Drug Discontinuation in Studies Including a Switch From an Originator to a Biosimilar Monoclonal Antibody: A Systematic Literature Review

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ABSTRACT

Purpose: In observational studies of patients switched from stable treatment with an originator monoclonal antibody (mAb) to a biosimilar, higher rates of biosimilar discontinuation versus those observed in blinded switching studies have been reported. Because this observation relates to the real-world setting, it has been suggested that switching outside of clinical trials may be associated with nocebo effects. However, real-world data on drug discontinuation and nocebo effects after switching to mAb biosimilars remain limited. This systematic review collated information from switching studies regarding discontinuation rates of biosimilar mAbs and investigated the subjectivity of reasons for discontinuation to determine the impact of potential nocebo responses.

Methods: MEDLINE (via PubMed), EMBASE, Cochrane Library, and abstract databases of selected congresses were screened for reports of mAb switching studies with a minimum post-switch follow-up ≥6 months and accessible information on discontinuation rates.

Findings: A total of 14 observational studies were included, all of which involved a switch to CT-P13. Ten interventional studies involving a switch to other biosimilar mAbs were excluded from the analysis because nocebo effects relate to the observational setting only. Eleven studies (78.6%) reported biosimilar discontinuation rates that were higher than expected based on data pertaining to long-term use of the originator infliximab and clinical trials involving a switch to CT-P13 (>10% per year; range, 12.2%—28.2%). Eight studies attributed a proportion of discontinuations to subjective disease worsening or subjective adverse events. Subjective adverse event reports were identified in 7 of the observational studies.

Implications: Discontinuation rates of biosimilar mAbs may increase due to subjective effects after switching from an originator mAb. These findings highlight the need for further patient education and well-designed, observational switching studies as well as the collection and analysis of identifiable pharmacovigilance and postmarketing data of biologics, including biosimilars. The collection of real-world results is particularly pertinent for mAbs other than CT-P13, for which there is currently a lack of observational switching data. (*Clin Ther.* 2019;41:155—173)

Keywords: biologics, biosimilars, nocebo, real-world, switch.

INTRODUCTION

Over the past 2 decades, biopharmaceuticals (or "biologics") have revolutionized treatment options for a wide range of diseases, including cancer and immune-mediated inflammatory diseases. Today, as data exclusivity periods of many biologics have expired or will expire in the coming years,

Accepted for publication November 4, 2018
https://doi.org/10.1016/j.clinthera.2018.11.002
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manufacturers may develop follow-on versions, named "biosimilars," that are similar to their respective "originator"/"innovator" biologic in terms of quality, safety, and efficacy. However, because of difficulties in the reverse engineering process (ie, the high molecular complexity of biologics and the proprietary nature of the originator product's manufacturing process), biosimilars are expected to exhibit minor differences versus the originator biologic due to, for example, divergence in cell lines and purification methods used for manufacturing.[1,2]

Owing to the expected product differences, the European Medicines Agency, the US Food and Drug Administration, and the World Health Organization have issued regulatory guidance documents under which biosimilar candidates are approved based on stringent requirements for head-to-head analytical, nonclinical, and clinical evaluations with the originator biologic.[3–5] The aim of these comparative investigations is to show that product differences do not translate into clinically meaningful differences in efficacy and safety. Under these regulatory principles, a number of biosimilars have been approved for human use and have entered clinical practice. However, there are currently many challenges that limit the clinical uptake of biosimilars, including, but not limited to, a lack of understanding among patients and health care professionals (HCPs) of how biosimilars are developed and approved, concerns over immunogenicity, and divergence in policies on substitution/interchangeability, pricing, and reimbursement of biologics across jurisdictions.[6,7]

In general, there are 3 settings in which biosimilars may be used: (1) for initiation of treatment in patients who have not received previous treatment with the originator product (ie, treatment-naive patients); (2) in clinically stable patients who have received treatment with the originator product but who will be switched to treatment with the biosimilar (ie, treatment-experienced patients); and (3) in patients who have received treatment with a biosimilar but will be switched to treatment with a different biosimilar. In the latter 2 settings, HCPs may have limited information available regarding switching in their specific patient populations, as premarketing studies showing the safety of switching to or between biosimilars are not a requisite for the regulatory approval of biosimilars. As such, it is important to assess the potential consequences of switching in the real-world setting.

Recently, real-world, open-label studies have reported higher-than-expected drug discontinuation rates (>10%) in patients with immune-mediated inflammatory diseases who were switched from stable treatment with the originator infliximab to the biosimilar CT-P13.[8–10] "Expected" discontinuation rates refer to those reported for the following: (1) originator infliximab during long-term, stable treatment; and (2) CT-P13 during the blinded NOR-SWITCH study.[11–14]

Notably, because higher-than-expected discontinuation rates have been reported for biosimilar monoclonal antibodies (mAbs) in the observational setting only, it has been suggested that the increased discontinuation rates are potentially attributable to a "nocebo" effect. The nocebo effect is the negative counterpart of the placebo effect, which, in the context of biologic switching studies, relates to a perceived induction/worsening of symptoms or loss of effect induced by switching to the biosimilar that cannot be attributed to the biosimilar's pharmacologic action.[15] In some cases, the misattribution of symptoms to the change in medication may occur due to patient perceptions that are founded on the aforementioned lack of awareness of how biosimilars are developed and/or communications between patients and HCPs regarding the switch that are unintentionally negative.[16]

Several accounts of the nocebo effect have been reported in the context of switching patients to small-molecule generic drugs.[17,18] However, a clear distinction exists between generic drugs and biosimilars, because biosimilars, by definition, are considered to be similar but not identical to the originator product. As such, data concerning potential nocebo effects cannot be extrapolated from generic switching studies to the field of biologics. Moreover, potential nocebo effects in biosimilar switching studies must be investigated carefully and in their own right because objective treatment effects may also vary between originator and biosimilar products, and it is crucial to avoid confusing such effects with nocebo responses.[19] However, real-world experience with biosimilars of highly complex biologics, such as mAbs, is still limited given that the first biosimilar mAb, CT-P13, was approved only recently (2013 in Europe; 2016 in the United States).

The objective of the current review was therefore to collate available evidence from switching studies to investigate whether: (1) discontinuation rates of

biosimilar mAbs reported in real-world switching studies may be higher than expected based on data pertaining to long-term use (≥3 years) of the originator product and blinded switching studies; and (2) these higher-than-expected discontinuation rates may occur for subjective reasons, potentially indicative of nocebo responses. In addition, available information on educational interventions and decision-making strategies between patients and HCPs was collected to discuss possible approaches that improve patient benefit.

