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REVIEW

Nonmedical Switching From Originators to Biosimilars: Does the Nocebo Effect Explain Treatment Failures and Adverse Events in Rheumatology and Gastroenterology?

Roy Fleischmann · Vipul Jairath · Eduardo Mysler · Dave Nicholls · Paul Declerck

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ABSTRACT

The act of nonmedical switching, defined as switching stable patients who are generally doing well with their current therapy from an originator biologic to its biosimilar, has been endorsed as a reasonable treatment strategy. The safety and efficacy of nonmedical switching have been evaluated in randomized controlled and real-world evidence studies, which have demonstrated that although many patients maintain treatment response after the switch, some patients experience therapy failure, resulting in therapy discontinuation. It has been postulated that the vast majority, if not all, of these treatment failures result from a "nocebo effect", defined as patients' negative expectations toward the therapy change. Reports suggest that the risk of a nocebo effect is higher following a mandated nonmedical switch. Although the nocebo effect is a well-recognized phenomenon in pain studies, evidence is limited in immune-mediated diseases primarily because it is difficult to quantify, especially retrospectively. In spite of this, numerous biosimilar studies in patients with immune-mediated diseases have concluded that nonmedical switching failures are due to a nocebo effect. The objective of this narrative review was to explore the reasons for nonmedical switch failure or discontinuation and the role of the nocebo effect among patients with inflammatory rheumatic and gastrointestinal diseases who switched from an originator biologic to its biosimilar.

Keywords: Biosimilar; Nocebo; Nonmedical switch; TNF inhibitor

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R. Fleischmann (✉)
University of Texas Southwestern Medical Center, Metropleac Clinical Research Center, 8144 Walnut Hill Lane, Dallas, TX 75231, USA
e-mail: rfleischmann@arthdocs.com

V. Jairath
Division of Gastroenterology, Departments of Medicine, Epidemiology and Biostatistics, University Hospital, Western University, Room A10-228, London, ON, Canada

E. Mysler
Organización Médica de Investigación, Callao 384 Piso 2 Dto 6, CABA, C1022AAQ Buenos Aires, Argentina

D. Nicholls
Coast Joint Care, University of the Sunshine Coast, Maroochy Waters Shopping Centre, Denna Street, Maroochydore, QLD 4558, Australia

P. Declerck
University of Leuven, Campus Gasthuisberg O&N 2, Herestraat 49, P.B. 820, 3000 Leuven, Belgium

Key Summary Points

This article explores the possibility that a nocebo effect may be a contributing factor for loss of efficacy and/or adverse outcomes following a nonmedical switch from an originator biologic to its biosimilar.

The reviewed evidence suggests that some patients who lose efficacy or have an adverse event after a nonmedical switch to a biosimilar may regain treatment control by switching back to the originator therapy.

Overall, more robust and well-designed nonmedical switching studies are needed to evaluate the impact of the nocebo effect.

Patient education may help minimize misconceptions about therapy changes and prevent or reduce nocebo effect.

Based on the current evidence, patients who switch to a biosimilar and lose treatment response or experience an adverse event should have the right to reestablish therapy with the originator, taking into consideration any associated potential immunogenic risks.

INTRODUCTION

The introduction of biologic therapies has resulted in substantial benefits in the treatment of chronic immune-mediated inflammatory diseases (IMIDs) such as rheumatoid arthritis (RA) and inflammatory bowel diseases (IBDs) [1, 2]. The recent introduction of biosimilars, biologic therapeutics that are highly similar but not identical to their respective originator biologic products [3, 4], has changed the treatment landscape of chronic IMIDs by providing patients with additional, presumably more accessible, therapeutic options [5]. The demonstration of biosimilarity does not require all aspects of the biosimilar and originator products to be identical; however, biosimilars undergo a rigorous comparative preapproval testing process, with approval based on the totality of the resulting evidence that shows a high degree of similarity between the originator and biosimilar [3, 4]. Multiple reports from head-to-head trials in rheumatic diseases have demonstrated that treatment of biologic-naive patients with either an originator biologic or its biosimilar resulted in generally similar efficacy and safety profiles. Approximately 70% of patients achieved a predefined clinical response on the primary efficacy endpoints (usually an American College of Rheumatology 20% improvement response [ACR20] [6]) with both the originator and the biosimilar [7–10]. Of note, biosimilar clinical trials are powered for efficacy; safety or immunogenicity has not been a primary endpoint in any biosimilar clinical trial with most of them having no more than 350 patients per arm.

In some countries and among some payers, the act of nonmedical switching from an originator product to its biosimilar (or vice versa) has been mandated as a treatment strategy in patients who are stable and generally doing well with the originator biologic [11–14]. Nonmedical switching is often driven by economic reasons [2, 5], and the practice has been deemed reasonable in patients with IMIDs based on several tumor necrosis factor (TNF) inhibitor studies [14–16]. However, there has been criticism of these studies for not being properly controlled and failing to include well-defined, meaningful endpoints [17]. The key study supporting nonmedical switching is NOR-SWITCH, a Norwegian nationwide randomized controlled trial (RCT) that investigated switching from the originator infliximab to its biosimilar CT-P13 versus continued use of the originator in patients with stable control of IMID for a minimum of 6 months. The primary endpoint was the noninferiority of switching compared with not switching as assessed by disease worsening not more than 30% in the pooled cohort of six IMIDs (32% with Crohn's disease, 19% with ulcerative colitis, 19% with spondyloarthritis, 16% with rheumatoid arthritis, 7% with chronic plaque psoriasis, and 6% with psoriatic

arthritis). The overall discontinuation rates were similar between patients who switched and those who did not (8% vs. 10%; Fig. 1a), and disease worsening rates fell within the prespecified noninferiority margin of 15% in the pooled analysis (26% for patients who continued on originator and 30% for those who switched) [14]. Although the study was not powered to show noninferiority in individual diseases, five out of the six IMID cohorts did not meet the prespecified non-inferiority margin for disease worsening; a critical appraisal of the design issues and difficulties in interpreting the NOR-SWITCH study has been published elsewhere [18]. In several other RCT switching studies, similar discontinuation rates were generally observed between non-switch and switch groups among biologic-naive patients who were failing methotrexate (Fig. 1a) [15, 16, 19–22].

The safety and efficacy of nonmedical switching have also been investigated in several real-world evidence (RWE) studies of infliximab and etanercept [11, 13, 23–26]. Although these studies generally reported favorable outcomes, higher risk of failure or treatment withdrawal was observed in some of these studies among patients who switched compared with those who continued the originator therapy [11, 13, 26]. Of interest, several studies allowed switchback to the originator therapy after nonmedical switch failure and demonstrated that patients often regain efficacy or experience resolution of adverse events after resuming the originator therapy [27–29]. These findings suggest that some patients do not maintain treatment response following a nonmedical switch, leading to higher discontinuation rates than would be expected without a switch. However, the reasons for these failures have not been well investigated.

