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REVIEW



Switchback from biosimilar tumor necrosis factor-alpha inhibitors to reference medicines: a review

Robert Moots^{a,b}, Sascha Gerdes^c, Giampiero Girolomoni^d, Jonas Halfvarson^e, Charlotte Both^{f*}, Ines Brückmann^f and Silvio Danese^g

^aDepartment of Rheumatology, Liverpool University Hospitals NHS Foundation Trust, Liverpool, UK; ^bFaculty of Health, Care and Medicine, Edge Hill University, Ormskirk, UK; ^cCenter for Inflammatory Skin Diseases, Department of Dermatology, University Hospital Schleswig-Holstein, Campus Kiel, Kiel, Germany; ^dDepartment of Medicine, University of Verona, Verona, Italy; ^eDepartment of Gastroenterology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden; ^fGlobal Medical Affairs, Sandoz International GmbH, Holzkirchen, Germany; ^gGastroenterology and Endoscopy, IRCCS Ospedale San Raffaele and University Vita-Salute San Raffaele, Milan, Italy

ABSTRACT

Introduction: Switching from reference biologics to biosimilars usually occurs for non-medical reasons, such as cost-driven formulary changes. However, despite biosimilars having the same efficacy and similar safety profiles as their reference products, some patients discontinue treatment and ‘switchback’ to the reference product.

Areas covered: In this narrative review, the authors examine the frequency and causes of switchback reported in journal articles and congress abstracts published between 2016 and 2023, evaluating patients who switched from biosimilars back to the reference biologic. As almost all publications focused on tumor necrosis factor inhibitors, and so the authors restricted their analysis to this drug class.

Expert opinion: Evidence suggests that switchback rates are low, with most studies of at least 100 patients reporting rates of less than 20%. The main reasons for switchback are typically patient-reported loss of effectiveness (usually judged subjectively) and side effects. These findings support the view that the nocebo (‘negative placebo’) effect is a plausible and likely contributor to switchback. Healthcare professional and patient education on the effectiveness and safety of biosimilars is needed and will be vital to counter misinformation and minimize the nocebo effect, allowing biosimilars to continue contributing to sustainability in healthcare.

PLAIN LANGUAGE SUMMARY

Biologic medicines are used to treat conditions such as autoimmune disorders, diabetes, and cancer. However, their high costs limit access for many patients. Once the patent for a biologic expires, biosimilar versions of the biologic can be used to treat the same diseases as the original, or ‘reference’, product. Biosimilar manufacturers must show that a biosimilar is as safe and efficacious as its reference product. Because biosimilars tend to be more affordable than their reference products, many healthcare providers switch patients onto biosimilars when they become available. We wanted to find out how many of these patients subsequently switchback to the reference product, and why. We searched for articles and congress abstracts, published between 2016 and 2023, that evaluated patients who switched back from a biosimilar to the reference biologic. Of the identified publications, most presented data for biosimilars of etanercept, adalimumab, and infliximab. Switchback rates varied greatly, but most studies including at least 100 patients reported switchback rates of less than 20%. In other words, most patients who switched to biosimilars remained on them. The main reasons for switchback were patient-reported loss of effectiveness, and side effects. However, loss of effectiveness was usually judged subjectively. This suggests that the nocebo – or ‘negative placebo’ effect, in which patients have negative expectations about biosimilars – may contribute to switchback. Better patient and physician understanding of the effectiveness and safety of biosimilars can help counter the nocebo effect and support shared decision-making in healthcare.

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KEYWORDS

Switchback; biosimilar; adalimumab; etanercept; infliximab; nocebo

1. Introduction

Biologic therapies have been used successfully to treat many conditions, but are often associated with high costs due in part to the complexity of drug development [1,2]. After patent expiry and loss of exclusivity of these original biologic

treatments, biosimilar medicines can be used to treat the same diseases as the reference medicine, offering competitive pricing owing to streamlined clinical development and regulatory requirements [3,4]. By passing on these cost savings, biosimilar manufacturers enable larger numbers of patients to

CONTACT Robert Moots  robert.moots@liverpoolft.nhs.uk  Clinical Sciences Centre, Aintree University Hospital, Longmoor Lane, Liverpool L9 7AL, UK
*Affiliation at time of manuscript initiation.

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Article highlights

- Despite biosimilars having the same efficacy and similar safety profiles as their reference products, some patients discontinue treatment and ‘switchback’ to the reference product.
- This narrative literature review was carried out to examine the frequency and causes of switchback in patients treated with tumor necrosis factor (TNF) inhibitor biosimilars.
- Of the relevant publications identified, most presented findings from retrospective observational cohort studies or registry-based analyses in Europe.
- In studies with ≥ 100 patients, switchback rates differed greatly, but were relatively low ($\leq 20\%$) in the majority of studies.
- No major differences were observed in switchback rates between different TNF inhibitors, or between therapeutic areas including inflammatory arthritis, inflammatory bowel disease, and others.
- The most common reasons for switchback were patient-reported loss of effectiveness – usually judged based on subjective self-reported responses, rather than objective measures of disease severity – and adverse events.
- Overall, switchback rates were low, supporting the view that the nocebo (‘negative placebo’) effect is a plausible and likely contributor to switchback.
- Continued education of healthcare professionals and patients on the effectiveness and safety of biosimilars is essential to minimize the nocebo effect and secure their contribution to sustainability in healthcare.

access effective and safe therapies [3,5], leading to improved clinical outcomes, fewer long-term complications, and lower healthcare costs over a patient’s lifetime [5–10].