MATERIALS AND METHODS

Study Selection Method

We searched for studies that involved at least 1 treatment switch from an originator therapeutic mAb to a biosimilar thereof. Studies were selected for inclusion if the follow-up period was ≥6 months, drug discontinuation rates could be identified or calculated, and if the mean or median duration of treatment on the originator mAb was disclosed and reported as ≥3 years (ie, patients could be considered stable on the originator therapy and therefore less likely to discontinue treatment irrespective of switching) (Figure 1). Interventional and/or blinded clinical trials were excluded from the analysis as higher-than-expected discontinuation rates have been reported in the observational setting only.

MEDLINE (via PubMed), EMBASE, and the Cochrane Library were searched to identify all indexed reports of relevant studies published up until May 31, 2018 (see Supplemental Table I in the online version at https://doi.org/10.1016/j.clinthera.2018.11.002 for search terms). Only English-language papers were considered for inclusion. Titles and abstracts were screened to determine whether they met the prespecified inclusion criteria listed in Figure 1; full manuscripts of all articles not excluded by title or abstract screening were obtained and reviewed to assess eligibility according to these same criteria. In addition, to identify studies that have not yet been published, abstract databases of selected congresses were hand-searched (see Supplemental Table II in the online version at https://doi.org/10.1016/j.clinthera.2018.11.002 for details).

Bias and Quality Assessment Within Studies

To ascertain validity of the observational studies, bias and methodologic quality of all included studies (including abstracts) was examined by using the validated Downs and Black method, which was modified to accommodate the open-label, observational design of the selected studies.[20] Specifically, 3 questions relating to internal validity (items 14, 23, and 24 concerning randomization and allocation concealment) and 1 question relating to statistical power (item 27) were not applicable due to the unblinded and observational nature of the studies. The quality analysis was performed by a single reviewer and independently verified by a second reviewer.

Data Extraction

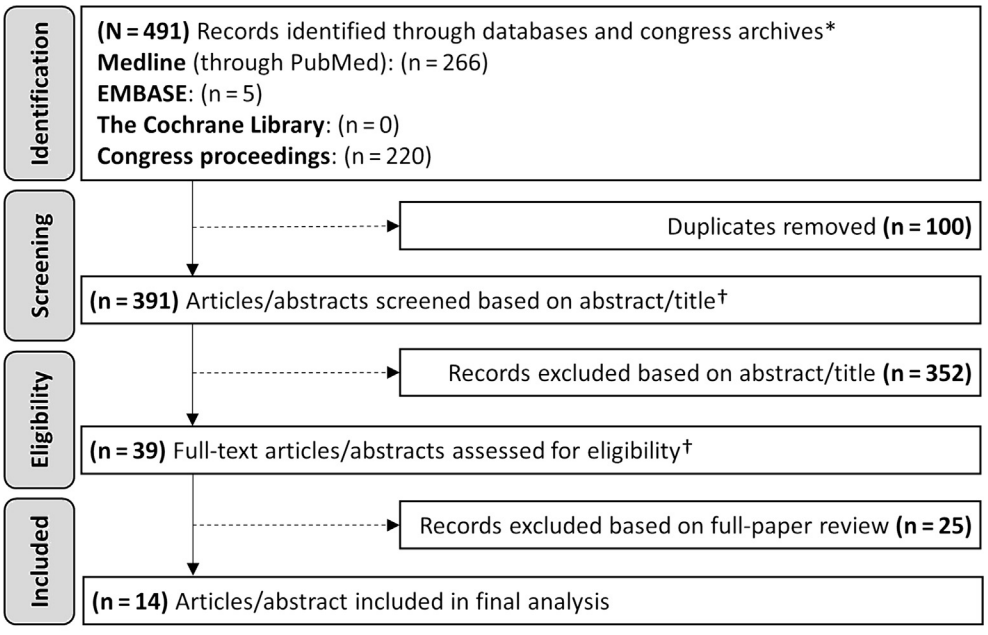
Data extracted from each of the eligible studies included study design, types of intervention, study populations (ie, participants, therapeutic indications, control cohorts, sample size), duration of post-switch follow-up, mean/median duration of pre-switch treatment with the originator mAb, calendar period of the study, biosimilar discontinuation rates, reasons for biosimilar discontinuation, proportion of discontinuations attributed to subjective effects, rates of re-switch to the originator mAb, outcomes after re-switch to the originator mAb, educational interventions, and information concerning patient empowerment or shared decision-making approaches.

Data were extracted by a single reviewer and independently verified by a second reviewer. In cases of disagreement, consensus data were used in the analyses. Author listings and medical centers at which the studies were conducted were analyzed to ensure that there was no extraction of duplicate data from separate study reports.

Summary Measures

To determine whether biosimilar mAb discontinuation rates were "higher than expected," mean/median percentage discontinuation rates reported in the included studies were compared with those reported in studies of: (1) long-term use of the corresponding originator product; and (2) interventional and/or blinded clinical trials involving a switch to the same biosimilar.

Biosimilar mAb discontinuation rates were additionally analyzed per therapeutic indication and according to duration of post-switch follow-up, mean/median duration on originator product treatment, and calendar period of the switch. The



***Limits:**
Database searches: articles published up to May 2018
Congress archive searches: abstracts from congresses up to 2017
†**Exclusion criteria:**
Interventional and/or blinded study; no mAb product; no switching element; review or nonclinical data; case reports (n<20); study in pediatric population; follow-up <6 months; longer follow-up reported elsewhere; treatment duration on originator product is <3 years; not English.
†**Inclusion criteria:**
Unblinded, prospective or retrospective, observational real-world study; study includes a single treatment switch from an originator mAb to its biosimilar; publication states or data allow calculation of discontinuation rate; treatment duration on originator product is ~3 years or more.

Figure 1. Adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram delineating the study inclusion process. mAb = monoclonal antibody.

latter analysis was considered important to account for contemporaneous differences in the availability of other therapies, which can influence discontinuation rates.[13]

Data on subjectivity of reasons behind drug discontinuation were extracted as assessed and reported in respective publications to investigate the impact of potential nocebo effects on biosimilar mAb discontinuation rates. Reported successful outcomes following re-switch to the originator product were assessed to confirm the subjectivity of the biosimilar discontinuation events.

Additional Analyses

An analysis of safety reports was performed to investigate the potential subjectivity of adverse events (AEs) reported in the included switching studies. This analysis included an assessment of the type of AEs reported as well as the incidence of events that can be considered objective (post-switch

antidrug antibody [ADA] development and infusion reactions).