NOCEBO EFFECT

It has been suggested that treatment failure following a nonmedical switch results from a "nocebo effect" [28]. The nocebo effect was first described in the 1960s and is defined as a negative outcome or failure of therapy (e.g., disease worsening or occurrence of a new or worsening adverse event) resulting from a patient's negative expectations toward a new therapy or a change in therapy [30]. Although most research into this effect has been done in the area of pain [31], the nocebo effect has also been reported in clinical drug trials and clinical practice in patients with other diseases [31, 32]. Reports have demonstrated that disclosure of potential side effects of a therapy may result in occurrence of that effect, independent of the pharmacologic characteristics of the drug [31]. Switching therapies may also negatively impact medication adherence and could be associated with poorer clinical outcomes [32]. In some instances, although initial cost savings were achieved with switching, the total overall cost of care increased because of increased physician visits or hospitalizations [32]. The nocebo effect can be influenced by the manner in which information is presented to the patient. Communication between the physician and patient can play a major role in the patient's treatment expectations and, consequently, have either a positive or a negative impact on the outcome of medical therapy [33, 34]. In contrast, a positive consequence, or placebo effect, is the more well-known aspect of the phenomenon that results when a patient expects, and therefore experiences, a positive outcome, even with a sham treatment [35].

Treatment discontinuations among patients who undergo nonmedical switch from an originator TNF inhibitor to its biosimilar and subsequent failure to maintain treatment response or experience an adverse event could be explained by the nocebo effect in many instances. This has been reported particularly following a mandated nonmedical switch in stable patients who had been doing well with their previous therapy [11, 36–39]. However, the current evidence regarding this is limited, as it is difficult to identify or quantify, especially retrospectively. RWE studies often lack adequate design (such as lack of control groups and high heterogeneity across patient populations and trials) and do not collect all the data needed to assess the reasons for treatment failure (i.e., whether it was due to the disease course or the nonmedical switch from the originator to the biosimilar). Furthermore, the definition of

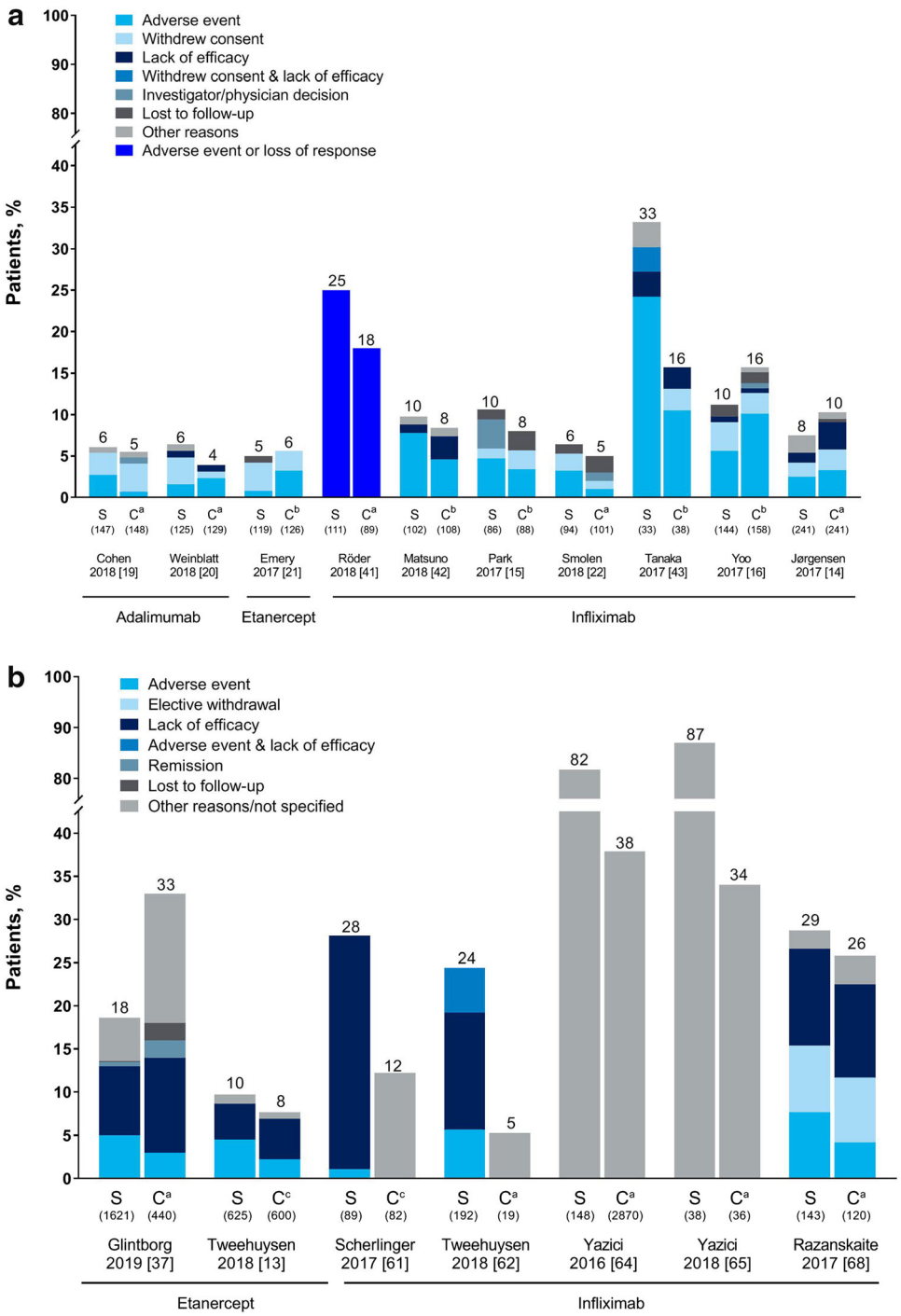

Fig. 1 Proportion of patients who discontinued therapy after switch from the originator therapy to biosimilar (switch group) versus the control group in **a** randomized controlled trials and **b** real-world evidence studies. [a]Control group consisted of patients who continued on originator therapy. [b]Control group consisted of patients who continued on biosimilar therapy. [c]Control group consisted of historical cohort. *C* control group, *S* switch group

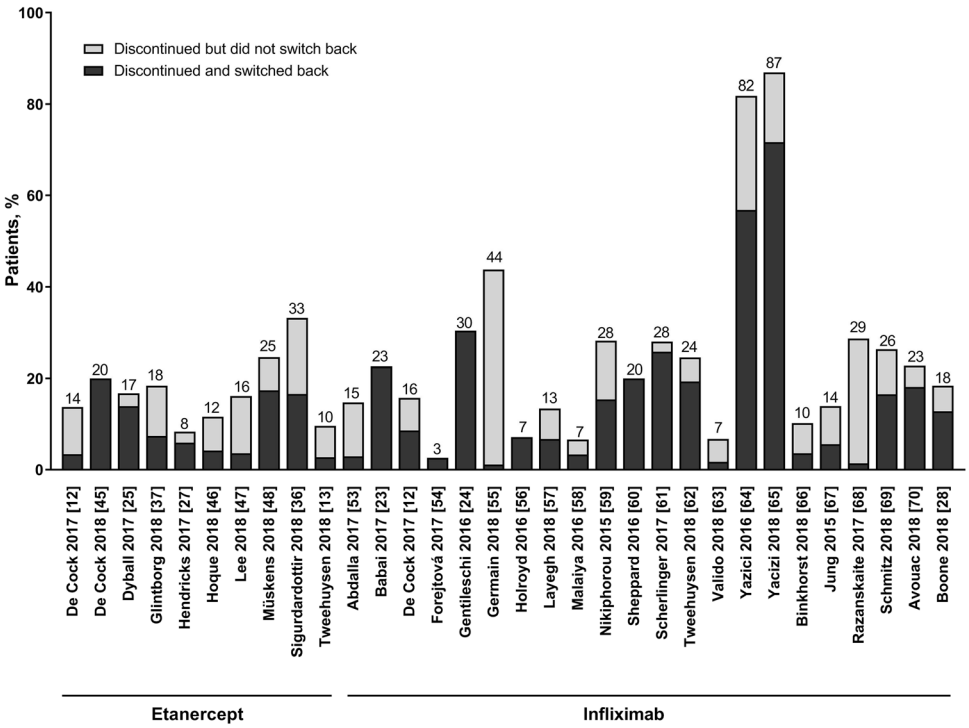

Fig. 2 Proportion of patients in real-world evidence studies who discontinued biosimilar therapy after nonmedical switch from the originator therapy by those who did and did not switch back to originator