The European Medicines Agency considers approved biosimilars to be interchangeable with their reference biologic and its other biosimilars [11], and has approved over 15 biosimilars of tumor necrosis factor (TNF) inhibitors for the treatment of inflammatory diseases, including for infliximab [12–15], etanercept [16–18], and adalimumab [19–28] (Table 1). Switching from reference biologics to biosimilars usually occurs for non-medical reasons, such as cost-driven formulary changes by healthcare systems or insurance companies [29]. In Europe, this is often at the discretion of the prescribing physician [30]. However, despite evidence to the contrary [31–36], many

physicians and patients are still hesitant to switch owing to concerns they may have over the safety or effectiveness of biosimilars [36,37]. Cases have also been reported of patients occasionally discontinuing treatment with a biosimilar, and choosing to ‘switchback’ to the reference medicine.

A comprehensive review of data for the rate of switchbacks, and reasons for switchback, is currently lacking. To address this knowledge gap, we sought to identify and review studies reporting switchback rates.

2. Literature search strategy

For this narrative literature review, we conducted electronic searches of Embase[®] and Medline[®] databases to identify journal articles and congress abstracts published in English between January 1, 2016 and March 8, 2023. Searches were conducted using the search terms: ‘biosimilars’, ‘switchback’ (including ‘switching’, ‘switch’, ‘back switch’, ‘reswitch’, ‘backswitching’, ‘back-switchers’, ‘restarted’, or ‘switched back’). Only full articles and abstracts comprising data on switchback rates for biosimilars of adalimumab, etanercept, and infliximab were included in this review. Other biosimilars were excluded by the authors due to the low number of articles. Studies that included data for the proportion of patients who discontinued a biosimilar, and not specifically the proportion that switched back to the reference product, were also excluded. In addition, further hand-searching was performed to identify additional articles and abstracts, with author-suggested publications also considered for inclusion.

While no restriction was placed on the mechanism of action of the biosimilars and their reference biologics, the scope was ultimately refined to focus on biosimilars of TNF inhibitors based on the literature search. Outcomes related to effectiveness and safety following switchback were not reported by all studies, but were extracted and summarized where available. As terminology varied across publications, the phrases ‘loss of effect’, ‘loss of response’, and ‘loss of effectiveness’ have been grouped conceptually for synthesis purposes.

Table 1. Tumor necrosis factor inhibitor biosimilars approved by the European Medicines Agency (as per December 2025).

Reference product	Indications for which biosimilars are approved ^a	Biosimilar	Date of biosimilar approval
Infliximab	Rheumatoid arthritis	Inflectra [12]	Sept 2013
	Psoriatic arthritis	Remsima [13]	Sept 2013
	Ankylosing spondylitis	Flixabi [14]	May 2016
	Psoriasis	Zessly [15]	May 2018
	Crohn’s disease		
Etanercept	Ulcerative colitis		
	Rheumatoid arthritis	Benepali [16]	Jan 2016
	Juvenile idiopathic arthritis	Erelzi [17]	June 2017
	Psoriatic arthritis	Nepexto [18]	May 2020
	Axial spondyloarthritis, including ankylosing spondylitis		
Adalimumab	Psoriasis		
	Rheumatoid arthritis	Amgevita [19]	Mar 2017
	Juvenile idiopathic arthritis	Imraldi [20]	Aug 2017
	Psoriatic arthritis	Hefiya [21]	July 2018
	Axial spondyloarthritis, including ankylosing spondylitis	Hulio [22]	Sept 2018
	Psoriasis	Hyrmoz [23]	July 2018
	Hidradenitis suppurativa	Idacio [24]	April 2019
	Crohn’s disease	Amsparity [25]	Feb 2020
	Ulcerative colitis	Yuflyma [26]	Feb 2021
	Non-infectious uveitis	Libmyris [27]	Nov 2021
		Hukyndra [28]	Nov 2021

^aAll biosimilars are approved for all indications of their respective reference products.

3. Switchback with approved TNF inhibitor biosimilars

3.1. Experience of switchback with approved TNF inhibitor biosimilars

For this review, we focused on switchback rates for TNF inhibitor biosimilars reported in studies that included at least 100 patients (Tables 2 and 3; Tables S1 and S2). Most were retrospective observational cohort studies or registry analyses performed in European countries. Follow-up durations, where specified, ranged from 3 months to approximately 5 years. The majority of publications included in this review reported switchback data for patients treated with etanercept ($n=35$), adalimumab ($n=17$), and infliximab ($n=13$), with some presenting data for more than one biosimilar, either separately or combined. In addition, published articles reported switchback data for specific and cross indications (e.g. infliximab and adalimumab) whereas others were cross indications only (e.g. etanercept). Data from abstracts were across multiple/cross indications.

3.2. Switchback rates

Switchback rates varied greatly in the literature, but reported switchback rates tended to be less than 20%. In other words, most patients who switched to biosimilars remained on them. Switchback rates among these studies increased with length of follow-up, from 7.7% for studies with follow-up of 0–6 months, to 12.2% with ≥ 6 –12 months, 9.8% with 12–24 months, and 27.3% with ≥ 24 months follow-up. Switchback rates for patients tended to range between 12–17%: 15.2% for inflammatory arthritis (rheumatoid arthritis [RA], axial spondyloarthritis [AS], including ankylosing spondylitis, and psoriatic arthritis [PsA]); 16.9% for studies focusing on inflammatory bowel disease (IBD), and 12.4% for studies that combined data across multiple indications (Figure 1).