RESULTS

Study Selection and Quality

The search of MEDLINE, EMBASE, and the Cochrane Library identified a total of 271 citations (Figure 1). After adjusting for duplicate reports, 171 citations remained. Of these, 145 studies were discarded because screening of the title and abstract revealed that these publications did not meet the inclusion criteria. The full text of the remaining 26 publications was appraised, and 11 publications met the criteria for inclusion in the review.[8–10,21–28] In total, 10 published, interventional mAb switching studies were not included in the analysis (summarized in Supplemental Table III in the online version at https://doi.org/10.1016/j.clinthera.2018.11.002).[12,29–37] All 11 studies included in the analysis were observational because higher-than-expected discontinuation rates have been reported in the real-world setting only.

An additional 3 studies that met the inclusion criteria were identified by hand-searching abstract databases of key congresses (see Supplemental Resource Congress Abstracts S1–S3 in the online version at https://doi.org/10.1016/j.clinthera.2018.11.002). Five abstracts concerning interventional switching studies were excluded (see Supplemental Table III and Supplemental Resource Congress Abstracts S4–S8 in the online version at https://doi.org/10.1016/j.clinthera.2018.11.002).

The overall quality indices according to the Downs and Black quality analysis for each study ranged from 12 to 22, with a median value of 18 (fair quality) (Figure 2). Only 1 study was considered poor quality (quality index 12), which should be considered when interpreting results of this investigation.

Study Characteristics

A total of 14 studies were identified for inclusion in the review.[8–10,21–28] All of these studies included a single, nonmedical switch from the reference infliximab to the biosimilar infliximab (CT-P13).

Among the 14 included studies (Table I), 2 were observational cohort studies of nationwide registries (DANBIO [Danish Registry for Biological Treatment in Rheumatology] and BSRBR-RA [British Society of Rheumatology Biologics Register for Rheumatoid Arthritis], with 802 and 70 switched patients, respectively) and 3 were multicenter, prospective, observational cohort studies (including 192, 133, and 125 switched patients).[9,10,23,28] The remaining 9 reports were single-center observational studies in patients with various rheumatic diseases (n = 39, 89, 34, 27, and 45), inflammatory bowel disease (IBD; n = 98, 143, and 72), or both rheumatic diseases and IBD (n = 260). Of the 9 single-center studies, only 1 reported a retrospective design.[8,21,22,24–27]

Discontinuation Rates in Real-world Switching Studies

The threshold for considering the biosimilar mAb discontinuation rates "higher than expected" was >10% based on the following rationale:

1. In large registry studies, the discontinuation of the originator infliximab per year was <10% for patients with rheumatoid arthritis (RA) who had been receiving infliximab treatment for ≥3 years.[11,13] Similarly, in a single-center, observational cohort study in 614 consecutive patients with Crohn's disease, yearly discontinuation rates of 7.1% to 10.7% were reported over a median follow-up time of 4.6 years.[14]
2. In the NOR-SWITCH study, a multicenter, 52-week, randomized, double-blind, Phase IV trial that included a switch from the originator infliximab to the biosimilar CT-P13 in patients with immune-mediated inflammatory diseases, discontinuation rates were reported at 10.4% and 7.5% for patients who remained on treatment with the originator product versus those who switched to CT-P13, respectively.[12]

Discontinuation rates of the biosimilar mAb reported in real-world switching studies identified by the literature search ranged from 2.8% to 28.2% (Table I). In 8 of the included studies, the post-switch follow-up period was ~1 year (11–15.8 months).[9,21–23,25,27,28] In these 8 studies, discontinuation rates ranged from 9.7% to 28.2%, with 7 studies reporting a discontinuation rate >10%. These 7 reports may be considered higher than expected based on annual discontinuation rates reported in the NOR-SWITCH study and in studies of long-term originator infliximab use. One study had a follow-up period of 2 years and reported a biosimilar mAb discontinuation rate of 13.3%, which

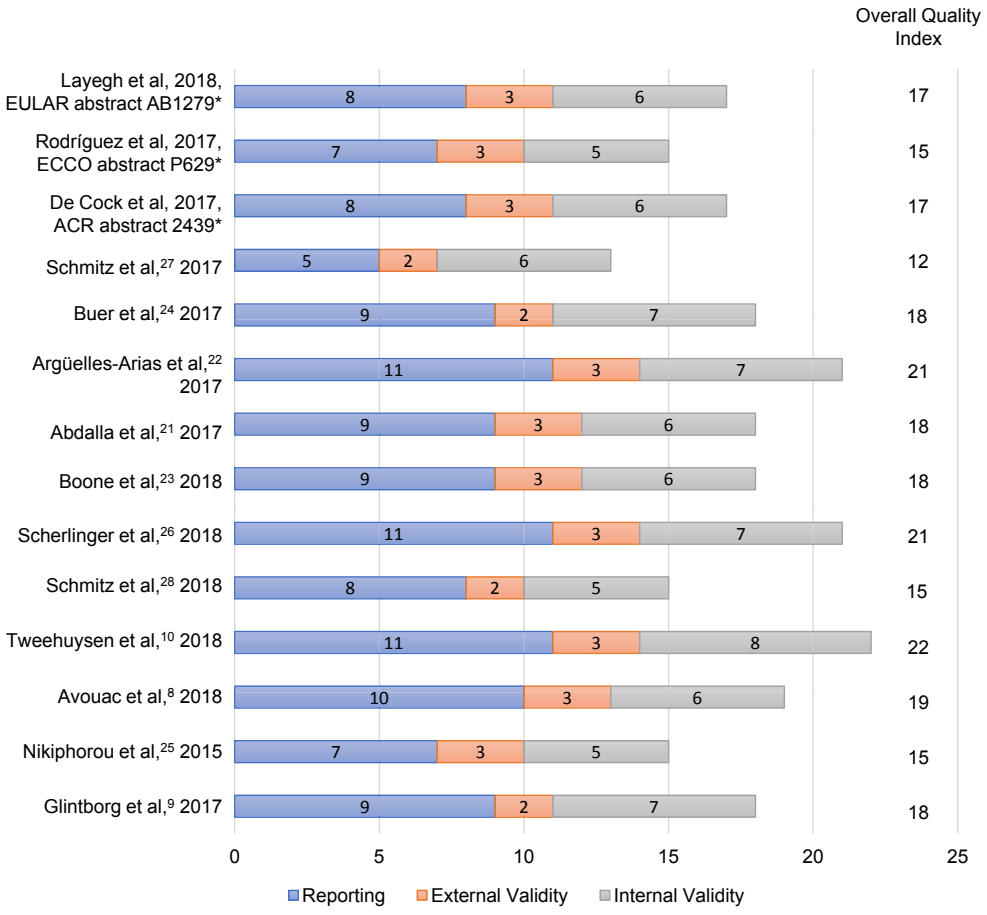


Figure 2. Downs and Black quality scoring of all included studies. An overall quality index (maximum, 24) is provided for each study by calculating the sum of scores for reporting (maximum, 11), external validity (maximum, 3), and internal validity (maximum, 10). Indices ≥20 were considered good, 15 to 19 fair, and ≤14 poor.[20]
ACR = American College of Rheumatology; ECCO = European Crohn's and Colitis Organisation; EULAR = European League Against Rheumatism.
*See Supplemental Resource Congress Abstracts S1 to S3 in the online version at https://doi.org/10.1016/j.clinthera.2018.11.002.

