/42	Percentage of pts with ≥ 1 AE Continued LBEC0101: 70 ($n = 49$) Switched to LBEC0101: 71 ($n = 55$) Percentage of pts with ≥ 1 SAE Continued LBEC0101: 9 ($n = 6$) Switched to LBEC0101: 10 ($n = 8$)	ADA positive after switching: Continued LBEC0101: 1% ($n = 1$) Switched to LBEC0101: 1% ($n = 1$)

ACR20/50/70 American College of Rheumatology response of ≥ 20%/ ≥ 50%/ ≥ 70%, *ADA* anti-drug antibody, *AE* adverse event, *CDAI* clinical disease activity index, *CI* confidence interval, *CRP* C-reactive protein, *DAS28* DAS 28-joint count, *EULAR* European Alliance of Associations for Rheumatology; *FACIT* Functional Assessment of Chronic Illness Therapy, *LSM* least square mean, *PASI* Psoriasis Area and Severity Index, *PsO* psoriasis, *pt* patient, *RA* rheumatoid arthritis, *(ref-) ETN* (reference) etanercept, *SAE* serious AE, *SD* standard deviation, *SDAI* simplified disease activity index, *SE* standard error, *TEAE* treatment-emergent AE

Table 2 Summary of real-world data on switching between reference and biosimilar etanercept

#	Trial name/reference	Trial design	Trial length	Trial population	Efficacy outcomes	Safety profile
SDZ-ETN						
1	COMPACT [29]	Multicentre, multi-country (Europe and Canada), prospective, non-interventional, cohort study	1 year	Group A: 572 pts switched from ref-ETN or another ETN biosimilar to SDZ-ETN (RA, *n* = 295; PsA, *n* = 117; AxSpA, *n* = 160) Group B: 171 pts switched from non-ETN-targeted therapies to SDZ-ETN (RA, *n* = 88; PsA, *n* = 36; AxSpA, *n* = 47) Group C: 713 biologic-naive pts started on SDZ-ETN (RA, *n* = 451; PsA, *n* = 135; AxSpA, *n* = 127) Group D: 10 DMARD-naive RA pts started on SDZ-ETN	Mean (SD) change from baseline in DAS28-ESR score at year 1 RA pts: − 0.4 (1.6) Mean (SD) change from baseline in ASDAS/BASDAI scores at year 1 AxSpA pts: − 0.1 (1.0)/− 0.5 (2.2) Percentage of pts achieving disease remission at year 1 RA pts: 52 (*n* = 218) PsA pts: 62 (*n* = 65) AxSpA pts: 26 (*n* = 40)	Percentage of pts with ≥ 1 TEAE Group A: 48 (*n* = 272) Group B: 57 (*n* = 97) Group C: 56 (*n* = 399) Group D: 60 (*n* = 6) Percentage of pts with ≥ 1 SAE Group A: 4 (*n* = 22) Group B: 6 (*n* = 10) Group C: 4 (*n* = 26) Group D: 0 (*n* = 0)

Table 2 continued

#	Trial name/reference	Trial design	Trial length	Trial population	Efficacy outcomes	Safety profile
SB4						
2	[31]	Observational Danish registry study	1 year	Continued ref-ETN: 440 pts (RA, *n* = 286; PsA, *n* = 56; AxSpA, *n* = 98) Switched to SB4 at study start: 1621 pts (RA, *n* = 933; PsA, *n* = 351; AxSpA, *n* = 337)	Change in median (IQR) DAS28 score 3 months after switching from ref-ETN to SB4 RA pts: 0.0 (− 0.4 to 0.5) PsA pts: 0.1 (− 0.4 to 0.5) Change in median (IQR) BASDAI/ASDAS score 3 months after switching from ref-ETN to SB4 PsA pts: 1 (− 3 to 10)/0.1 (− 0.2 to 0.6) Among the 120 back-switchers, lack of effect was the primary reason for switching back to ref-ETN	Percentage of pts discontinuing treatment due to AEs Ref-ETN: 10 (*n* = 14) Switched to SB4: 26 (*n* = 77)