3.3. Demographics and disease characteristics

Comparisons of the demographic and/or disease characteristics of patients who switched back to the reference product with those who continued on a biosimilar are sparse, though there are conflicting reports regarding the influence of gender on switchback rate. Although some studies report no difference in gender and age distributions between individuals who switched back and those who did not [38,42–44,49,50,55,57,59], other studies found that female patients were more likely to switchback than male patients [39,40,47,48,58,85]. Additional characteristics reported to be more common among patients who switched back included longer previous biologic treatment [49,59], a higher baseline disease activity [58,85], and a diagnosis of RA [48,49,79].

3.4. Reasons for switchback

Although patients may report subjective reasons for switchback (Tables 2 and 3), there is a lack of associated data on whether subjective reasons were accompanied by changes in objective

measures of disease activity. However, where these data were collected, it was commonly reported that concurrent changes in objective measures of disease activity were not generally seen in patients switching back due to subjective reasons [46,49,52,56,58–60,71,73]. Consistently, one non-interventional, multicenter cohort study from the Netherlands reported that patients who switched back to reference infliximab due to increases in objective measures of disease activity had higher treatment discontinuation rates than those who switched back due to subjective symptoms [40].

3.5. Etanercept

Reported switchback rates from an etanercept biosimilar to the reference product in the literature (Tables 2 and 3; Tables S1 and S2) tended to be lower than 20% (Figure 1, Tables 2 and 3), ranging from 2.1% to 37%. In a large and relatively long-duration study that examined switchback rates across indications for 5907 patients over a median follow-up of approximately 5 years [43], it was noted that a significant number of patients alternated between the reference product and biosimilar during follow-up, suggesting that some of the back switches may reflect varying product availability, with the biosimilar and reference products in practice viewed as fully interchangeable [43].

Across indications, including RA, many studies did not report the reasons for switching back to the reference product, those that did typically cited patient-reported loss of effect and/or adverse events (AEs). In an analysis of 1621 patients with RA, AS, or PsA in the DANBIO registry, for example, which has prospective coverage of >95% of adults treated with biological disease-modifying antirheumatic drugs in Denmark, switchback rates below 10% were observed over a median follow-up of approximately 1 year [49]. Upon return to the reference product, disease activity levels were compared with those at biosimilar initiation: this revealed that while patient-reported global assessment scores had changed, C-reactive protein (CRP) and swollen joint counts were virtually unaltered [49].

3.6. Adalimumab

In studies that reported switchback rates from an adalimumab biosimilar to the reference product, follow-up ranged from 3 to 18 months and about half of the studies examined switchback across multiple indications. Switchback rates ranged from 1.6% to 33%, but tended to be below 20% (Figure 1, Table 2, Table 3). The most common reasons given for switchback were lack of effectiveness of the biosimilar and AEs, most notably pain on injection.

In a prospective pseudo-randomized analysis of 1318 patients in the DANBIO registry, for example, 3.6% of patients with rheumatological conditions who switched from reference adalimumab to a biosimilar switched back over a 12-month period, with half reporting that they did so due to ineffectiveness of the biosimilar. Notably, however, changes in CRP levels and Health Assessment Questionnaire scores were close to zero at the time of switching back [58]. Findings from smaller, prospective observational studies were generally similar to those of the larger registry study, albeit with slightly higher switchback rates. The

Table 2. Summary of full-text articles reporting rates of switchback to the reference medicine in >100 patients treated with a biosimilar.