was within the expected range (see Supplemental Resource Congress Abstract S3 in the online version at https://doi.org/10.1016/j.clinthera.2018.11.002). The remaining 5 studies reported a post-switch follow-up time <9 months, and discontinuation rates ranged from 2.8% to 28.1%, with only 1 study reporting a discontinuation rate <10% (2.8%).[8,10,24,26] Therefore, a total of 11 studies (78.6%) reported a higher-than-expected discontinuation rate.

This phenomenon was observed across all immune-mediated inflammatory diseases for which infliximab is approved in the European Union and the United States (RA, ankylosing spondylitis, spondyloarthritis [SpA], psoriatic arthritis, Crohn's disease, and ulcerative colitis). Although the lowest reported discontinuation rates (2.8%−12.2%) were all notably related to patients with IBD (Crohn's disease or ulcerative colitis), this finding was not a consistent observation, with a discontinuation rate of 26.3% reported in the 2018 study by Schmitz et al.[28] With the exception of the 1 study by Layegh et al[38] reporting a discontinuation rate of 13.3% over a 2-year follow-up, biosimilar mAb discontinuation rates were

Table I. Discontinuation rates in real-world studies among patients who were switched from the originator to the biosimilar product.

Reference	Study*	Calendar Period of Study	Prior Originator Treatment Duration	Follow-up Period After Switch	Indication	No. of Patients	Discontinuation Rate, % (No.)
Glintborg et al,[9] 2017	Observational cohort study from a nationwide registry (DANBIO, Denmark)	May 2015—September 2016	6.8 y (mean)	1 y	RA, PsA, AxSpA	802	16.5% (132)
Nikiphorou et al,[25] 2015	Single-center, prospective, observational study in Finland	NR	4.1 y (mean)	11 mo	RA, AS, PsA, JIA, CRA	39	28.2% (11)†
Avouac et al,[8] 2018	Single-center, prospective, observational cohort study in France	October 2015—July 2016	7.4 (RA), 6.7 (AS), 4.7 (CD), 3.1 (UC)	34 wk	RA, SpA, IBD, other	260	23.0% (59)
Tweehuysen et al,[10] 2018	BIO-SWITCH: multicenter, prospective, observational cohort study in the Netherlands	July 2015—December 2015	7.0 y (median)	6 mo	RA, PsA, AS	192	24.5% (47)
Schmitz et al,[28] 2018	Multicenter, prospective, observational cohort study in the Netherlands	NR	4.3 y (median)	1 y	IBD	133	26.3% (35)
Scherlinger et al,[26] 2018	Single-center, prospective, observational cohort study in France	November 2015—October 2016	39 infusions (median)‡	33 wk (median)	RA, SpA	89	28.1% (25)
Boone et al,[23] 2018	Multicenter, prospective, observational cohort study in the Netherlands	July 2016—April 2017	3.9 (CD), 3.5 (UC), 3.6 (RA), 2.9 PsA, 4.6 (AS) y (means)	1 y	IBD, RA, SpA	125	18.4% (23)
Abdalla et al,[21] 2017	Prospective, observational, single-center cohort study in Ireland.	April 2014—August 2015	57 mo (median)	15.8 mo (mean)	RA, AS, PsA, SpA, JIA	34	14.7% (5)
Argüelles-Arias et al,[22] 2017	Prospective, observational, single-center study in Spain	March 2015—February 2016	297 (CD), 203 (UC) wk (median)	1 y	CD, UC	98	12.2% (12)

(*continued on next page*)

Table I. (*Continued*)

Reference	Study*	Calendar Period of Study	Prior Originator Treatment Duration	Follow-up Period After Switch	Indication	No. of Patients	Discontinuation Rate, % (No.)
Buer et al,[24] 2017	Prospective, open-label, single-center study in Norway	September 2015 —April 2016	87 (CD), 57 (UC) mo (median)	6 mo	CD, UC	143	2.8% (4)
Schmitz et al,[27] 2017	Prospective, observational, single-center cohort study in the Netherlands	NR	143 mo (median)	1 y	RA, PsA, AS, SpA, other	27	26% (7)
De Cock et al,[45] 2017, ACR abstract 2439[§]	Observational cohort study from a nationwide British registry	NR	5.3 y (median)	6 mo	RA	70	15.7% (11)
Rodríguez et al, 2017,[42] ECCO abstract P629[§]	Single-center, observational, retrospective study in Spain	NR	51 mo (mean)	1 y	IBD	72	9.7% (7)
Layegh et al,[38] 2018, EULAR abstract AB1279[§]	Single-center, observational cohort study in the Netherlands	July 2015 —January 2018	17 y (median)	2 y	RA, PsA	45	13.3% (6)

ACR = American College of Rheumatology; AS = ankylosing spondylitis; AxSpA = axial spondyloarthritis; CD = Crohn's disease; CRA = chronic reactive arthritis; DANBIO = Danish Registry for Biological Treatment in Rheumatology; ECCO = European Crohn's and Colitis Organisation; EULAR = European League Against Rheumatism; IBD = inflammatory bowel disease; JIA = juvenile idiopathic arthritis; NR = not reported; PsA = psoriatic arthritis; RA = rheumatoid arthritis; UC = ulcerative colitis.

* All studies involved a switch from the originator infliximab to the biosimilar infliximab (CT-P13).

† In 3 of these 11 patients, infliximab antidrug antibodies were found at the test taken before the first CT-P13 infusion and, therefore, CT-P13 was discontinued once the results were available.

‡ Equivalent to ~5.2 years based on median 7-week infusion interval.