flare can be problematic. In patients with RA, for example, a definition of a flare can be assessed either by clinical disease activity or by patient-reported outcomes, and different definitions of flare with varying levels of sensitivity/specificity and validation have been used across trials. To assess clinical disease activity, at a minimum, the patient should be evaluated via a 28-joint count, an inflammatory marker (e.g., C-reactive protein), and possibly an ultrasound evaluation of the joints to evaluate subclinical joint inflammation; however, these metrics were not uniformly obtained in the controlled clinical trials, let alone RWE studies. A recent critique of the DANBIO registry highlighted some of the methodological defects of a mandatory nonmedical switching study that limited the evidence and suggested that the results cannot be translated to carry out nonmedical switching in clinical practice [40].

To explore the possibility of a nocebo effect following a nonmedical switch between an originator TNF inhibitor and its biosimilar, we assessed the current evidence from existing RCTs and RWE studies (from both published articles and congress abstracts) that investigated nonmedical switching from originators infliximab, etanercept, and adalimumab to their respective biosimilars in patients with rheumatic or gastrointestinal IMIDs. Because no validated metric exists to detect a nocebo effect, we used discontinuation data and rate of switching back to the originator biologic after the switch as surrogate indicators of treatment failure following a nonmedical switch.

LITERATURE SEARCH

A literature search of databases, including Embase® and MEDLINE®, was performed to identify nonmedical switching studies. The search was limited to English language, humans, and publication dates from January 1, 2012, to February 21, 2019; both original papers and congress abstracts were included. Studies were included if they fulfilled the following inclusion criteria: investigated switch from an

originator TNF inhibitor to its biosimilar in patients with rheumatic or gastrointestinal IMIDs and reported either discontinuation data for RCTs or switchback data for RWE studies. Switchback data were defined as percentage of patients who switched back to the originator after a failure of a nonmedical switch from the originator to its biosimilar. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

DISCONTINUATION FOLLOWING A NONMEDICAL SWITCH

A total of ten RCTs (adalimumab, two studies; etanercept, one study; infliximab, seven studies) [14–16, 19–22, 41–43] and 37 RWE studies (etanercept, 15 studies; infliximab, 22 studies [one study reported data separately for infliximab and etanercept and was counted twice]) [12, 13, 23–25, 27, 28, 36, 37, 44–70] in patients with rheumatic or gastrointestinal IMIDs were identified (Table 1).

In the RCTs, discontinuation rates ranged from 5 to 33% in the switch groups and from 4 to 18% in the control group (Fig. 1a). Adverse events and withdrawal of consent were generally the most commonly reported reasons for discontinuation. The discontinuation rates were similar between the switch and control groups with the exception of one study that reported high discontinuation rate for the switch group (33%) versus the control group (16%) [43].

Among the RWE studies, discontinuation rates after the nonmedical switch also varied widely, ranging from 3 to 87% (median, 22%) among the 22 infliximab studies and from 8 to 33% (median, 17%) among the ten etanercept studies (Table 2). In general, the discontinuation rates in the rheumatic disease studies varied more widely (median [range], 18% [3–87%]) compared with the IBD studies (20% [10–29%]); however, only four IBD studies were assessed compared with 26 rheumatic disease studies (Table 2).

Seven RWE studies included a control group [13, 37, 61, 62, 64, 65, 68]; of these, notably greater proportions of patients in the switch groups discontinued therapy in four studies (range, 24–87%) compared with the control groups (range, 5–38%; Fig. 1b) [61, 62, 64, 65]. In the remaining three studies, the discontinuation rates were either similar between the groups (10% vs. 8% and 29% vs. 26%) or lower in the switch group versus the control group (18% vs. 33%) [13, 37, 68]. In the latter study (DANBIO), the switchers in general had lower disease activity at baseline and received concomitant methotrexate more frequently than non-switchers [37]. When compared with the historic cohort, the baseline characteristics were similar to the switchers, while the 1-year crude retention rate was lower among the switchers (82%) versus the historic cohort (88%) [37].

The most commonly reported reasons for biosimilar discontinuation in the RWE studies included loss of response/inefficacy, adverse events, or subjective reasons/nocebo effect. However, based on the information provided, it is impossible to distinguish whether the loss of efficacy or adverse events that led to discontinuation were caused by the pharmacologic activity, or lack thereof, of the biologic itself or by switching-related factors such as a nocebo effect. The rationale for attributing these discontinuations to subjective reasons or nocebo effect was based on the patients' use of subjective complaints (typically described as the patients subjectively feeling worse without objective deterioration of disease activity), rather than objective measures of worsening. However, subjective patient-reported complaints are demonstrated to be as valid as objective measures in determining whether a medication differs from placebo and are equally important in assessing therapy success in patients with RA [71]. Appropriately designed studies have not yet been performed and are needed in the future to assess the exact reasons for discontinuation and the potential contribution of the nocebo effect to discontinuation rates. Studies, if any, assessing the way to prevent the nocebo effect or its success have not been published.

It is noteworthy that discontinuation rates in historical controls may include not only stable patients who have received the originator for at least 1 year but also patients who have

Table 1 Summary of RCT and RWE studies assessing a nonmedical switch from an originator biologic to its biosimilar reporting discontinuation data

Study	Biosimilar (study name)	Population	Patients in switch group, *n*	Remission/disease activity at time of switch	Baseline and patient characteristics
RCTs					
Adalimumab					
Cohen et al. [19]	BI 695501 (VOLTAIRE-RA)	Rheum	147	NR	Duration on originator: 24 weeks Conmeds: MTX (100%); OCS and NSAIDs allowed
Weinblatt et al. [20]	SB5	Rheum	125	Mean DAS28(ESR): 3.7	Mean age: 52 years Female: 84% Mean disease duration: 5 years Duration on originator: 24 weeks Conmeds: MTX (100%)
Etanercept					
Emery et al. [21]	SB4	Rheum	119	ACR20: 82%	Mean age: 52 years Female: 84% Mean disease duration: 6 years Duration on originator: 52 weeks Conmeds: MTX (100%)
Infliximab					
Röder et al. [41]	CT-P13	IBD	111	Remission: 83%	Mean age: 37 years Female: 47%
Matsuno et al. [42]	NI-071	Rheum	102	Mean DAS28(ESR): 6.0 Mean DAS28(CRP): 5.1	Mean age: 54 years Female: 83% Duration of disease: < 3 to ≥ 10 years Conmeds: MTX (100%); CS: 36%
Park et al. [7, 15]	CT-P13 (PLANETAS)	Rheum	86	ASAS20: 76%	Median age: 39 years Female: 14% Duration on originator: 54 weeks Conmeds: OCS and NSAIDs allowed