Indication	Study design	No. of patients treated with biosimilar	Follow-up, months	Duration of biosimilar use	Switchback rate, n (%)	Outcomes after switchback	Main reasons for switchback		
							NR	Loss of effect	ISR/ AEs pain
INFLXIMAB									
Rheumatoid arthritis									
Lin et al. [38]	R/O (U.S.A.)	IP: 139 PP: 286	25	NR	IP: 102 (73.4) PP: 214 (74.8)	NR	NR		
IBD									
Lin et al. [38]	R/O (U.S.A.)	IP: 610 PP: 1062	24	NR	IP: 426 (69.8) PP: 776 (73.1)	NR	NR		
Mahmmod et al. [39]	R/O (Netherlands)	758	18	133 days	75 (9.9)	16% discontinued RP after median of 18.3 months	*	*	*
Meijboom et al. [40]	R/O (Netherlands)	198	43	Median: 8.6 months	49 (24.7)	25% discontinued RP by end of follow-up	*	*	*
Axial spondyloarthritis									
Lauret et al. [41]	P/O (France)	135	36	NR	27 (20.0)	NR	*		
Cross-indication									
Fitzgerald et al. [42]	R/O (France)	IP: 571 PP: 1109	IP: 10.5 PP: 11	IP: 130 days PP: 140 days	IP: 90 (15.8) PP: 200 (18.0)	IP: 37.8% discontinued RP within a mean of 170 days PP: 44.5% discontinued RP within a mean of 173 days	NR		
Jourdain et al. [43]	L (France)	9417	60	Median: 3.5 ^a	2054 (21.8)	NR	NR		
Reuber et al. [44]	R (Germany)	2956	12	NR	(30.2) ^b	NR	NR		
Saxby et al. [45]	P/O (UK)	250	3–6	NR	2 (0.8)	Efficacy was regained (n = 1) and AEs ceased (n = 1)	*	*	*
Tweehuysen et al. [46]	R (Netherlands)	192	6	NR	37 (19.3)	NR	*	*	*
ETANERCEPT									
Cross indication									
Bruni et al. [47]	R/O (Italy)	220	12	7 months	18 (8.2)	14/18 patients had a good response with RP	*	*	*
Felis-Gienza et al. [48]	R/O (Poland)	162	3–6	NR	24 (14.8)	23/24 patients showed a response and/or resolution of AEs	*	*	*
Glintborg et al. [49]	Registry (Denmark)	1621	13	Median: 120 days	Overall: 120 (7.4)	87% of patients remained on RP after median of 236 days	*	*	*
Rheumatoid arthritis									
Axial spondyloarthritis									
Psoriatic arthritis									
Jourdain et al. [43]	L (France)	933 337 351	NR	NS	80 (8.6) 20 (5.9) 20 (5.7)	NR	*	*	*
Meijboom et al. [50]	Cohort (Netherlands)	5907	60	Median: 3.5 ^a	2183 (37.0)	NR	NR		
Parisi et al. [51]	P/O (Italy)	342	53	~200 days	47 (13.7)	17% switching to another biologic within a year	*	*	*
Reuber et al. [44]	R (Germany)	236	36	NR	5 (2.1)	NR	NR		
Saxby et al. [45]	P/O (UK)	2956 298	12 3–6	NR	(30.2) ^b 13 (4.4)	Efficacy was regained (n = 7) and AEs ceased (n = 5)	*	*	*
Sigurdardottir et al. [52]	Registry (Sweden)	143	18	NR	19 (13.3)	NR	*	*	*
ADALIMUMAB									
IBD									
Deprez et al. [53]	P/O (Belgium)	110	12	NR	18 (16.4)	NR	*	*	*
Derikx et al. [54]	R/O (Scotland)	256	13.7	7.1 months	4 (1.6)	NR	*	*	*
Psoriasis									
Loft et al. [55]	Registry (Denmark)	348	15	NR	9 (2.6)	~7 patients continued RP	*	*	*

(Continued)

Table 2. (Continued).

Indication	Study design	No. of patients treated with biosimilar	Follow-up, months	Duration of biosimilar use	Switchback rate, n (%)	Outcomes after switchback	Main reasons for switchback		
							NR	Loss of effect	ISR/ AEs pain
Uveitis									
Murray et al. [56]	R/O study (UK)	102	12	6 months	24 (23.5)	NR			*
Cross indication									
Bruni et al. [57]	R/O (Italy)	172	18	NR	11 (6.4)	NR		*	*
Jourdain et al. [43]	L (France)	9285	36	Median: 1.5 ^a	3055 (32.9)	NR	NR	*	*
Nabi et al. [58]	Registry (Denmark)	1318	12	Median: 174 days before switchback	48 (3.6)	NR		*	*
van Adrichem et al. [59]	P/O (Netherlands)	603	12	NR	40 (6.6)	24 patients experienced clinical improvement		*	
Scirvo et al. [60]	P/O (Italy)	110	4	NR	12 (10.9)	NR		*	*
Rheumatoid arthritis		33			3 (9.1)		NR		
Psoriatic arthritis		40			4 (10.0)		NR		
Axial spondyloarthritis		37			5 (13.5)		NR		

Abbreviations: AE, adverse event; AS, axial spondyloarthritis; GI, gastrointestinal; IBD, inflammatory bowel disease; IP, incident population; ISR, injection site reaction; L, longitudinal; NR, not reported; O, observational; P, prospective; PP, prevalent population; R, retrospective; RP, reference product.

^aUnit of time (months or years) not specified.

^bPercentage alone reported.

French longitudinal cohort study described above, in the etanercept section, also included 9285 patients who switched from reference adalimumab to a biosimilar. During a median follow-up of 3 years, 33% switched back to the reference product, but some of these switches may have reflected varying product availability [43].

3.7. Infliximab

Reports of switchback from an infliximab biosimilar to the reference product varied from those that included all infliximab indications without distinguishing between them to others focusing on patients with IBD, AS, or RA. There was a mixture of retrospective and prospective studies, and follow-up periods ranged from 3 months to just over 3.5 years. Switchback rates tended to be below 20%, ranging from 0.8% to 75% (Figure 1, Table 2, Table 3). In a French longitudinal study that included 9417 patients, 22% of patients were found to have switched back from biosimilar infliximab to the reference product; however, reasons for the switchback and subsequent clinical outcomes were not reported [43]. In an outlier study assessing US Veterans Healthcare Administration data, a 75% switchback rate was observed; however, the authors caution that multiple formulary changes during their 2-year retrospective observation period may explain the unusually high switching rates they observed [38].

4. Perceptions of switchback, future perspectives, and strategies

4.1. Patient-reported reasons for switchback

The most common reasons for switchback were patient-reported loss of effectiveness and AEs, which is consistent with a previous review that investigated why patients change from one biologic therapy to another (including biosimilar switchback) [86]. Notably, in the studies identified, patients who discontinued a biosimilar were more likely to switchback to the reference product than to swap to a medication with a different mechanism of action. Given that biosimilars work in the same way as their reference products – and have been shown to have equivalent efficacy, safety, and impact on quality of life – it has been reported that the nocebo effect is a likely and plausible contributor to decisions to discontinue biosimilars [44,49,50,58,59].