§ See Supplemental Resource Congress Abstracts S1 to S3 in the online version at https://doi.org/10.1016/j.clinthera.2018.11.002.

>14.5% in all studies that included patients with rheumatic diseases.

The mean/median duration of treatment with the originator infliximab before switching to CT-P13 varied across studies from 2.9 to 17 years. No clear relationship between duration of originator treatment and discontinuation rate was observed (see Supplemental Figure in the online version at https://doi.org/10.1016/j.clinthera.2018.11.002), and higher-than-expected biosimilar discontinuation rates were reported irrespective of pre-switch treatment duration with the originator infliximab.

The calendar period of the study was reported or could be estimated (based on the date of the switch and length of the follow-up period) in 9 studies.[8–10,21–24,26] Two studies were completed before 2016 and reported biosimilar mAb discontinuation rates of 14.7% and 24.5%.[10,21] An additional 5 studies were conducted in the years 2015 and/or 2016 and reported discontinuation rates of 2.8%, 12.2%, 16.5%, 23.0%, and 28.1%.[8,9,22,24,26] The remaining 2 studies were conducted between 2016–2017 and 2015–2018 and reported discontinuation rates of 18.4% and 13.3%, respectively (see Supplemental Resource Congress Abstract S3 in the online version at https://doi.org/10.1016/j.clinthera.2018.11.002).[23]

Notably, only 3 studies included control cohorts for comparison of discontinuation rates; the remaining studies reported biosimilar mAb discontinuation within the switch cohort only. The study by Scherlinger et al[26] included a historic cohort of 82 patients treated with the originator infliximab and a prospective cohort of 29 treatment-naive patients who had initiated treatment with CT-P13; discontinuation rates reported in these control cohorts were significantly lower than the 28.1% discontinuation rate reported in the switch cohort (12% and 10%, respectively; $P = 0.0002$). In the study by Tweehuysen et al,[10] a control cohort of 19 patients who did not consent to switching and remained on the originator infliximab treatment was used; although discontinuation was reported at 5.2% in the control cohort versus 24.5% in the switch cohort, the control cohort lacked sufficient statistical power for accurate comparison. In contrast, Glintborg et al[9] compared crude and adjusted retention rates of the switch cohort versus a historic cohort treated with the originator infliximab using Cox regression analysis. Although the crude retention rates were similar in the switch and historic cohorts (84.1% and 86.2%), adjusted retention rates differed significantly (86.8% vs 83.4%; $P = 0.03$), corresponding to a significantly higher risk of treatment withdrawal in the switch cohort versus the historic cohort (hazard ratio, 1.31 [1.02–1.68]; $P = 0.03$).

Reasons for Discontinuation and Potential Nocebo Effects

Lack of efficacy and AEs were frequently reported as the reason for discontinuation (Table II). Across the 13 studies that provided reasons for biosimilar mAb discontinuation, lack of effect and AEs collectively accounted for discontinuation rates ranging from 1.4% to 28.1% of the total patient populations.

A subset of studies reported whether the health symptoms reported (loss of effect or AEs) that led to discontinuation were subjective (only perceptible to the patient) or objective (pertaining to the pharmacologic action of the biosimilar mAb) (Table II). Although these studies used heterogeneous approaches for categorization, overall, a considerable proportion of health symptoms could be categorized as subjective, which may be indicative of potential nocebo effects.

Scherlinger et al[26] and Boone et al,[23] respectively, reported that 12.4% and 12.8% of patients discontinued the biosimilar mAb due to subjective loss of effect or subjective AEs. Similarly, Abdalla et al,[21] Schmitz et al,[28] Layegh et al,[38] Nikiphorou et al,[25] and Avouac et al[8] reported that 2.9%, 6.0%, 6.7%, 15.4%, and 18.0% of patients discontinued the biosimilar mAb due to perceived higher disease activity that was not objectified with higher disease activity scores. Furthermore, although Tweehuysen et al[10] did not quantify the rate of subjective discontinuations, it was reported that discontinuation was mainly due to an increase in subjective measures (eg, patients' global assessment of disease activities and/or subjective AEs), suggesting potential nocebo effects and/or incorrect causal attribution effects.

Outcomes After Re-initiation of the Originator mAb

The percentage of patients re-initiating originator infliximab treatment after discontinuation of the biosimilar mAb was reported in 9 of the 14 identified studies and ranged from 2.9% to 25.8% of the total study population, corresponding to 20.0% to 92.0%

Table II. Main reasons for discontinuations, categorization of health complaints (where available), and re-initiation of originator.

Reference	No. of Patients Discontinued/No. Overall Patients	Lack of Effect as Reasons for Discontinuation, No. (%) of Patients*	AEs as Reasons for Discontinuation, No. (%) of Patients*	Switched Back to Originator, No. (%) of Patients*	No. of Patients With Successful Outcome/No. Patients Switched Back
Glintborg et al,[9] 2017	132/802	71 (8.9)	37 (4.6)	NR	NR
Nikiphorou et al,[25] 2015	11/39†	6 (15.4): subjective effects	2 (5.1)	6 (15.4)	NR
Avouac et al[8] 2018	59/260	47 (18): subjective effects	5 (1.9)	47 (18)	42/47
Tweehuysen et al,[10] 2018	47/192	26 (13.5)‡ 10 (5.2): combination AE/lack of effect‡	11 (5.7) • 8 (4.2): subjective effects • 3 (1.5): objective effects	37 (19.3)	NR
Schmitz et al[28] 2018	35/133	12 (9.0) • 8 (6.0): subjective effects • 4 (3.0): objective effects	13 (9.8)	22 (16.5)	NR
Scherlinger et al,[26] 2018	25/89	24 (27.0) • 11 (12.4): subjective effects • 13 (14.6): objective effects	1 (1.1) • 0 (0.0): subjective effects • 1 (2.2): objective effects	23 (25.8)	18/23
Boone et al,[23] 2018	23/125	23 (18.4): combination AE/lack of effect • 16 (12.8): subjective effects • 7 (5.6): objective effects		16 (12.8)	16 (12.8)
Abdalla et al,[21] 2017	5/34	3 (8.8) • 1 (2.9): subjective effects • 2 (5.9): objective effects, sustained secondary failure (pre- and post-switch)	1 (2.9)	1 (2.9)	NR
Argüelles-Arias et al,[22] 2017	12/98	2 (2.0)	5 (5.1)	NR	NR
Buer et al,[24] 2017	4/143	0 (0)	2 (1.4)	NR	NR

Table II. (*Continued*)