Table 2 continued

#	Trial name/reference	Trial design	Trial length	Trial population	Efficacy outcomes	Safety profile
3	[32]	Open-label cohort study conducted in the Netherlands	24 weeks	Continued ref-ETN: 600 pts (RA, $n = 422$; PsA, $n = 109$; AxSpA, $n = 69$) Switched to SB4 at study start: 625 pts (RA, $n = 433$; PsA, $n = 128$; AxSpA, $n = 64$)	Change from baseline in median (IQR) DAS28-CRP score at week 24 (RA and PsA pts only) Ref-ETN: -0.26 ± 0.99 Switched to SB4: -0.01 ± 0.93 Change from baseline in median (IQR) BASDAI score at week 24 (AS pts only) Ref-ETN: 0.24 ± 0.23 Switched to SB4: 0.30 ± 0.24	Percentage of pts discontinuing treatment due to AEs Ref-ETN: 28 Switched to SB4: 47
4	[40]	Norwegian retrospective, comparative database study	104 weeks	Continued ref-ETN: 644 PsA pts Continued SB4: 252 PsA pts Switched from ref-ETN to SB4: 242 PsA pts	Mean (95% CI) change in DAS28 score from baseline to week 52 Ref-ETN: 2.8 (2.6–3.0) SB4: 2.5 (2.3–2.7) Switchers: 2.3 (2.1–2.5) Change in mean (95% CI) DAS28 score from week 52 to week 104 Ref-ETN: 2.4 (1.9–2.5) SB4: 2.2 (1.9–2.5) Switchers: 2.2 (1.9–2.4)	Percentage of pts discontinuing treatment due to AEs Ref-ETN: 22 SB4: 14 Switchers: 13

Table 2 continued

#	Trial name/reference	Trial design	Trial length	Trial population	Efficacy outcomes	Safety profile
5	[33]	Italian real-life observational study	3 years	Switched to SB4 at study start: 236 pts (RA, $n = 120$; PsA, $n = 80$; AS, $n = 36$)	Mean (IQR) DAS28 values in RA pts Baseline: 2.4 (1.9–2.9) Year 3: 2.5 (2–3) Mean (IQR) DAPSA values in PsA pts Baseline: 3.1 (2.7–4.0) Year 3: 4.6 (3.2–7.5) Mean (IQR) BASDAI values in AS pts Baseline: 1.0 (0.6–1.5) Year 3: 1.1 (0.8–2.25)	Percentage of pts discontinuing treatment due to AEs 24 ($n = 10$)
6	[36]	Italian retrospective study	18 months	Switched from ref-ETN to SB4: 220 pts (RA, $n = 85$; PsA, $n = 81$; AxSpA, $n = 33$; 14 JIA; 7 other condition)	Percentage of pts who stopped SB4 due to lack/loss of efficacy 6 ($n = 19$) Number of pts with disease under control at last follow-up Receiving ref-ETN: $n = 14$ Receiving SB4: $n = 190$ Receiving other therapy: $n = 16$	Percentage of pts with ≥ 1 AE 23 ($n = 50$) Percentage of pts who stopped SB4 due to AEs 5 ($n = 11$)

Table 2 continued

#	Trial name/reference	Trial design	Trial length	Trial population	Efficacy outcomes	Safety profile
7	COMPANION-B [30]	Prospective, multinational (Canada and Australia), multicentre, observational study	1 year	Continued on ref-ETN: 109 RA pts Switched to SB4 at study start: 54 RA pts	Percentage of pts (95% CI) with disease worsening at year 1 Continued on ref-ETN: 23 (15–32) Switched to SB4: 18 (8–31) Percentage of pts with DAS28-ESR increase of ≥ 1.2 from baseline and minimum score of 3.2 at year 1 Continued on ref-ETN: 22 ($n = 22$) Switched to SB4: 14 ($n = 7$)	Percentage of pts with ≥ 1 non-serious treatment-related AE Continued on ref-ETN: 3 ($n = 3$) Switched to SB4: 13 ($n = 7$) Percentage of pts with ≥ 1 SAE Continued on ref-ETN: 9 ($n = 9$) Switched to SB4: 6 ($n = 3$)

Table 2 continued

#	Trial name/reference	Trial design	Trial length	Trial population	Efficacy outcomes	Safety profile
8	[41]	Italian descriptive study	1 year	Switched to SB4 at study start: 87 pts (RA, *n* = 48; PsA, *n* = 26; AS, *n* = 13)	Median (IQR) DAS28 values in RA pts Before switch: 2.5 (1.8–4.8) 1 year after switch: 2.84 (1.8–4.7) Median (IQR) DAPSA values in PsA pts Before switch: 10.0 (6.0–31.0) 1 year after switch: 14.9 (6.4–40.8) Mean (IQR) BASDAI values in AS pts Before switch: 1.7 (1.3–9.0) 1 year after switch: 1.75 (1.0–5.6)	Number of pts discontinuing treatment due to AEs *n* = 2
9	[38]	Open-label, prospective study	1 year	Switched from ref-ETN to SB4: 87 PsA pts	Percentage of pts who maintained a cDAPSA of ≤ 13 at year 1 87.3 (*n* = 76)	NR