4.2. Disease severity/activity

There is a scarcity of data regarding the change in disease severity or activity that prompted biosimilar discontinuation, or the outcomes following switchback. Limited reports indicate a common theme of perceived loss of biosimilar effectiveness prior to switchback based on patient-reported impairment of subjective disease measures, such as tender/swollen joints or disease flares [45,46,48,49,58,73], as opposed to changes in objective markers of inflammation, such as CRP levels. For example, in a Danish analysis, patients who switched back reported loss of efficacy using the Patient Acceptable Symptom State Questionnaire, and were less likely

Table 3. Summary of abstracts reporting rates of switchback to the reference medicine in >100 patients treated with a biosimilar.

Main reasons for switchback								
Indication	Study design	No. of patients treated with biosimilar	Follow-up, months	Duration of biosimilar use	Switchback rate, n (%)	Outcomes after switchback	Loss of effect	
							NR	ISR/ AEs pain
INFLIXIMAB								
IBD								
Inserra et al. [61]	R (Italy)	117	NR	NR	2 (1.7)	NR	NR	
Petitdidier et al. [62]	P/O (France)	113	12	NR	1 (0.9)	Re-achieved clinical remission	Patient decision	
Cross indication								
Davies et al. [63]	Registry (UK)	206	22.5	5 months	71 (7.3) (N = 966) ^a	NR		*
ETANERCEPT								
Rheumatoid arthritis								
Baganz et al. [64]	P/O (Germany)	113	12	NR	9 (8.0)	NR	NR	
Patel et al. [65]	R (UK)	168	NR	NR	18 (10.7)	11 patients confirmed improvement in DAS-28 score at 3 months and one patient switched to rituximab		*
Rokad et al. [66]	P/O (UK)	1160	18	NR	133 (11.5)	NR		*
Shah et al. [67]	P/O (UK)	151	NR	NR	8 (5.3)	NR		*
Cross indication								
Alten et al. [68]	R (Germany)	813	NR	2 months	65 (8.0)	NR	NR	
Ahmad et al. [69]	R (UK)	105	NR	NR	3 (2.8) ^b	NR	NR	
Alten et al. [70]	R (Sweden)	1179	NR	Average 43 days until switchback	(7) ^c	NR	NR	
Alkoky et al. [71]	P/O (UK)	158	6	NR	14 (8.9)	All 14 patients achieved improvement		*
Alten et al. [72]	R/O (Germany)	4471	33	3–4 months	937 (21.0)	NR	NR	
Dahanayake et al. [73]	R (UK)	202	20	Up to 20 months	27 (13.4)	NR		*
Davies et al. [63]	Registry (UK)	206	22.5	5 months	71 (7.3) (N = 966) ^a	NR		*
Fernández et al. [74]	R (Spain)	117	NR	3.5 months	11 (9.4)	NR		*
Moorthy et al. [75]	R (UK)	362	NR	NR	21 (5.8)	NR	Patient decision	
Sada et al. [76]	R/O (Spain)	176	18	NR	25 (14.2)	Three did not achieve a good response	NR	*
Smith and Fawthrop [77]	R (UK)	217	NR	3 months	10 (4.6)	AEs appeared to be resolving shortly after switchback		*
Tweehuysen et al. [78]	P (Netherlands)	625	6	NR	17 (2.7)	NR		*
ADALIMUMAB								
Rheumatoid arthritis								
Jin et al. [79]	R/O (Germany)	1024	NR	13.1 months	147 (14.4)	NR	NR	
IBD								
Moore et al. [80]	R/O (UK)	392	NR	NR	33 (8.4)	NR		*
Norredinvand et al. [81]	R/O (UK)	113	NR	NR	17 (15.0)	15 patients continued with RP		*
Ankylosing spondylitis								
Jin et al. [79]	R/O (Germany)	1240	NR	14.2 months	162 (13.1)	NR	NR	
Psoriatic arthritis								
Jin et al. [79]	R/O (Germany)	787	NR	13.6 months	88 (11.2)	NR	NR	
Cross indication								
Gohil et al. [82]	R/O (UK)	266	NR	NR	67 (25.1)	NR		*
Rosember et al. [83]	R/O (UK)	744	NR	Median: 97 days	32 (4.3)	NR		*
Alten et al. [70]	R/O (Sweden)	107	NR	Average 57 days until switchback	(6) ^c	NR	NR	
Redeker et al. [84]	P/O (Germany)	111	6	NR	6% vs 5% among patients with baseline CCI of 0 vs ≥ 1 ^c	NR		*

(Continued)

Table 3. (Continued).

Indication	Study design	No. of patients treated with biosimilar	Follow-up, months	Duration of biosimilar use	Switchback rate, n (%)	Outcomes after switchback	Main reasons for switchback		
							NR	Loss of effect	ISR/AEs/pain
Redeker et al. [85]	P/O (Germany)	111	24	NR	18 (16.2)	NR	NR	NR	NR
Rheumatoid arthritis	As above	23			2 (8.7)	NR	NR	NR	NR
Axial spondyloarthritis	As above	68			11 (16.2)	NR	NR	NR	NR
Psoriatic arthritis	As above	15			4 (26.7)	NR	NR	NR	NR
Other	As above	5			1 (20.0)	NR	NR	NR	NR

Abbreviations: AE, adverse event; CCI, Charlson Comorbidity Index; DAS-28, Disease Activity Score-28 joints; IBD, inflammatory bowel disease; ISR, injection site reaction; L, longitudinal; NR, not reported; O, observational; P, prospective; R, retrospective; RP, reference product.