Reference	No. of Patients Discontinued/No. Overall Patients	Lack of Effect as Reasons for Discontinuation, No. (%) of Patients*	AEs as Reasons for Discontinuation, No. (%) of Patients*	Switched Back to Originator, No. (%) of Patients*	No. of Patients With Successful Outcome/No. Patients Switched Back
Schmitz et al,[27] 2017	7/27	2 (7.4%) • 1 (3.7): objective effects • 1 (3.7): unknown (DAS28 score not measured)	2 (7.4)	NR	NR
De Cock et al,[45] 2017, ACR Abstract 2439[§]	11/70[‖]	NR	NR	6 (8.6%)	NR
Rodríguez et al, 2017,[42] ECCO Abstract P629[§]	7/72	4 (5.6)	0 (0)	NR	NR
Layegh et al, 2018,[38] EULAR Abstract AB1279[§]	6/45	4 (8.9) • 3 (6.7) subjective effects • 1 (2.2) objective effects	2 (4.4)	3 (6.7)	NR

ACR = American College of Rheumatology; AE = adverse event; DAS28 = Disease Activity Score 28; ECCO = European Crohn's and Colitis Organisation; EULAR = European League Against Rheumatism; NR = not reported.

* Percentage of overall patient population.

† In 3 of these 11 patients, infliximab antidrug antibodies were found at the test taken before the first CT-P13 infusion and, therefore, CT-P13 was discontinued once the results were available.

‡ Although no specific numbers are provided for subjective and objective effects, Tweehuysen et al[10] showed that discontinuation was mainly due to an increase in subjective measures such as tender joint count and patients' global assessment of disease activities.

§ See Supplemental Resource Congress Abstracts S1 to S3 in the online version at https://doi.org/10.1016/j.clinthera.2018.11.002.

‖ Relating to patient population with available 6 months' follow-up data (n = 70); total patient population was N = 180.

of patients who discontinued the biosimilar mAb (Table II). In 3 of these 9 studies, the authors provided information on clinical outcomes following re-initiation of the originator product.

Scherlinger et al[26] reported re-initiation of the originator infliximab in 23 of 25 patients who discontinued the biosimilar; the remaining 2 patients switched to an alternative tumor necrosis factor (TNF)-α inhibitor. The reasons for discontinuation in these 23 patients were as follows: 11 reports of objective clinical worsening (RA, n = 4; SpA, n = 7), 11 reports of subjective clinical worsening (RA, n = 3; SpA, n = 8), and 1 report of mild serum sickness–like disease (RA, n = 1). Initial efficacy was regained after switching back to the originator in 7 of 12 patients with demonstrated disease worsening on the biosimilar mAb and in all 11 patients who requested a re-switch based on perceived disease worsening, giving an overall successful outcome in 78.3% of patients who re-initiated treatment with the originator product. The mild serum sickness–like disease reported for 1 patient persisted after re-switching to the originator, and infliximab was subsequently substituted with another biologic agent with good clinical outcome.

Similarly, Avouac et al[8] reported re-initiation of the originator infliximab in 47 of 59 patients who stopped treatment with the biosimilar mAb (RA, n = 5; axial SpA, n = 33; Crohn's disease, n = 3; uveitis, n = 1; other rheumatic diseases, n = 5); the remaining 12 patients switched to a different biologic agent (n = 7) or remained biologic free (n = 5). Unfortunately, it is not clearly stated whether these 47 patients correspond to the group of patients discontinuing the biosimilar mAb due to subjective disease worsening. After a mean follow-up time of 32.3 weeks following the re-switch, 5 of the 47 patients who re-initiated treatment with the originator product had their treatment interrupted due to secondary lack of efficacy. The remaining 42 patients maintained stable or had improved disease activity scores, giving an overall successful outcome in 89.4% of patients who re-switched to the originator infliximab.

In addition, Boone et al[23] briefly reported that re-switch to the originator infliximab was successful in all of the 16 IBD and rheumatology patients (12.8%) who discontinued treatment for subjective reasons.

Educational Interventions and Shared Decision-Making

Only 5 of the 14 reports provided information on educational/communication strategies related to the treatment switch.

Schmitz et al[28] reported that all patients with IBD received a letter from their gastroenterologist, which explained the treatment switch and highlighted that the biosimilar mAb is considered highly similar to the originator infliximab. Patients were then switched to the biosimilar mAb unless they expressed severe doubts; in these cases, a thorough explanation of the biosimilar concept was provided by the physician that could persuade patients to switch. Similarly, in the study by Layegh et al,[38] all patients were informed of the switch via letter and were later contacted by an HCP for further questions and to confirm whether they agreed to the switch; patients in doubt were advised to contact their treating rheumatologist, and treatment with the biosimilar was initiated once an agreement was met (see Supplemental Resource Congress Abstract S3 in the online version at https://doi.org/10.1016/j.clinthera.2018.11.002). Tweehuysen et al[10] also reported that all patients were informed by letter of the option to switch to the biosimilar mAb; however, patients who did not agree on the switch were able to continue treatment with the originator infliximab without further dialogue.

In contrast, Scherlinger et al[26] reported that all patients were given homogeneous, oral information on the clinical efficacy and safety of biosimilars by the attending physician. The information communicated was agreed upon by all HCPs before initiation of the study. Before switching, patients were informed that they could re-switch to the originator infliximab upon simple request. After giving oral consent, patients began treatment with the biosimilar.

Finally, in the study by Boone et al,[23] patients were switched to the biosimilar mAb on the basis of shared decision-making and patient empowerment. Patients were provided written information on the switch, which delineated the objective of cost reduction and the concept of similar quality, efficacy, and safety between biosimilars and originator products; the information also provided links to additional resources, such as the European Commission's guide

for patients taking biosimilars. Oral clarification was provided by HCPs upon request, and patients providing voluntary informed consent began treatment with the biosimilar mAb.

Notably, all of these studies attributed a proportion of biosimilar mAb discontinuations to subjective effects, suggesting the possibility for residual deficiencies in communication strategies that could lead to potential nocebo effects.

AE Analysis

Post-switch AEs were reported according to type in 11 of the 14 observational switching studies, and AEs that may be considered subjective, including arthralgia, myalgia, fatigue, headache, general malaise, and hyperventilation, were reported in 7 of these studies (Table III). However, similar AEs were also reported frequently in both the switch and control cohorts of the NOR-SWITCH study.

Infusion reaction and ADA development rates, which may be considered more objective events, were reported infrequently in the observational switching studies but did not show an increased trend versus data from the NOR-SWITCH study, in which post-switch ADA development and infusion reactions were reported in 7.9% and 2.0% of patients who switched to CT-P13, respectively.