Table 1 continued

Study	Biosimilar (study name)	Population	Patients in switch group, *n*	Remission/disease activity at time of switch	Baseline and patient characteristics
Smolen et al. [22]	SB2	Rheum	94	ACR20: 71%	Mean age: 53 years Female: 82% Mean disease duration: 6 years Duration on originator: 54 weeks Conmeds: MTX (100%)
Tanaka et al. [43]	CT-P13	Rheum	33	Mean DAS28(ESR): 3.8 Mean DAS28(CRP): 3.0	Mean age: 56 years Female: 79% Mean disease duration: 9 years Duration on originator: 54 weeks Conmeds: MTX (100%); OCS allowed
Yoo et al. [16]	CT-P13 (PLANETRA)	Rheum	144	ACR20: 77%	Median age: 49 years Female: 85% Duration on originator: 54 weeks Conmeds: MTX (100%)
Jørgensen et al. [14]	CT-P13 (NOR-SWITCH)	IMID[a]	240[a]	Median HBI (CD, *n* = 77): 2 Median PMS (UC, *n* = 46): 0 Mean ASDAS (SpA, *n* = 46): 2.1 Mean DAS28 (RA, *n* = 38): 2.2 Mean DAS28(CRP) (PsA, *n* = 16): 2.2	Mean age: 48 years Female: 36% Mean disease duration: 18 years Mean duration on originator: 7 years Conmeds: immunosuppressive (54%); prednisolone (5%)
RWE studies					
Etanercept					
Alten et al. [44][b]	NS	Rheum	2229	NR	NR

Table 1 continued

Study	Biosimilar (study name)	Population	Patients in switch group, *n*	Remission/disease activity at time of switch	Baseline and patient characteristics
De Cock et al. [12][b,c]	SB4	Rheum	29	Median DAS28(CRP): 2.7	Median age: 65 years Female: 72% Median disease duration: 14 years Median duration on originator: 5 years
De Cock et al. [45][b]	NS	Rheum	5	NR	NR
Dyball et al. [25][b]	SB4	Rheum	38	Mean DAS28: 3.1	Mean age: 59 years Female: 69%
Glintborg et al. [37][b]	SB4 (DANBIO)	Rheum	1621	Remission (RA, *n* = 933): 65% Remission (PsA, *n* = 351): 70% Remission (axSpA, *n* = 337): 28%	Median age: 48–61 years Female: 34–74% Median duration on originator: 4–6 years Conmeds: MTX (15–60%)
Hendricks et al. [27][b]	SB4 (DANBIO)	Rheum	85	NR	NR
Hoque et al. [46][b]	NS	Rheum	113	NR	Mean age: 53 years
Lee et al. [47][b]	SB4	Rheum	56	NR	Mean age: 40–57 years Female: 66%
Müskens et al. [48][b]	NS	Rheum	69	Mean DAS28/ASDAS: 3.1	Median duration on originator: 5 years
Patel et al. [49][b]	NS	Rheum	168	NR	NR
Scherlinger et al. [50]	SB4	Rheum	44[d]	Mean DAS28: 2.1	Mean age: 51 years Female: 56% Mean disease duration: 12 years Mean originator use: 4 years Conmeds: csDMARDs, 54%
Shah et al. [51][b]	SB4	Rheum	115	Mean DAS28: 3.0	NR

Table 1 continued

Study	Biosimilar (study name)	Population	Patients in switch group, *n*	Remission/disease activity at time of switch	Baseline and patient characteristics
Sigurdardottir et al. [36][b]	SB4	Rheum	145	NR	NR
Smith et al. [52][b]	SB4	Rheum	217	NR	NR
Tweehuysen et al. [13]	SB4 (BIO-SPAN)	Rheum	625	Median DAS28(CRP): 1.9 Median BASDAI: 3.1	Mean age: 57 years Female: 55% Median disease duration: 9 years Conmeds: NSAIDs (57%), DMARDs (56%), steroids (9%)
Infliximab					
Abdalla et al. [53]	CT-P13	Rheum	34	Remission: 100%	Mean age: 55 years Female: 50% Mean disease duration: 15 years Median duration on originator: 57 months Conmeds: MTX (35%), steroids (6%)
Babai et al. [23][b]	NS	Rheum	53	NR	NR
De Cock et al. [12][b,c]	CT-P13	Rheum	70	Median DAS28(CRP): 2.7–2.9	Median age: 66–70 years Female: 75–87% Median disease duration: 19–21 years Median duration on originator: 7–8 years
Forejtová et al. [54][b]	CT-P13	Rheum	38	Mean ASDAS: 1.3 Mean BASDAI: 1.7	Mean age: 44 years Female: 16% Mean disease duration: 16 years Mean duration on originator: 86 months Conmeds: DMARDs (11%), steroids (8%)
Gentileschi et al. [24]	CT-P13	Rheum	23	Remission: 100%	Mean duration on originator: 72 months

Table 1 continued

Study	Biosimilar (study name)	Population	Patients in switch group, *n*	Remission/disease activity at time of switch	Baseline and patient characteristics
Germain et al. [55]	CT-P13	Rheum	89	NR	NR
Holroyd et al. [56][b]	CT-P13	Rheum	56	Mean DAS28 (RA, *n* = 29): 3.3 Mean BASDAI (AS, *n* = 14): 3.5	Mean age: 59 years Female: 54% Mean disease duration: 18 years Mean duration on originator: 8 years Conmeds: MTX (63%), other DMARDs (13%)
Layegh et al. [57][b]	CT-P13	Rheum	45	Mean DAS28(ESR): 2.34	Mean age: 65 years Female: 71% Median disease duration: 17 years Conmeds: MTX (69%)
Malaiya et al. [58][b]	CT-P13	Rheum	30	Mean DAS28 (RA, *n* = 18): 3.7 Mean BASDAI (AS, *n* = 7): 4.9 Mean PsARC SJC (PsA, *n* = 5): 12.8	NR
Nikiphorou et al. [59]	CT-P13	Rheum	39	NR	Mean age: 53 years Female: 56% Mean duration on originator: 4 years Conmeds: MTX (79%), other DMARDs (38%), prednisolone (18%)
Sheppard et al. [60][b]	CT-P13	Rheum	25	NR	NR
Scherlinger et al. [61]	CT-P13	Rheum	89	Mean BASDAI (SpA, *n* = 75): 2.0 Mean ASDAS(CRP) (SpA): 1.4 Mean DAS28(CRP) (RA, *n* = 14): 2.1 Remission (RA): 79%	Mean age: 51 years Female: 43% Mean disease duration: 16 years Median originator infusions: 39 Conmeds (RA): MTX (93%) Conmeds (SpA): DMARDs (56%)