^aAnalysis includes all individuals receiving either infliximab or etanercept.

^bOne individual who switched back to etanercept reference product subsequently switched to adalimumab.

^cPercentage alone reported.

to be in remission based on the Disease Activity Score-28 joints/Ankylosing Spondylitis Disease Activity Score scales. However, changes in CRP levels in the same patients at the time of switching back were close to zero [58]. Similarly, in other studies, decisions to switchback were based on reported ineffectiveness [66], including subjective lack of effect [48] and subjective deterioration [71], in the absence of any significant changes in clinical rating scales.

4.3. Adverse events

When AEs were reported as the main reason for switching back, these were often subjective, such as pain at the injection site, or nonspecific [40,46,49,53,54,65,80,81]. Importantly, self-reported side effects – including pain at the injection site – were reduced in patients who received training in the use of injection devices upon being switched to a biosimilar TNF inhibitor [87–89].

4.4. The ‘nocebo’ effect

Several reports suggest that the nocebo effect is a plausible, likely contributing factor to discontinuation of biosimilars and subsequent switchback [39,40,44,46,48–50,53,57–59]. These reports are consistent with regulatory agencies concluding that biosimilars have equivalent efficacy and safety compared with reference biologics [11,90]. In addition, several comprehensive reviews of switching from reference products to biosimilars have concluded that there are no significant differences in safety, efficacy, or discontinuation rates between biosimilars and their reference products [36,91,92].

Although all individuals can be susceptible to the nocebo effect, some groups appear to be at higher risk [93]. In general, it is observed that women are more susceptible than men, with the underlying mechanisms likely to be multifactorial [94,95]. People with higher levels of baseline anxiety also appear more vulnerable [95,96], and there is some evidence that older age and lower socioeconomic status may further increase susceptibility [95]. Within the literature, there is a lack of consensus regarding the effect of gender on the rate of switchback: while some studies find higher rates of switchback in women [39,40,47,48,58,85], others found no effect of gender or age [38,42–44,49,50,55,57,59]. Importantly, most studies did not systematically examine the characteristics of individuals who did and did not switchback. Addressing this knowledge gap would be valuable for developing targeted interventions to mitigate the nocebo effect.

4.5. Communication strategies and interventions

Evidence-based strategies shown to minimize the nocebo effect include providing extensive and comprehensive information on the treatment; increasing patients’ and healthcare providers’ understanding about the nocebo effect itself; and optimizing communication between the patient and clinician to ensure that consultations are based on empathy and trust [93]. When sharing information with patients regarding a biosimilar, physicians could explain that the majority of patients will experience no differences versus the reference

	Number of studies	Lowest rate (%)	Highest rate (%)	Average rate (%)
Across all indications				
Infliximab	12	0.8	75.0	23.3
Adalimumab	17	1.6	33.0	12.6
Etanercept	25	2.1	37.0	10.4
Across all drugs				
Multiple indications/other ^b	33	0.8	37.0	12.4
Inflammatory arthritis (RA, AS, PsA)	10	5.3	75.0	15.2
IBD	9	0.9	73.0	16.9

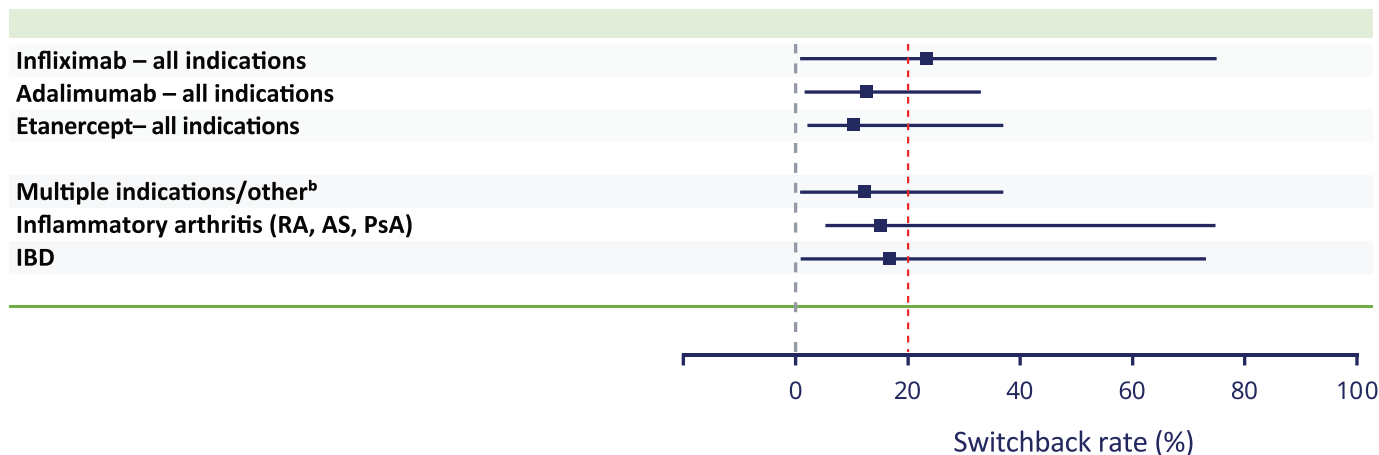


Figure 1. Forest plot and table of the highest and lowest switchback rates^a by drug and indication across full-text articles and abstracts in >100 patients.