DISCUSSION

Based on the data presented in the current study, there is evidence supporting the observation of higher-than-expected discontinuation rates of biosimilar mAbs in real-world switching studies. Because these higher discontinuation rates could be attributed, in part, to subjective disease worsening or subjective AEs, this observation may be indicative of potential nocebo effects in mAb switching studies.

All 14 studies included in the analysis involved a single, nonmedical switch to the infliximab biosimilar CT-P13; 10 studies involving a switch to other biosimilar mAbs were identified but not included because they were interventional and, therefore, could not offer information on subjective treatment discontinuation and potential nocebo effects (see Supplemental Table III and Supplemental Resource Congress Abstracts S1–S3 and S5–S8 in the online version at https://doi.org/10.1016/j.clinthera.2018.11.002).[5,8–10,12,21–32,34,36] Although the inclusion of data concerning infliximab only may be considered a limitation of this study, it is important to note that the phenomenon of higher-than-expected discontinuation rates in patients switched from the originator to the biosimilar is not an isolated effect limited to infliximab but has also been observed in real-world studies with etanercept (a fusion protein of the TNF receptor to the constant end of the immunoglobulin G1 antibody). For instance, in a large observational cohort study from the DANBIO registry, 17.0% of a total of 1623 patients with rheumatic diseases who were switched from the originator etanercept to the biosimilar SB4 discontinued SB4 treatment within the first year after the switch (see Supplemental Resource Congress Abstract S9 in the online version at https://doi.org/10.1016/j.clinthera.2018.11.002).

In general, data regarding switching of therapeutic mAbs other than infliximab that are used in other indications (eg, oncology) remain scarce. To date, no data have been reported from real-world switching studies in oncology that would allow investigation of potential nocebo effects relating to anticancer mAb products. As such, in the oncology setting, the consequences of switching between originator mAbs and their respective biosimilar(s) are as yet unknown, and switching to a biosimilar in the concerned patient populations should be considered carefully. Further switching studies in oncology indications may therefore be valuable to dispel concerns relating to switching that may drive treatment discontinuations (eg, potential for immune responses).[39] It is also noteworthy that although studies involving a switch from an originator mAb to a biosimilar was the focus of the current review, no accounts of switching from one biosimilar to another were identified by the literature search, suggesting a need for further data on switching in this field as well.

Furthermore, there are few biosimilar switching studies that aim to directly quantify or assess nocebo responses as a measured outcome. As such, the full impact of nocebo effects on patients who are switched to biosimilar mAbs remains difficult to estimate. In one recently published systematic review, the biosimilar nocebo effect was investigated as a primary topic of focus by comparing discontinuation rates and reasons for discontinuation in observational versus blinded switching studies.[40] Similar to our findings, the authors described biosimilar discontinuation rates in the range of 0.0%–33.3%. However, the subjectivity of reasons for discontinuation was not investigated in detail, and

Table III. Analysis of adverse events (AEs) reported in observational biosimilar monoclonal antibody switching studies.

Reference	Type of AEs Reported	Infusion Reactions, No. (%)*	ADA Development, No. (%)*,†
Glintborg et al,[9] 2017	NR	NR	NR
Nikiphorou et al,[25] 2015	NR	NR	NR
Avouac et al,[8] 2018	Purpura, cholangiocarcinoma, infusion reaction, transitory increased liver enzyme levels‡	1 (0.4)	NR
Tweehuysen et al,[10] 2018	Arthralgia, fatigue, pruritus, myalgia, rash, influenza-like illness	1 (0.5)	2 (1.5)
Schmitz et al,[28] 2018	General malaise, fatigue, arthralgia, skin problems, infusion reaction‡	NR	3 (2.3)
Scherlinger et al,[26] 2018	Infusion reactions (chills, fever), nonserious infections, mild headache	2 (2.2)	NR
Boone et al,[23] 2018	Diminished effect, chills during infusion, numbness of facial skin, tingling limbs, headache§	NR	5 (4.0)
Abdalla et al,[21] 2017	Death, malignancy, tuberculosis, infections, gastroenteritis	1 (2.9)	NR
Argüelles-Arias et al,[22] 2017	Skin reaction, abdominal pain, headache, paresthesia during infusion, Sweet's syndrome, polyarthralgia, palpitations	2 (2.0)	NR
Buer et al,[24] 2017	Infusion reaction, rash, arthralgia, large B-cell lymphoma	5 (3.5)	3 (2.1)
Schmitz et al,[27] 2017	Hyperventilation, suspected vasculitis‡	NR	0 (0)
De Cock et al,[45] 2017, ACR abstract 2439‖	NR	NR	NR
Rodríguez et al,[42] 2017, ECCO abstract P629‖	Mostly infections	NR	NR
Layegh et al,[38] 2018, EULAR abstract AB1279‖	Malignancy‡	NR	NR

ACR = American College of Rheumatology; ADA = antidrug antibody; ECCO = European Crohn's and Colitis Organisation; EULAR = European League Against Rheumatism; NR = not reported.
* Percentage of the total patient population.
† Includes ADAs developed post-switch only.
‡ AEs reported for patients who discontinued treatment only.
§ AEs reported in the "nocebo group" only.
‖ See Supplemental Resource Congress Abstracts S1 to S3 in the online version at https://doi.org/10.1016/j.clinthera.2018.11.002.

variability in clinical follow-up periods and duration of treatment on the originator product were not accounted for. As such, the study provided few data with regard to nocebo responses. In a further systematic review by Numan and Faccin,[41] biosimilar discontinuation rates in switching studies were reported in a broader range of 0%–87%. However, this study also did not consider the influence of follow-up periods and duration of originator treatment and did not assess potential nocebo responses.