Table 1 continued

Study	Biosimilar (study name)	Population	Patients in switch group, *n*	Remission/disease activity at time of switch	Baseline and patient characteristics
Tweehuysen et al. [62]	CT-P13 (BIO-SWITCH)	Rheum	192	Mean DAS28(CRP) (RA, *n* = 75): 2.1 Mean DAS28(CRP) (PsA, *n* = 50): 2.3 Mean BASDAI (AS, *n* = 67): 3.8	Mean age: 55 years Female: 52% Median disease duration: 14 years Median duration on originator: 7 years Conmeds: DMARDs (53%), MTX (41%), NSAIDs (49%), steroids (7%)
Valido et al. [63][b]	CT-P13	Rheum	60	DAS28(CRP) (RA, *n* = 16): 2.4 DAS28(CRP) (PsA, *n* = 8): 1.4 ASDAS (AS, *n* = 36): 1.6	Median age: 53 years Female: 35% Median duration on originator: 8 years Median disease duration: 17 years Conmeds: MTX (68%)
Yazici et al. [64][b]	CT-P13	Rheum	148	NR	Mean age: 44 years Female: 51% Conmeds: MTX (21%), SSZ (14%)
Yazici et al. [65]	CT-P13	Rheum	92	NR	Mean age: 43 years Female: 52% Mean duration on originator: 438 days Conmeds: MTX (32%); steroids (83%); NSAIDs (91%), SSZ (29%)
Binkhorst et al. [66]	CT-P13	IBD	197	NR	Median age: 43 years Female: 51% Conmeds: thiopurines (40%), 5-ASA (17%), MTX (6%), steroids (3%)

Table 1 continued

Study	Biosimilar (study name)	Population	Patients in switch group, *n*	Remission/disease activity at time of switch	Baseline and patient characteristics
Jung et al. [67]	CT-P13	IBD	36	NR	Mean age (CD/UC): 25/34 years Female (CD/UC): 26%/44% Conmeds (CD/UC): 5-ASA (59%/44%), antibiotics (26%/22%), AZA (52%/44%), steroids (11%/22%)
Razanskaite et al. [68]	CT-P13	IBD	143	Median IBD-Control-8: 11	Median age: 39 years Female: 57% Median disease duration: 6 years Median originator infusions: 10 Conmeds: AZA/6-MP (59%), MTX (12%), 5-ASA (8%), steroids (6%)
Schmitz et al. [69]	CT-P13	IBD	133	Remission/mild disease (CD, *n* = 65/UC, *n* = 29): 82%/90%	Median age (CD/UC): 41/49 years Female (CD/UC): 60%/46% Median duration on originator (CD/UC): 53/50 months Conmeds (CD/UC): thiopurines (39%/47%), steroids (5%/4%), thiopurines + steroids (1%/2%), MTX (1%/0%)
Avouac et al. [70]	CT-P13	IMID[e]	260	DAS28 (RA): 3.4 ASDAS (axSpA): 1.8 BASDAI (axSpA): 2.9 HBI (CD): 0.8 PMS (UC): 0.7	Mean age: 47 years Female: 45% Mean disease duration: 15 years Mean duration on originator: 6 years Conmeds: DMARDs (54%), steroids (18%), NSAIDs (15%)

Table 1 continued

Study	Biosimilar (study name)	Population	Patients in switch group, *n*	Remission/disease activity at time of switch	Baseline and patient characteristics
Boone et al. [28]	NS	IMID[f]	125	Median DAS28(ESR) (RA): 3.1 Median DAS28(ESR) (PsA): 4.0 Mean BASDAI (AS): 4.5	Mean age: 46–59 years Female: 30–80% Mean duration on originator: 3–5 years Conmeds: immunosuppressives (0–100%)

5-ASA 5-aminosalicylic acid, *6-MP* 6-mercaptopurine, *ACR20* $\geq$ 20% improvement from baseline in American College of Rheumatology criteria, *AS* ankylosing spondylitis, *ASAS20* 20% improvement in the Assessment of SpondyloArthritis International Society Working Group criteria response, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *axSpA* axial spondyloarthritis, *AZA* azathioprine, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *CD* Crohn's disease, *Conmed* concomitant medication, *CRP* C-reactive protein, *DA* disease activity based on HBI and Simple Colitis Score, *DAS28* 28-joint Disease Activity Score, *DMARD* disease-modifying antirheumatic drug, *ESR* erythrocyte sedimentation rate, *HBI* Harvey-Bradshaw Index, *IBD* inflammatory bowel disease, *IMID* immune-mediated inflammatory disease, *MTX* methotrexate, *NR* not reported, *NS* not specified, *NSAID* nonsteroidal anti-inflammatory drug, *CS* corticosteroid, *PCDAI* Pediatric Crohn's Disease Activity Index, *PMS* partial Mayo score, *PsA* psoriatic arthritis, *PsARC SJC* Psoriatic Arthritis Response Criteria–swollen joint count, *RA* rheumatoid arthritis, *RCT* randomized controlled trial, *Rheum* rheumatic conditions, *RWE* real-world evidence, *SpA* spondyloarthritis, *SSZ* sulfasalazine, *UC* ulcerative colitis

[a] One patient who had been randomized to switch from infliximab originator to biosimilar CT-P13 withdrew consent and did not receive treatment; this patient was counted in neither the switch group nor among those who discontinued from the switch group, presumably because consent withdrawal preceded treatment administration

[b] Congress abstract

[c] Of 511 patients switched from etanercept originator to biosimilar SB4, 6-month follow-up data are available for 29 patients. Of 180 patients switched from infliximab originator to biosimilar CT-P13, 6-month follow-up data are available for 70 patients. Baseline characteristics are for entire switched population for either etanercept (n = 511) or infliximab (n = 180)

[d] Baseline demographics and disease characteristics are for n = 48

[e] axSpA, n = 131; CD, n = 41; RA, n = 31; UC, n = 23; other rheumatic diseases, n = 20; uveitis, n = 8; other, n = 6

[f] CD, n = 73; UC, n = 28; AS, n = 10; RA, n = 9; PsA, n = 5

only recently begun treatment [61]. It has been shown that 12-month retention rates increase incrementally with each subsequent year of treatment in patients receiving etanercept or infliximab with rheumatic or psoriatic diseases [72, 73], suggesting that patients who have received at least 1 year of biologic therapy are less likely to discontinue treatment than patients initiating therapy. Of the RWE studies reviewed here, the median duration on the originator before the nonmedical switch ranged from 4 to 8 years on originator infliximab and 4 to 6 years on originator etanercept (Table 1). Because these patients had largely received originator treatment for at least 1 year, it can be inferred that the discontinuation rates following these patients' nonmedical switch to a biosimilar might be expected to be lower than those reported by any historical comparator group. Interestingly, the discontinuation rates following a nonmedical switch were similar to those newly initiating TNF inhibitor therapy.

Table 2 Discontinuations after switching from an originator to its biosimilar and percentage of patients who switched back to the originator

Study	Elective switch	Follow-up duration	Discontinued after switch, *n*/*N* (%)	Reason for discontinuation, *n* (%)	Switchback overall [among discontinuers], *n*/*N* (%)	Reason for switchback, *n* (%)	Switchback successful, *n*/*N* (%)
Etanercept–Rheum							
Alten et al. [44][b]	NR	3–4 months[a]	NR	NR	320/2229 (14)	NR	NR
De Cock et al. [12][b]	Yes	6 months	4/29 (14)[c]	NR	1/29 (3) [1/4 (25)]	NR[c]	NR
De Cock et al. [45][b]	NR	2 years	1/5 (20)	AEs: 1 (100)	1/5 (20)[d] [1/1 (100)][d]	AEs: 1 (100)	NR
Dyball et al. [25][b]	NR	NR	6/36 (17)	IE: 4 (67) AEs: 2 (33)	5/36 (14) [5/6 (83)]	IE: 4 (80) AEs: 1 (20)	NR
Glintborg et al. [37][b]	No	1 year	299/1621 (18)	IE: 137 (46) AEs: 77 (26) Other/several: 39 (13) Not stated: 29 (10) Death: 9 (3) Remission: 8 (3)	120/1621 (7) [120/299 (40)]	IE: 62 (52) AEs: 47 (39) NR: 11 (9)	Yes: 104 (87) UNK: 16 (13)
Hendricks et al. [27, 94][b]	No	8 months	7/85 (8)	LOE: 5 (71) AEs: 1 (14) LOE + AE: 1 (14)	5/85 (6) [5/7 (71)]	LOE: 3 (60) AEs: 1 (20) LOE + AE: 1 (20)	Yes: 5 (100)
Hoque et al. [46][b]	NR	Mean, 11.5 months	11/94 (12)	NR	4/94 (4) [4/11 (36)]	NR	NR