Table 2 continued

#	Trial name/reference	Trial design	Trial length	Trial population	Efficacy outcomes	Safety profile
10	[37]	British, single-centre, retrospective, observational study	≤ 20 months	Switched from ref-ETN to SB4 at study start: 72 pts (RA, *n* = 36; PsA, *n* = 13; AxSpA, *n* = 23)	Percentage of pts who switched back to ref-ETN within 6 months 26.4 (RA pts, *n* = 12; PsA pts, *n* = 2; AxSpA pts, *n* = 5) Reasons for back-switch LOE: 58% AEs: 32% Infection: 5% Difficulty using the pen device: 5%	Reported AEs Headache, dyspnoea, weight gain, hair loss, rash, fatigue
SB4 and SDZ-ETN						
11	[34]	Retrospective chart review	≤ 32 weeks	Switched from ref-ETN to SB4 to SDZ-ETN: 100 pts (RA, *n* = 54; PsA, *n* = 19; AxSpA, *n* = 27)	Retention rate 6 months after the second switch 89%	Overall, 14 AEs were reported in 8 pts No re-transitioning to ref-ETN due to AEs occurred
12	[42]	Italian multicentre, prospective, observational, cohort study	1 year	Switched from ref-ETN to SB4 to SDZ-ETN: 76 PsO pts	Median (range) PASI scores over the observation period At 3 months: 1 (0–2) At 12 months: 0.5 (0–1) Mean (SD) duration of SDZ-ETN treatment 17.7 ± 6.4 months After the switch from SB4 to SDZ-ETN, 2 pts developed a flare-up	No treatment-emergent SAEs reported

Table 2 continued

#	Trial name/reference	Trial design	Trial length	Trial population	Efficacy outcomes	Safety profile
LBEC0101						
13	KURAMA cohort [35]	Japanese single-centre, retrospective study	48 weeks	Switched from ref-ETN to LBEC0101: 11 RA pts	Mean DAS28-ESR scores before and after switching No significant difference ($p = 0.58$)	NR
YLB113						
14	[39]	Japanese retrospective study	1 year	Switched from ref-ETN to YLB113: 41 RA pts	Mean DAS28 score At time of switching: 2.5 Year 1 after switching: 2.6 Number of pts in remission At time of switching: $n = 20$ Year 1 after switching: $n = 21$	Percentage of pts with ≥ 1 AE after switching 12.2 ($n = 5$) AEs leading to discontinuation were not observed in any pts

AE adverse event, *AS* ankylosing spondylitis, *ASDAS* ankylosing spondylitis disease activity score, *AxSpA* axial spondyloarthritis, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *CI* confidence interval, *(c)DAPSA* (clinical) disease activity index for psoriatic arthritis, *CRP* C-reactive protein, *DAS28* DAS 28-joint count, *DMARD* disease-modifying antirheumatic drug, *ESR* erythrocyte sedimentation rate, *IQR* interquartile range, *JIA* juvenile idiopathic arthritis, *LOE* loss of efficacy, *NR* not reported, *PASI* Psoriasis Area and Severity Index, *PsA* psoriatic arthritis, *PsO* psoriasis, *pt* patient, *RA* rheumatoid arthritis, *(ref-)ETN* (reference) etanercept, *SAE* serious AE, *SD* standard deviation, *TEAE* treatment-emergent AE