Abbreviations: AS, axial spondyloarthritis; IBD, inflammatory bowel disease; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

^aSwitchback rates were calculated at the study level and were not weighted according to any factors, including study size or follow-up duration.

^b'Other' includes patients with psoriasis and uveitis.

product, for example [97]. In a randomized controlled study on itch, the use of verbal suggestion to induce positive expectations was found to reduce and even reverse the nocebo effect [98].

Relatively few studies have evaluated interventions aimed at mitigating the nocebo effect in the specific context of switching to biosimilars [99]. However, Tweehuysen et al. found that an enhanced communication strategy – whereby patients were given information about the reasons for the switch (namely to reduce costs and to reduce the likelihood of injection site reactions) – resulted in a treatment persistence rate of 90% over 6 months for patients with rheumatic disease who switched to biosimilar etanercept, compared with 92% for those who received the reference product [100]. Petit et al. similarly found that a tailored communication strategy, in which all members of a multidisciplinary team spoke with 'one voice' to provide patients with consistent messaging, and in which nurses had a prominent role as the first point of contact when announcing the switch, resulted in a biosimilar retention rate higher than that in a historical non-switch cohort [101].

4.6. Patient preference

Other factors that may affect switchback rates include device preferences. Patients who reported injection-site pain after administration of a biosimilar via a prefilled pen were found to experience less pain when a prefilled syringe was used to administer the biosimilar instead [45].

4.7. Limitations and future studies

The original aim of this literature search was to summarize switchback rates irrespective of biosimilar product type or indication; however, this was not possible owing to a lack of literature on biosimilars other than TNF inhibitors. One of the possible explanations for the lack of published reports on biosimilar switchback in the oncology field is that switchback may be rare among oncology patients; if true, this could reflect differing attitudes among oncologists versus rheumatologists and gastroenterologists, with the former having greater trust in biosimilars. Alternatively, given that many cases of switchback are due to cost-driven formulary changes, it is possible that patients receiving relatively short-term treatment for oncology indications are less likely to experience switchback than patients receiving chronic lifelong treatment with TNF inhibitors.

No geographic restrictions were placed on this literature search; however, the majority of the identified studies were conducted in Europe. The geographical bias of the publications identified in this literature search may therefore reduce the generalizability of the findings to other regions. The overrepresentation of European countries likely reflects the supportive policy environment for biosimilar adoption in Europe and the fact that the European Medicines Agency (EMA) established guidelines for biosimilar use earlier than other regulatory bodies [102]. Consequently, Europe has seen greater market penetration of biosimilars than most other

regions. In the Asia-Pacific region, regulatory frameworks for biosimilars have often been based on EMA and WHO guidance, but policies vary widely across countries, as do incentives for biosimilar adoption [102–104]. In the U.S.A., although the US Food and Drug Administration has approved multiple TNF inhibitor biologics, litigation related to patent law has greatly delayed their entry into the market [105]. For example, biosimilar versions of adalimumab and etanercept were approved in 2016, yet adalimumab biosimilars did not launch until 2023, and biosimilar etanercept is not expected to enter the US market before 2029 [105].

Another limitation of the current analysis is that many studies relied upon subjective self-reports of loss of effectiveness, rather than measuring changes in disease activity using validated clinical rating scales – such as the Simplified Disease Activity Index and – which have been shown to accurately reflect both objective and subjective worsening of disease [106]. Other studies used CRP levels as a proxy for inflammatory disease activity. However, CRP is a nonspecific inflammatory marker that can fluctuate for a variety of reasons, and may therefore be poorly suited to revealing changes in disease activity in conditions such as RA [107] and PsA [108]. The utility of CRP as a biomarker is also limited in IBD, where it has been shown to be more useful as a marker of disease activity in Crohn's disease than in ulcerative colitis [109]. Additional limitations include the heterogeneity of study designs and the variability in terminology used to report perceived loss of biosimilar effectiveness. Most studies were retrospective and many were available only as non-peer-reviewed congress abstracts containing limited details, precluding a more comprehensive analysis. Further studies are ongoing to assess the impact of biosimilar uptake and patient retention, including the observational HYRISS study (NCT05633771) of an adalimumab biosimilar in patients with IBD, which will specifically evaluate the impact of the nocebo effect on discontinuation rates.

5. Conclusion

This review summarizes the rates at which patients undergoing treatment with biosimilar TNF inhibitors for inflammatory diseases switched back to the reference products, and the reasons given for switchback, as based on current literature. The proportion of patients that switched back to the reference product varied across studies; however, most reported relatively low rates of 20% or less. While caution is required when comparing studies due to differences in sample size, study duration, and type, no obvious patterns were observed in switchback rates across the different TNF inhibitors or therapy areas. The rate of switchback increased with length of follow-up, from 7.7% for studies with ≤ 6 months to 27.3% for those with ≥ 24 months, which is broadly similar to patterns observed with the reference products.