Table 2 continued

Study	Elective switch	Follow-up duration	Discontinued after switch, *n*/*N* (%)	Reason for discontinuation, *n* (%)	Switchback overall [among discontinuers], *n*/*N* (%)	Reason for switchback, *n* (%)	Switchback successful, *n*/*N* (%)
Lee et al. [47][b]	NR	8 months	9/56 (16)	LOE: 8 (89) AE: 1 (11)	2/56 (4) [2/9 (22)]	NR	NR
Müskens et al. [48][b]	Yes	Median, 307 days	17/69 (25)	NR	12/69 (17) [12/17 (71)]	AEs: 7 (58) LOE + AE: 3 (25) LOE: 2 (17)	NR
Patel et al. [49][b]	NR	NR	NR	NR	18/168 (11)	IE: 11 (61) AE: 7 (39)	Yes: 11 (61) UNK: 6 (33)
Scherlinger et al. [50]	R[e]	NR	NR	NR	3/44 (7)	Flare: 2 (67) Other: 1 (33)	Yes: 3 (100)
Shah et al. [51][b]	NR	4 months	NR	NR	8/115 (7)	AE: 5 (63) Flare: 2 (25) Other: 3 (38)	NR
Sigurdardottir et al. [36][b]	No	544 days	48/145 (33)	Subjective: 24 (50) NR: 24 (50)	24/145 (17) [24/48 (50)]	Subjective: 24 (100)	NR
Smith et al. [52][b]	NR	NR	NR	NR	10/217 (5)	AEs: 5 (50) Flare: 3 (30) AEs + flare: 1 (10) Missing: 1 (10)	8/10 (80) UNK: 2 (20)

Table 2 continued

Study	Elective switch	Follow-up duration	Discontinued after switch, *n*/*N* (%)	Reason for discontinuation, *n* (%)	Switchback overall [among discontinuers], *n*/*N* (%)	Reason for switchback, *n* (%)	Switchback successful, *n*/*N* (%)
Tweehuysen et al. [13]	Yes	6 months	60/625 (10)	AEs: 28 (47) IE: 26 (43) Pregnancy: NR (4) Malignancy: 2 (3) Other: 2 (3)	17/625 (3) [17/60 (28)]	NR	NR
Infliximab–Rheum							
Abdalla et al. [53]	Yes	Mean, 15.8 months	5/34 (15)	Failure: 2 (40) AEs: 1 (20) Subjective: 1 (20) Pregnancy: 1 (20)	1/34 (3) [1/5 (20)]	Subjective: 1 (100)	NR
Babai et al. [23][b]	NR	6 months	12/53 (23)	AEs + LOE partial: 8 (67) AEs + LOE total: 4 (33)	12/53 (23) [12/12 (100)]	AEs + LOE partial: 8 (67) AEs + LOE total: 4 (33)	Yes: 7 (58) UNK: 3 (25)
De Cock et al. [12][b]	Yes	6 months	11/70 (16)[c]	NR	6/70 (9) [6/11 (55)]	NR[c]	NR
Forejtová et al. [54][b]	NR	6 months	1/38 (3)	Subjective: 1 (100)	1/38 (3) [1/1 (100)]	Subjective: 1 (100)	NR
Gentileschi et al. [24]	NR	Mean, 1.7 months	7/23 (30)	LOE: 7 (100)	7/23 (30) [7/7 (100)]	LOE: 7 (100)	Yes: 5 (71)
Germain et al. [55]	NR	Median, 120 weeks	39/89 (44)	NR	1/89 (1)[d] [1/39 (3)][d]	Subjective: 1 (100)	Yes: 1 (100)

Table 2 continued

Study	Elective switch	Follow-up duration	Discontinued after switch, *n*/*N* (%)	Reason for discontinuation, *n* (%)	Switchback overall [among discontinuers], *n*/*N* (%)	Reason for switchback, *n* (%)	Switchback successful, *n*/*N* (%)
Holroyd et al. [56][b]	R[e]	5 months	4/56 (7)	IE: 3 (75) AEs: 1 (25)	4/56 (7) [4/4 (100)]	IE: 3 (75) AEs: 1 (25)	NR
Layegh et al. [57][b]	R[e]	2 years	6/45 (13)	Subjective: 3 (50) Malignancy: 2 (33) IE: 1 (17)	3/45 (7) [3/6 (50)]	Subjective: 3 (100)	NR
Malaiya et al. [58][b]	Yes	3 months	2/30 (7)	Subjective: 1 (50) Medical problem: 1 (50)	1/30 (3) [1/2 (50)]	Subjective: 1 (100)	NR
Nikiphorou et al. [59]	NR	Medium: 11 months	11/39 (28)	Subjective: 6 (55) ADAs: 3 (27) AEs: 2 (18)	6/39 (15) [6/11 (55)]	Subjective: 5 (83) AEs: 1 (17)	NR
Sheppard et al. [60][b]	R[e]	NR	5/25 (20)	AEs: 4 (80) LOE: 1 (20)	5/25 (20) [5/5 (100)]	AEs: 4 (80) LOE: 1 (20)	Yes: 4 (80) UNK: 1 (20)
Scherlinger et al. [61]	R[e]	Medium: 33 weeks	25/89 (28)	LOE: 13 (52) Subjective: 11 (44) AEs: 1 (4)	23/89 (26) [23/25 (92)]	LOE: 11 (48) Subjective: 11 (48) AEs: 1 (4)	Yes: 18 (78)
Tweehuysen et al. [62]	Yes	6 months	47/192 (24)	IE: 26 (55) AEs: 11 (23) IE + AEs: 10 (21)	37/192 (19) [37/47 (79)]	IE: 23 (62) IE + AEs: 8 (22) AEs: 6 (16)	NR
Valido et al. [63][b]	Yes	Mean, 261 days	4/60 (7)	LOE: 3 (75) AEs: 1 (25)	1/60 (2) [1/4 (25)]	NR	NR
Yazici et al. [64][b]	NR	Mean, 9 months	121/148 (82)	NR	84/148 (57) [84/121 (69)]	NR	NR