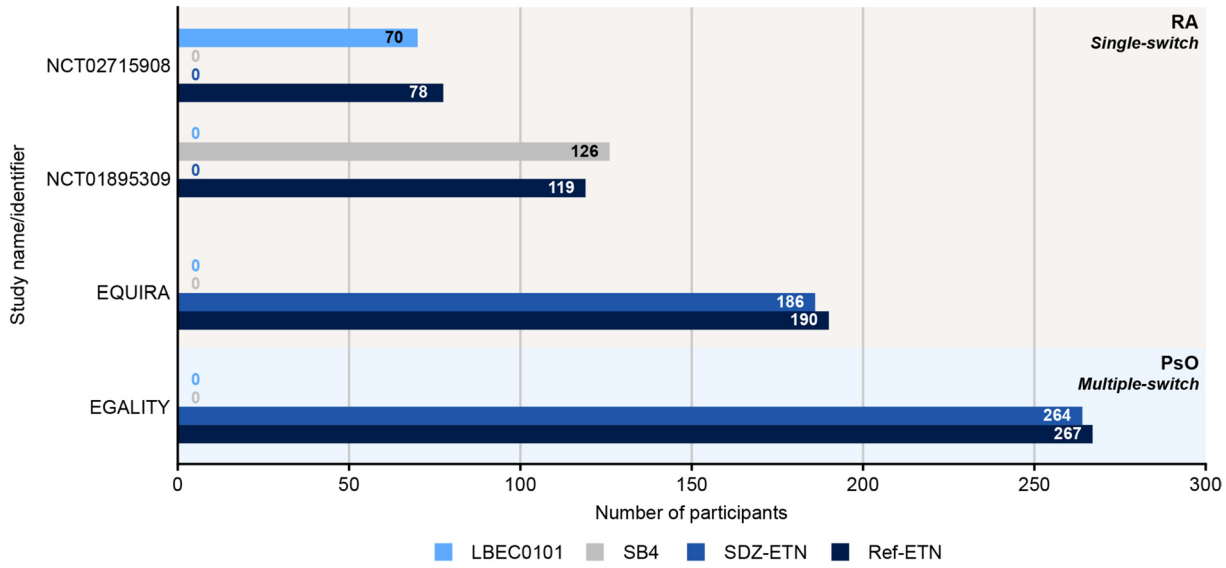

Fig. 2 Number of participants in controlled clinical trials of etanercept biosimilar switching by treatment allocated at baseline. *PsO* psoriasis, *RA* rheumatoid arthritis, *(ref-)ETN* (reference) etanercept

Randomised switching clinical trials evaluating two other etanercept biosimilars, LBEC0101 and SB4, were carried out in patients with RA and yielded similar results to the trials with SDZ-ETN. In the clinical trial of LBEC0101 (NCT02715908), improvements in DAS28 with erythrocyte sedimentation rate (DAS28-ESR), DAS28-CRP and ACR response rate achieved in the 52-week randomised run-in period were sustained in patients who continued receiving the same treatment for another 48 weeks and in those who switched from LBEC0101 to reference etanercept at week 52 [27]. Comparable outcomes in the continuous treatment and switched groups were maintained until trial end, with similar proportions of patients in both groups achieving good or moderate EULAR responses and disease remission at week 100 [27]. Similarly, in the SB4 clinical trial (NCT01895309), switching from reference etanercept to SB4 at week 52 resulted in comparable ACR and EULAR responses, remission rates and improvements in disease activity at week 100 relative to continuous treatment with SB4 [28].

Safety and Immunogenicity

No new or unexpected safety signals were reported upon switching in any of the four clinical trials (Table 1) [25–28]. Across the three single-switch trials in patients with RA, differences in the proportion of patients with at least one treatment-emergent adverse event (TEAE) between switchers and non-switchers ranged from − 4.9% with SDZ-ETN to 1.1% with SB4 [25, 27, 28]. In the multiple-switch EGALITY trial of SDZ-ETN in patients with PsO, the difference in the proportion of patients with at least one TEAE between switchers (pooled switched SDZ-ETN and switched reference etanercept) and non-switchers (pooled continued SDZ-ETN and continued reference etanercept) was 1.7% [26]. Switching between reference and biosimilar etanercept did not result in negative immunogenicity outcomes in any of the four clinical trials [25–28]; the presence of anti-drug antibodies was infrequent and comparable between switchers and non-switchers (Table 1) [25–28].