There have been few studies of biosimilar switchbacks within the last 10 years, particularly outside of Europe. Due to the potential contribution of the nocebo effect to switchback, improvement of patients' and healthcare professionals' understanding of the effectiveness and safety of biosimilars is of great importance [59,86,93,95]. Structured communication and

shared decision-making strategies may mitigate early, subjective treatment discontinuation [86,95], ensuring that biosimilars continue to contribute to sustainability in healthcare [59].

6. Expert opinion

If a biosimilar is licensed and approved on the basis that it is clinically indistinguishable from the reference biologic, one might predict that there should be no clinical problems when a patient treated with an expensive reference biologic is switched to a less expensive biosimilar: a win–win situation for both patients and their local health economies!

Patients may sometimes request to switchback from a biosimilar to a reference biologic based on their unhappiness with the idea of having being switched from a 'good' expensive drug to one that is cheaper and which they fear may therefore be inferior. The nocebo effect, a 'fear of harm,' is the opposite of the well-known placebo effect and typically manifests with subjective patient-reported (as opposed to objective physician-measured) loss of effectiveness.

A variety of neurobiological, psychosocial, and contextual influences are thought to contribute to the nocebo effect. Patients may develop negative expectations about treatment outcomes due to prior negative experiences – such as having previously experienced adverse effects with similar medications. Alternatively, they may receive negative information from the media, from peers, or even from healthcare professionals. The latter is often inadvertent; for example, outlining the risk of AEs associated with a treatment during the process of obtaining informed consent can, in some cases, be sufficient to trigger the nocebo effect. Interestingly, there was no obvious difference between switchback rates for infliximab, which is administered intravenously, versus etanercept and adalimumab, which are administered subcutaneously and where patients may thus observe differences in administration device or packaging upon being switched to a biosimilar. The absence of a difference in switchback rates may indicate that most clinicians discuss product switches with their patients beforehand.

The neurobiological mechanisms underlying the nocebo effect are less well characterized than those of the placebo effect. However, the nocebo effect has been associated with changes in brain activity as well as with alterations in neuroimmune interactions; and with changes in the activity of the opioid, endocannabinoid, and dopamine neurotransmitter systems. Such changes confirm that the nocebo effect has a neurophysiological basis, as opposed to being solely a psychological phenomenon.

The nocebo effect is likely to play a greater role during the first months after a therapy switch, before patients have become accustomed to the new treatment. Later switchbacks may be more likely driven by a genuine loss of therapeutic effect or objectively measurable changes in disease activity that develop over time. This temporal distinction between an early, predominantly psychologically mediated switchback and a later, potentially pharmacologically driven switchback has rarely been examined systematically and warrants further research.

Immunogenicity is a potential concern with biosimilars, as subtle changes in structure, such as differences in glycosylation patterns due to differences in the expression systems used in manufacture, can in principle introduce differences between the biosimilar and reference biologic. These differences may impact the immunogenicity of the biosimilar, which may in turn impact efficacy or rates of AEs for a minority of individuals, without causing clinically significant differences between the biosimilar and its reference product at the population level [110,111]. As clinical trials of biosimilars are less extensive than those of reference biologics, data from post-marketing real-world studies of biosimilars are mandatory to detect signals that might indicate problems when patients switch between a reference biologic and a biosimilar. It is reassuring that this review on biosimilar switchback for biologics inhibiting TNF-alpha has not identified any major objective issues, such as new immunogenicity or allergic reactions, and that overall, the number of patients requiring a switchback is relatively low, with no specific issues for individual drugs or diseases. This suggests that a key factor contributing to switchback is likely to be a nocebo response, rather than a true pharmacological event. As such, this review reinforces the need for appropriate education of both patients and healthcare professionals to minimize the nocebo effect and maximize the benefit to healthcare economies of moving to lower cost, yet equally effective, biosimilar drugs.

It is important to acknowledge that real-world switchback behaviors may be influenced by between-region differences in healthcare financing systems, tender structures, substitution rules, and patient co-payment models. Tender decisions that favor the reference biologic have the potential to lead to switchback, but we did not identify any studies reporting this as a major trigger. By contrast, switching from one biosimilar to another biosimilar of the same reference product is common, likely due to tender outcomes and varying product availability.

Over the next 5 years, biosimilar use is set to extend much further, as additional biosimilars are produced and further reference biologics come off patent. These developments may stimulate competition and reduce acquisition costs – providing the opportunity for more patients in more countries to benefit from these highly effective treatments. Furthermore, as the cost of biologics continues to decline with the expansion of the biosimilar market, there is potential for improved access to biologic therapies in orphan conditions, such as Behçet's, that would otherwise face prohibitive biologic costs.

Finally, we also anticipate the removal of the requirement for clinical comparative efficacy studies, which would streamline the biosimilar development process, potentially enabling the development of more biosimilars across a broad range of reference biologics and indications, which may ultimately drive more timely patient access to biologics. Advancements in analytical technologies, coupled with almost three decades of experience in biosimilar development, have shown that analytical and clinical pharmacokinetic studies are more sensitive at identifying relevant differences between a biosimilar and its reference medicine than comparative efficacy studies [112]. Work to refine the biosimilar development pathway has already begun, with the EMA initiating

efforts toward future guidelines in 2024, which may include the option for streamlined biosimilar development [113].

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Author contributions

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I Brückmann is an employee of Sandoz.

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