Table 2 continued

Study	Elective switch	Follow-up duration	Discontinued after switch, *n*/*N* (%)	Reason for discontinuation, *n* (%)	Switchback overall [among discontinuers], *n*/*N* (%)	Reason for switchback, *n* (%)	Switchback successful, *n*/*N* (%)
Yazici et al. [65]	NR	Mean, 15 months	80/92 (87)	NR	66/92 (72) [66/80 (83)]	NR	NR
Infliximab–IBD							
Binkhorst et al. [66]	Yes	2 infusions	20/197 (10)	Drug undetectable: 9 (45) Disease complaint: 3 (15) AEs: 3 (15) Subjective: 2 (10) AEs + other: 3 (15)	7/197 (4) [7/20 (35)]	Disease complaint: 3 (43) AEs: 3 (43) Subjective: 1 (14)	NR
Jung et al. [67]	NR	54 weeks	5/36 (14)	IE: 3 (60) Subjective: 1 (20) AEs: 1 (20)	2/36 (6) [2/5 (40)]	IE: 1 (50) Subjective: 1 (50)	Yes: 1 (50) UNK: 1 (50)
Razanskaite et al. [68]	R[e]	1 year	41/143 (29)	Nonresponse: 16 (39) AEs: 11 (27) Subjective: 11 (27) Pregnancy: 1 (2) Other: 2 (5)	2/143 (1) [2/41 (5)]	Subjective + AEs: 2 (100)	NR

Table 2 continued

Study	Elective switch	Follow-up duration	Discontinued after switch, *n*/*N* (%)	Reason for discontinuation, *n* (%)	Switchback overall [among discontinuers], *n*/*N* (%)	Reason for switchback, *n* (%)	Switchback successful, *n*/*N* (%)
Schmitz et al. [69]	R[e]	1 year	35/133 (26)	AEs: 13 (37) IE: 12 (34) Remission: 5 (14) Other: 3 (9) ADAs: 2 (6)	22/133 (17) [22/35 (63)]	NR	NR
Infliximab–IMID							
Avouac et al. [70]	Yes	Mean, 34 weeks	59/260 (23)	IE[f]: 47 (80) Lost to follow-up: 6 (10) AEs: 5 (8) Pregnancy: 1 (2)	47/260 (18) [47/59 (80)]	NR	NR[f]

Table 2 continued

Study	Elective switch	Follow-up duration	Discontinued after switch, *n*/*N* (%)	Reason for discontinuation, *n* (%)	Switchback overall [among discontinuers], *n*/*N* (%)	Reason for switchback, *n* (%)	Switchback successful, *n*/*N* (%)
Boone et al. [28]	Yes	9 months	23/125 (18)	Nocebo[h]: 16 (70) IE: 7 (30)	16/125 (13) [16/23 (70)]	Nocebo[l]: 16 (100)	Yes: 16 (100)

ADA antidrug antibody, *AE* adverse event, *IBD* inflammatory bowel disease, *IE* inefficacy, *IMID* immune-mediated inflammatory disease, *LOE* loss of efficacy, *NA* not applicable, *NR* not reported, *R* restricted, *Rheum* rheumatic conditions, *UNK* unknown

Subjective reasons were classified as subjective deterioration of disease (patient asked to switch back to originator without objective deterioration of disease or sustaining AEs), elective withdrawal and patient decision to discontinue/switch

[a] In general, patients switched back in 3–4 months (follow-up period not reported)

[b] Congress abstract

[c] Of the 511 (etanercept) and 180 (infliximab) originator-treated patients who switched to biosimilar, follow-up data were available for only 29 and 70 patients, respectively. Reasons for switchback for all seven patients treated with either infliximab or etanercept biosimilar: inefficiency, *n* = 3/7 (43%); AEs, *n* = 2/7 (29%); and missing, *n* = 2/7 (29%)

[d] No details were reported for the remaining 4 patients by De Cock et al. [45] and 38 patients by Germain et al. [55] who discontinued

[e] Patients were switched from originator to biosimilar as part of routine care. All patients received a letter and/or face-to-face consultation explaining the switch and/or urging them to switch. All patients agreed to the change in treatment except in Layegh et al. [57] in which two patients did not agree to switch and remained on originator and Scherlinger et al. [50] in which 6 patients refused to switch

[f] Most discontinuations related to inefficacy were due to deterioration of subjective measures of disease activity, which markedly improved after switchback to the originator therapy; however, further details were not provided

[h] Nocebo was defined as a response in which an unexplained, unfavorable therapeutic effect occurred following nonmedical switch from originator to biosimilar and was reversible after reinitiating the originator

The pooled discontinuation rates after a nonmedical switch were 17% (0–6 months after switch), 25% (6–12 months after switch) and 30% (> 12 months after switch) compared with an overall discontinuation rate of 21, 27, 37, and 50% at 6 months, 1 year, 2 years, and 5 years, respectively, reported with TNF inhibitors [74].

SWITCHBACK TO ORIGINATOR THERAPY

The overall incidence of switchback ranged from 1 to 72% (median, 11%) in the 22 infliximab studies and from 3 to 20% (median, 7%) in the 15 etanercept studies (Table 2). When assessing the rate only among those patients who discontinued therapy, the incidence of switchback ranged from 3 to 100% (median, 59%) among infliximab and etanercept studies; in six studies, 100% of patients who discontinued biosimilar therapy switched back to the originator (Fig. 2) [23, 24, 45, 54, 56, 60].

The reasons postulated for switchback included subjective reasons/nocebo response, loss of response/inefficacy, and adverse events (Table 2). Among the 12 studies that provided data for switchback success, 50 to 100% (median, 80%) of patients successfully resumed originator therapy. Although some reports have suggested that regaining clinical disease control or resolving adverse effects following switchback to the originator therapy was due to reversal of the nocebo effect [11, 28, 59, 61], without adequately controlled studies, other reasons (such as objective loss of efficacy or emergence of adverse events resulting from switch in therapy) cannot be excluded. Overall, these results demonstrate that a reasonable number of patients do not respond to nonmedical switch from originator TNF inhibitor to its biosimilar and switching back to the originator allows a majority of these patients to regain treatment response.

PATIENTS' CHOICE TO SWITCH

Some healthcare systems have introduced practices that involve involuntary switching for nonmedical reasons from originators to their biosimilars. In Europe, pharmacy-level substitution of originators to biosimilars is already possible in Czech Republic, Estonia, Latvia, Poland, Serbia, and Turkey (although physicians can opt out in each country), whereas nonmedical switching is currently allowed in 12 European countries (with or without the treating physician's consent) and the practice is likely to become more widespread in the future [75]. Because forced switching may exacerbate negative patient expectations, we investigated published reports to ascertain whether there are patterns of nonmedical switching failures based on voluntary versus nonvoluntary switching. Among the 37 RWE infliximab and etanercept studies evaluated, 11 allowed patients to choose whether to switch, ten studies did not allow patients to choose or "restricted" their choice, and the remaining 16 studies did not specify whether switching was voluntary (Table 2). In general, infliximab biosimilar discontinuation was numerically higher in the six studies in which it was mandated or patients' choice to switch was restricted (range, 7–29%; median, 23%) compared with the eight studies that allowed patients to choose whether to switch or not (range, 7–24%; median, 16%). A similar pattern was observed in the three etanercept switching studies that mandated or restricted patients' choice to switch (range, 8–33%; median, 18%) compared with the three studies that allowed patients to choose whether to switch (range, 10–25%; median, 14%; Table 2). Similarly, a higher percentage of patients who discontinued therapy switched back to the originator in studies that mandated or restricted choice to switch in the six infliximab (median [range], 78% [5–100%]) and three etanercept (50% [40–71%]) studies compared with the eight infliximab (53% [20–80%]) and three etanercept (28% [25–71%]) studies that allowed patients to choose. However, the rates were still high for patients who could choose.