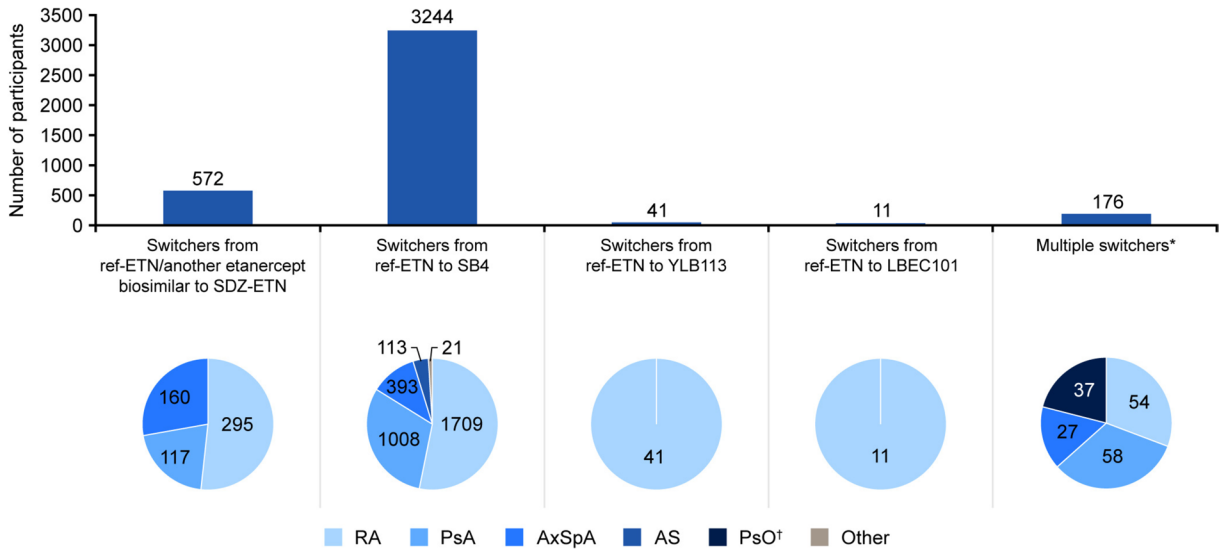

Fig. 3 Pooled number of patients undergoing switches from reference to biosimilar etanercept in real-world studies, stratified by type of treatment and by indication. *AS* ankylosing spondylitis, *AxSpA* axial spondyloarthritis, *PsA* psoriatic arthritis, *PsO* psoriasis, *RA* rheumatoid arthritis, *(ref-)ETN* (reference) etanercept. *Patients who switched between ref-ETN and at least two biosimilars; †Without concurrent PsA

Real-World Evidence

The real-world effectiveness and safety of switching between reference etanercept and its biosimilars was reported in 14 studies (Table 2) [29–42]. The real-world studies enrolled a total of 7174 patients, of whom 4044 switched between reference and biosimilar etanercept (SDZ-ETN, SB4, YLB113 or LBEC0101). More than half of all enrolled switchers had RA (Fig. 3). Of the 14 studies, nine investigated the effects of a single switch between reference etanercept and SB4 and two investigated the effects of multiple switching between reference etanercept, SB4 and SDZ-ETN. One single-switch study was performed each for SDZ-ETN, YLB113 and LBEC0101.

Effectiveness

Overall, switching between reference and biosimilar etanercept did not impact real-world effectiveness outcomes compared with continued treatment across various indications (Table 2) [29–42]. In the prospective COMPACT study ($N = 1466$), no major changes in RA, AxSpA or PsA disease activity were observed for up to 1 year after switching from reference etanercept to SDZ-ETN [29]. Likewise, in the prospective COMPANION-B study ($N = 163$), comparable effectiveness between SB4 and reference etanercept was observed over 1 year in patients with stable RA who voluntarily switched to SB4 [30]. The long-term maintenance of comparable treatment effectiveness following a single switch from reference etanercept to SB4 was confirmed in several retrospective real-world studies [36, 37, 40]. In two studies, effectiveness was also shown to be maintained upon multiple switching, from reference etanercept to SB4 and subsequently to SDZ-ETN [34, 42]. Although the real-world effectiveness of biosimilars YLB113 and LBEC0101 remains less well studied compared with SDZ-ETN and SB4, the two small real-world studies conducted to date found no significant differences in DAS28-ESR scores after a single switch from reference etanercept to YLB113 ($N = 41$) or LBEC0101 ($N = 11$) [35, 39].

Retention Rates

In the COMPACT study, the mean real-world, 1-year retention rate following a switch from reference etanercept to SDZ-ETN was 91.2% [29]. Across the SB4 studies, the mean reported 1-year retention rates among switchers ranged from 83.0% to 88.6% [31, 36, 37]. Retention rates for YLB113 and LBEC0101 have not been reported in the real-world switching studies published to date [35, 39].

Notably, in two real-world switching studies of SB4, the retention rates were slightly lower for patients with RA than for those with PsA, ankylosing spondylitis (AS) or AxSpA [31, 37]. In one of these studies ($N = 72$), higher duration on reference etanercept at baseline among patients with RA was associated with higher rates of SB4 withdrawal (odds ratio 1.43; 95% confidence interval 1.02–2.00); no such trends were observed for patients with AxSpA and PsA [37]. Loss of efficacy in patients with RA in this study was reflected by significant increases in all investigated subjective measures (DAS28; Patient Global Score; tender joint count; all $p < 0.05$) but only one of the three evaluated objective measures (CRP levels; $p < 0.05$), suggesting a potential nocebo effect [37]. Likewise, in the second study ($N = 1621$), in patients with RA who switched back to reference etanercept, changes in disease activity at time of switching back compared with SB4 start date were mainly observed in Patient Global Score, whereas changes in objective measures of CRP and swollen joint counts were close to zero, again suggestive of a nocebo effect [31]. In another study, which found similar retention rates for patients with RA, PsA and AS, the presence of comorbidities in these patients was associated with higher rates of SB4 discontinuation [33].

Safety

None of the real-world single- and multiple-switching studies reported any new or unexpected safety signals [29–42]. The safety profile was generally similar for patients who switched treatments and those who did not [29, 36, 41].

Patient-Reported Outcomes

Peer-reviewed data on patient-reported outcomes (PROs) following switching are limited. However, according to the current evidence, switching does not significantly affect PROs. In the COMPACT study in patients with RA, AxSpA or PsA, no major changes in PRO scores were observed over 12 months following a switch from reference etanercept to SDZ-ETN [29]. Likewise, real-world studies of SB4 in rheumatic diseases did not report any differences in Health Assessment Questionnaire Disability Index scores after switching, or between switchers and non-switchers [30, 34, 40].

DISCUSSION

Clinical and real-world evidence indicates that switching between reference and biosimilar etanercept does not impact the safety and efficacy of treatment [25–42]. None of the reviewed switching studies reported any new or unexpected safety signals, or major changes in treatment efficacy, following a treatment switch [25–42]. Although data on PROs are limited, the available evidence suggests that PROs remain consistent after a treatment switch [29, 30, 34, 40]. A potential nocebo effect was reported in only two of the 14 studies reviewed [31, 37]. These promising data should bolster confidence in both healthcare professionals and patients that switching between reference and biosimilar etanercept does not have an impact on treatment safety and efficacy. This may help to reduce the incidence of the nocebo effect and could improve global biosimilar adoption rates.

The different etanercept biosimilars showed similar effectiveness and safety outcomes across real-world studies; however, treatment retention rates were generally slightly lower for SB4 than SDZ-ETN [29–42]. It is important to note that these studies are not directly comparable, and observed differences in retention rates may be due to variability in several factors, including study length, recruitment time periods and geographical locations (Table 2). Another explanation may be varying patient satisfaction with

different autoinjector devices. In one retrospective study, 5% of patients reported difficulty with using the autoinjector device as the reason for withdrawal from SB4 treatment [37]. In line with these data, in a multinational survey, both patients and nurses displayed a higher preference for the SDZ-ETN autoinjector compared with the autoinjectors for reference etanercept and SB4 [43]. This preference was mainly due to the buttonless injection feature, visual feedback after injection and the convenient shape of the device [43].

Retention rates can also be affected by the incidence of the nocebo effect, necessitating a switch back to the less cost-effective reference etanercept [44]. In two real-world studies of SB4, patients who discontinued treatment after switching to the biosimilar had statistically significant increases in subjective measures of disease activity (e.g. DAS-28 or tender joint count) but no or only small changes in objective measures of inflammation (e.g. CRP level or the number of swollen joints), suggesting a potential nocebo effect [31, 37]. Notably, in these two studies, patients with RA had lower retention rates compared with those with PsA, AS or AxSpA, suggesting that the incidence of the nocebo effect might be higher in this patient population [31, 37, 45]. Interestingly, in one of these studies, patients with RA had the longest prior duration of treatment with reference etanercept [31]. Similarly, in the other study, longer baseline duration on reference etanercept among patients with RA was associated with an increased rate of biosimilar withdrawal [37]. This finding may, at least partly, be attributed to heightened anxiety regarding a change in treatment after a long period on reference etanercept, making the patients more vulnerable to the nocebo effect. However, development of the nocebo effect is also influenced by various other factors, including the individual patient's psychosocial disposition [23]. As such, because of the observational design of the two switching studies [31, 37], no definitive causal relationships between biosimilar discontinuation and the nocebo effect were confirmed.