Although forced switching may intensify negative expectations and contribute to higher discontinuation rates secondary to the possibility of a nocebo effect, it is reasonable to consider that not all discontinuations are due to nocebo effect. As there was no statistical analysis or detailed information on the patients' extent of freedom to choose or refuse to switch, it is difficult to draw any definite conclusion from these reports. Furthermore, one could reasonably postulate that, rather than experiencing a nocebo effect, some patients may have simply experienced a loss of efficacy or an adverse event when switched to a molecule that, although similar, was not identical. Nonetheless, forced switching raises ethical issues, and any nonmedical therapy switch should be conducted only in agreement with the patient and treating physician.

PATIENT EDUCATION

As nocebo effect is shown to be influenced by the nature of communication between a physician and patient, which subsequently can set patient's treatment expectations [33], informed and standardized patient education and sharing of adequate information are vital in making informed decisions regarding nonmedical switch and minimizing misconceptions about therapy changes and biosimilars [76–78]. A recent study assessing knowledge among patients with rheumatic diseases revealed that 65% of all patients and 66% of those receiving a biosimilar did not feel sufficiently informed about biosimilars [79]. In addition, among patients who were switched from the originator to a biosimilar, 38% were either not informed of the switch or were not asked their consent to the switch. This is alarming, especially when considering that understanding what biosimilarity means and receiving adequate information about biosimilars were associated with better biosimilar treatment adherence [79]. However, it should be noted that providing verbal or written communication before a switch may not guarantee positive outcomes, which was observed in the RWE studies reviewed. As reported in multiple studies, patients who were persuaded or urged to switch (i.e., restricted choice) and who received face-to-face consultation and/or written information regarding the switch and the biosimilar before the switch still had a considerably high incidence of discontinuation (7–29%) and switch-back (5–100%) in most of these studies [56, 57, 60, 61, 68, 69, 80]. This may be associated with an erroneous belief that biosimilars are lesser quality or have lower efficacy and safety than their originators [79, 81]. A recent review of nocebo effect following switching from originator TNF inhibitors to their biosimilars proposed the use of a consistent lexicon and language-use guideline, with the goal of ensuring unified communications around biosimilar medications [76]. However, although this approach may unify messaging and reduce miscommunication, it will not address reasons for treatment failure following a nonmedical switch that are not attributable to nocebo effect.

IS IT NOCEBO OR TRUE LOSS OF EFFICACY/ADVERSE EFFECTS?

As we have suggested previously, nocebo effect may explain a considerable number of treatment failures following a nonmedical switch, but one cannot exclude other reasonable explanations for the worsening of disease outcomes or occurrence of adverse events secondary to the switch. Because biologics are complex, micro-heterogeneous molecules that are highly sensitive to changes in both raw materials and manufacturing conditions, differences between biosimilars and their originator products can and do exist [82–84]. Although the clinical effect of these differences are not fully known, it is reasonable to postulate that the differences can cause individuals to respond differently to each molecule and raises the distinct possibility of altered outcomes that cannot be ignored [83, 85]. Potential immunogenic responses should also be acknowledged; because biosimilars are not exact copies of their originators, it has been suggested that switching to a biosimilar may trigger an immunogenic response to subtle differences in epitopes between biosimilar and the originator [4, 84, 86], potentially leading to loss of efficacy or adverse events in

individual patients [85]. Furthermore, some studies have demonstrated that patients who develop an immunogenic response against an originator biologic should not be switched to its biosimilar owing to cross-reactivity and thus a similar loss of treatment response [87–90]. To our knowledge, only one pooled analysis has assessed the associations between immunogenicity and adverse outcomes [85], and future studies are needed to fully assess the implications of immunogenic consequences on efficacy and safety following a nonmedical switch but also responses that go beyond immunogenicity (e.g., nocebo effect).

Currently, the question of whether all patients who develop an adverse event or lose efficacy after a switch to a biosimilar is due to a nocebo effect or differences between the originator and biosimilar cannot be answered owing to lack of well-designed, prospective and properly conducted, blinded clinical trials with appropriate control groups that could accurately investigate this question. In such trials, at minimum, patients should be randomized to groups that continue with the originator biologic, continue with the biosimilar, and switch from the originator to the biosimilar and vice versa multiple times, with a rescue option to use the original therapy in the event of therapeutic failure [91]. In addition, the cause of failure should be judiciously examined. A well-designed nocebo trial should also implement a questionnaire or a training system for physicians and nurses to avoid the nocebo effect. Until reliable evidence from such studies are available, distinguishing whether negative treatment outcomes are due to a nocebo effect versus loss of efficacy or an adverse event simply because they are not taking the same medication will continue to be challenging. For this reason, patients should be involved in the decision to switch. Of note, when physicians approach patients regarding nonmedical switching, one of the first obstacles they face is to explain that the reason for the therapy change is financial and not medical [92]. In addition, major concerns still exist among rheumatologists and gastroenterologists; a survey in the United States found that 84% of physicians did not support a switch involving stable patients [93]. Furthermore, a majority (> 57%) of physicians anticipated negative impacts on efficacy, safety and patient's mental health following a nonmedical switch, supporting the need of well-designed studies to assess the impact of such switches [93].

The limitations of this review include that it was narrative in nature rather than a more rigorous systematic review. The review was restricted to rheumatic diseases and IBD owing to the authors' expertise and because of the limited availability of published, fully peer-reviewed articles. Due to this, we included congress abstracts (including all etanercept RWE studies), which are restricted in the amount of study data that can be reported. Another limitation is that these analyses relied on how the original study authors categorized discontinuations; caution is therefore warranted when interpreting these data.

CONCLUSIONS

The nocebo effect in nonmedical switching from an originator biologic to its biosimilar may be a contributing factor for loss of efficacy or adverse outcomes following the switch but does not explain all failures. Some patients who fail a nonmedical switch may regain treatment control by switching back to the originator therapy. Discontinuation and switchback rates were somewhat higher in studies that did not allow patients to choose whether to switch therapies, suggesting that forced switching may intensify negative expectations and contribute to a higher rate of therapy discontinuation. However, due to the inconsistency and a lack of robustness among the studies conducted to date, it is difficult to estimate the true rate of nocebo response. More well-designed nonmedical switching studies are needed to evaluate the true impact of the nocebo effect.

Although patient education is vital in making informed decisions regarding a treatment switch and minimizing misconceptions about therapy changes, treatment failures have been observed even when consultation and information regarding the switch were provided before switching. This finding suggests that

more emphasis be placed on communication about nonmedical switching in general and allow for the fact that treatment failures may occur following a switch from an originator to a biosimilar irrespective of a nocebo effect. Regardless of whether discontinuation of therapy following a switch is due to the nocebo effect or other causes, the final outcome is an increase in the total cost of care because of increased physician visits or hospitalizations. Thus, better understanding of the causes for discontinuation may help prevent it and ultimately lead to cost reduction. If a nocebo effect is occurring in some patients, strategies are needed to predict or minimize it (e.g., effective patient education) and to separate it from other reasons for which patients may not be responding to the switch. Any decision to switch would be better done in agreement with the patient and their treating physician. Furthermore, based on current evidence, patients who switch and lose treatment response or have an adverse event should have the option to reestablish therapy with the originator. With biosimilars continuing to enter the market, understanding the potential reasons leading to nonmedical switch failures will enable providers to take appropriate steps to lower or prevent them.

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