In the absence of validated diagnostic criteria, the nocebo effect remains difficult to accurately quantify and is, therefore, understudied [46]; none of the 18 studies reviewed in this article quantified its influence [25–42]. In the broader literature, the reported incidence of the nocebo effect in patients with RA switching to biosimilars has been highly variable, with some studies finding no evidence of such effect and others reporting rates of up to 13.1% [47–50]. Although one retrospective study in patients with RA or AxSpA found that shared decision-making can reduce the rate of the nocebo effect compared with a systematic switch carried out without patient consultation [47], a systematic review conducted across a range of different biologic drugs concluded that the current quality of evidence on the biosimilar nocebo effect is insufficient to draw any meaningful conclusions [51]. Therefore, further retrospective switching studies designed to assess PROs and subjective disease activity measures are needed to evaluate the real-world prevalence of a nocebo effect following a biosimilar treatment switch across different indications. Such studies may help to identify those patient populations that will benefit most from strategies known to mitigate the nocebo effect, such as educational schemes and shared decision-making [52], with the aim to reduce back-switching to reference bDMARDs and maximise cost savings for healthcare systems.

Health Economics of Biosimilar Switching

Biosimilars have the potential to introduce price competition and make bDMARDs more affordable. The benefits of biosimilar adoption have already been observed in Europe, where the entry of biosimilar etanercept into the market led to price reductions and increased treatment utilisation [12]. In France, 5 years after biosimilar etanercept introduction, the market share of reference etanercept had reduced from 100% to 26%, whereas the market share of SDZ-ETN had increased from 0 to 57% (translating to cost savings of almost €137 million) [16]. However, percentage changes in anti-TNF price and market share after biosimilar introduction have been shown to differ by up to 71% and 92%, respectively, across different European countries [4]. The international differences in cost savings can be attributed, at least in part, to varying

biosimilar penetration rates, because of distinct regional-level biosimilar quotas, quota adherence monitoring mechanisms, insurer–manufacturer discount contracts and insurer–prescriber gain-sharing arrangements [53]. For example, in Norway, where physicians must use the cheapest available drug unless there is a clinical reason to do otherwise, the market share of biosimilar etanercept is above 82% [24]; however, similar strategies have been implemented in only approximately half of European countries [24].

Differences in biosimilar knowledge among physicians can also affect prescription rates [45]. Many patients find the switch between a reference and biosimilar medicine acceptable when it is recommended by their treating physician [54, 55]. However, not all physicians believe that the efficacy and manufacturing standards of biosimilar and reference biologics are equivalent [56], and some are hesitant to recommend a switch to patients who are doing well on the reference biologic [57]. According to patients concerned about biosimilar switching, biosimilar acceptance may be improved through the conduct of more clinical switching trials, more reassuring communication by healthcare professional teams, and greater patient involvement in the decision-making process [58]. Biosimilar utilisation may therefore be improved by implementing patient and physician education schemes, allowing patients to switch back if necessary, offering consultations with a pharmacist prior to the treatment switch and simplifying the reporting of adverse events suspected to result from switching [56, 57, 59].

Cost savings achieved following biosimilar introduction are also influenced by factors other than those discussed above. The first and second etanercept biosimilars to enter the European market reduced the volume-weighted average price per defined daily dose to a similar extent (9.3% vs. 9.1%) [12], highlighting that market saturation has the potential to reduce biosimilar and reference etanercept prices further. In addition, biosimilar manufacturing processes have a significant impact on the final price, with greater cost savings expected if these processes are streamlined [60]. Currently it takes approximately 7–8 years to develop a biosimilar [60]. In Europe, multiple trials are required to compare efficacy, safety, pharmacokinetic (PK), pharmacodynamic (PD) and immunogenicity outcomes between the proposed biosimilar and the reference medicine prior to biosimilar approval [61]. However, it has been suggested that in most cases, a combination of extensive comparative analytical studies and an abbreviated comparative clinical PK trial, with simple PD, safety and immunogenicity evaluation, may be sufficient to assess for biosimilarity [62]. Streamlining the PK/PD assessment should allow biosimilar drugs to be brought to the market faster and at a more competitive price. Developmental costs of biosimilars may also be reduced if the production process is further optimised. Currently, reference etanercept and its approved biosimilars are produced in a mammalian Chinese hamster ovary cell line [5, 63–65]. If it becomes possible to use plants to produce etanercept, manufacturing costs could be substantially reduced [60].

Finally, minimisation of payer costs may also improve cost savings following biosimilar introduction. In the UK, non-medical switching has been associated with an increase in payer costs due to the need for additional healthcare resources (e.g. healthcare professional visits, medical imaging, blood tests, hospitalisation and emergency room visits) to support patients during the transition [66]. Similarly, an analysis from Canada reported transient increases in drug refills and physician visits following a treatment switch [67]. On the basis of current real-world evidence, the increased need for physician visits during the treatment switch is unlikely to be due to changes in treatment efficacy or safety [29–42]. Another explanation for this phenomenon could be that patients and physicians are not fully confident in the equivalent safety and efficacy of biosimilar and reference etanercept and therefore opt for more frequent monitoring visits. As such, continuous education of patients and physicians about the current body of peer-reviewed evidence supporting biosimilar switching remains paramount.

Limitations

Overall, although this review provides valuable insights into the safety and efficacy of switching

between reference and biosimilar etanercept, several limitations should be considered when interpreting the findings reported herein. Firstly, the studies included in this review vary in terms of study design and patient characteristics. This variability limited direct comparisons across studies and might have introduced heterogeneity into the findings. Secondly, given this is a narrative review of real-world clinical data, the non-systematic approach of this review could be perceived as lacking objectivity and introducing selection bias. Although efforts were made to include a comprehensive range of studies, the manual selection process might have inadvertently excluded relevant articles. Finally, data on multiple switches between biosimilars, the impact of switching on PROs and the incidence of the nocebo effect remain limited and warrant further research. The available evidence suggests that PROs remain consistent after a treatment switch; however, the potential nocebo effect observed in some studies suggests that patient perceptions and psychological factors may influence treatment outcomes following a treatment switch. Further investigation into the impact of biosimilar switching on PRO outcomes and subjective measures of disease activity is needed to quantify the prevalence and impact of the nocebo effect in different patient populations and to develop strategies to mitigate its effects.

Future Directions

In the context of further clinical research, conducting more randomised controlled trials focussing on multiple switches and switching back to the reference product is warranted. In contrast, in the context of generating further real-world evidence, encouragement of the development and analysis of real-world registries and observational studies to assess switching outcomes in routine clinical practice would be beneficial. Clinicians and researchers may also further explore immunogenicity mechanisms, PROs, and the incidence of the nocebo effect post-switch.

CONCLUSIONS

The entry of biosimilar etanercept into the European market has yielded significant and sustained real-life cost savings in the treatment of inflammatory rheumatic and musculoskeletal diseases [16, 17, 66, 68]. To date, all controlled clinical trials and real-world studies have found that switching between reference and biosimilar etanercept does not impact treatment efficacy and safety [25–42]. These positive data should encourage more widespread adoption of etanercept biosimilars into treatment guidelines and clinical practice, helping to alleviate the financial burden of bDMARDs on healthcare systems. Cost savings associated with etanercept biosimilar use can be reinvested into healthcare systems to broaden patient access to bDMARDs and support development of innovative treatments [4]. Policymakers can leverage these data to promote biosimilar adoption and address barriers to biosimilar uptake, such as patient and physician education. Published data on the safety of multiple switches, the impact of switching on PROs and the impact of the nocebo effect on treatment persistence in different patient populations remain limited. These gaps in the literature warrant further research efforts to better understand the long-term effects of biosimilar switching and to develop strategies to optimise patient outcomes.

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Declarations

Conflicts of Interest. Marc Schmalzing declares having received compensation for consulting from Chugai/Roche, Hexal/Sandoz, Gilead, AbbVie, Janssen-Cilag, Boehringer Ingelheim, onkowissen.de, EUSA-Pharma, Novartis, AstraZeneca, Amgen, Medac, Lilly and Galapagos; speaker's fees from Novartis, AbbVie, AstraZeneca, Chugai/Roche, Janssen-Cilag, Gilead, Boehringer Ingelheim, Mylan, Galapagos and EUSA-Pharma; and travel grants from Chugai/Roche, Boehringer Ingelheim, Celgene, Medac, UCB, Mylan and Galapagos. Ayman Askari has no conflicts of interest to declare. Giampiero Girolomoni declares work as a consultant and/or speaker for AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Bristol-Meyers Squibb, Eli Lilly, LEO Pharma, Novartis, Pfizer, Samsung, Sanofi and UCB. Julio C. V. Perez-Coleman declares consulting fees from Sandoz, AbbVie and Novartis. Cristofer Salvati and Elena Bachinskaya are employees of Sandoz Limited.

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