Of the 14 CT-P13 studies identified for review, only 3 reported a biosimilar mAb discontinuation rate within the annual, <10% benchmark set by real-world studies of long-term originator infliximab

administration and the blinded NOR-SWITCH study.[11–14] Notably, Buer et al[24] attributed the low 2.8% discontinuation rate in patients with IBD to close clinical follow-up and frequent CT-P13 dose adjustments given as part of a therapeutic drug monitoring (TDM) approach (ie, adjustment of doses according to serum drug and ADA concentrations). Similarly, in the study by Rodríguez et al,[42] dose intensifications were reported for 13.9% of patients with IBD, and the biosimilar mAb discontinuation rate was within the expected range at 9.7% (see Supplemental Resource Congress Abstract S2 in the online version at https://doi.org/10.1016/j.clinthera.2018.11.002). However, dose modifications according to serum infliximab and ADA concentrations were also permitted in the 2018 study by Schmitz et al,[28] in which 26.3% of patients with IBD discontinued treatment with the biosimilar. Furthermore, in the 2017 study by Schmitz et al,[27] a TDM approach was used in patients with rheumatic diseases, yet the biosimilar mAb discontinuation rate was reported at 26.0%. Although the higher-than-expected discontinuation rate reported in the 2018 study by Schmitz et al could be partially attributed to subjective loss of efficacy, Buer et al and Rodríguez et al unfortunately did not discuss subjective effects or any educational/communication interventions used to mitigate such effects. As such, the reason underlying the improved outcome in these 2 switching studies cannot be fully determined. Conversely, Layegh et al[38] did report on patient communication but did not describe any TDM approach. In this study, discontinuation rates were within the expected annual range (13.3% over a 2-year follow-up), yet a proportion of discontinuations were still attributed to subjective effects (see Supplemental Resource Congress Abstract S3 in the online version at https://doi.org/10.1016/j.clinthera.2018.11.002).

In the 11 real-world switching studies that reported biosimilar mAb discontinuation rates above the 10% annual benchmark, higher-than-expected discontinuation rates did not correlate with follow-up period, duration of originator infliximab treatment, therapeutic indication, or calendar period and associated availability of other anti-TNF therapies (eg, European approval of the etanercept biosimilar Benepali® [Biogen, Hillerød, Denmark] in early 2016 and approval of adalimumab biosimilars Imraldi™ [Biogen] and Cyltezo™ [Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, Connecticut] in 2017). However, 7 of these 11 studies attributed a proportion of discontinuations to subjective disease worsening and/or subjective AEs that may indicate potential nocebo responses.[8,10,21,23,25,26,28] The assumption that these discontinuations were related to patients' perceptions of the biosimilar was further supported by the studies of Scherlinger et al[26] and Boone et al,[23] which found an improved outcome after patients reporting subjective effects were re-switched to the originator infliximab. The low number of studies reporting outcomes after re-switch to the originator product may, however, be considered a limitation of this review.

Furthermore, it must be noted that all of the studies included in this review were observational, and few included a control cohort. As such, the data reported herein are subject to a certain amount of inherent bias. Nonetheless, because the feasibility of assessing nocebo responses in the randomized, blinded setting is limited, analysis of potential biosimilar nocebo effects must currently be restricted to observational switching studies only. Although a randomized design for assessing nocebo responses has recently been proposed (a 4-arm study in which 2 arms continue with originator treatment and 2 arms switch to the biosimilar, but only 1 arm from the originator and switch cohorts is given correct information about the treatment they are receiving), the feasibility of such a study is limited due to the need for a proper informed patient consent.[19] In this context, further data from adequately designed observational switching studies are required to fully understand the impact of nocebo effects in patients undergoing a nonmedical switch to a biosimilar mAb. Further real-world data relating to post-switch discontinuations can also be acquired via pharmacovigilance activities. However, in this respect, it must be possible to attribute postmarketing events to the correct product by ensuring that the applicable regulatory guidelines on biologic nomenclature and traceability meet compliance requirements.[43,44]

Based on the potential increase in treatment discontinuations presented herein, the cost savings

when patients are switched to a biosimilar may be substantially smaller than expected, especially when considering the additional costs associated with the practical implementation of the switch. Thus, although the expectation of cost savings is a key driver of biosimilar uptake in clinical practice, it is clear that acceptance of biosimilars at the patient level needs to be addressed to achieve the estimated savings expected from the introduction of biosimilars.

Educational interventions and improved communication with patients have been proposed as methods to address patient concerns relating to biosimilars. However, all of the studies included in this review that reported educational interventions also attributed a proportion of discontinuations to subjective effects, suggesting that more than patient education on biosimilars and voluntary consent are required. Indeed, recommended key strategies to reduce the probability of treatment discontinuation due to nocebo effects include not only educational aspects but also engaging patients in treatment decisions; empowering patients to challenge treatment decisions and to ask questions freely; providing full transparency as to why the treatment is being switched and what the new treatment is; improving education of HCPs on the concepts of biosimilars and nocebo effects; and encouraging communication with patients in a manner that can be easily understood.[16]

For example, in a recent observational study, Tweehuysen et al[46] investigated the impact of different communication strategies by comparing drug persistence rates reported from the 2015 BIO-SWITCH study (involving a switch from the originator infliximab to CT-P13 with no enhanced communication strategy) versus the 2016 BIO-SPAN (BIOsimilar switch, Study on Persistence and role of Attribution and Nocebo) study (involving a switch from the originator etanercept to SB4 plus an enhanced communication strategy) (see Supplemental Resource Congress Abstract S10 in the online version at https://doi.org/10.1016/j.clinthera.2018.11.002). In patients switched to SB4, the enhanced communication included: notifying all patients at the same time; informing that the reasons for the switch were lower costs and fewer injection site reactions; and providing training for rheumatology and pharmacy staff about how to assuage patient concerns and how to respond if a patient has objective or subjective health reports. In the SB4 switch group, which received the enhanced communication, only 16 patients per 100 person-years discontinued biosimilar treatment, compared with 56 of 100 person-years in the CT-P13 switch group. Although the groups were not directly comparable, also because patients in the SB4 group were informed of an expected benefit (fewer injection site reactions), the study highlights the importance of an optimized communication strategy and shared decision-making process.

CONCLUSIONS

Subjective disease worsening and subjective AEs seem to be common contributors to higher-than-expected treatment discontinuation rates after a switch from an originator to a biosimilar mAb. This finding may have potential adverse effects on treatment outcomes. Further collection of real-world evidence from adequately designed switching studies, which aim to assess nocebo responses as a measured outcome, and from fully traceable postmarketing surveillance data is warranted to conclude if nocebo effects affect drug persistence of biosimilar therapeutic mAbs and to determine whether shared decision-making and patient empowerment could reduce the probability of subjective treatment discontinuation after a nonmedical switch to a biosimilar.

ACKNOWLEDGMENTS

Medical writing support was provided by Dr Joanna Hanley (SFL Regulatory Affairs & Scientific Communication) and funded by F. Hoffmann−La Roche Ltd. Dr Hanley provided writing support for the original manuscript draft and supported review, editing and visualization of the manuscript.

Writing - Review & Editing: Dr Bakalos and Dr Zintzaras. Both authors were responsible for the following: conceptualization, methodology, validation, formal analysis, and investigation. Both authors contributed equally to the manuscript and both approved the final article.

CONFLICTS OF INTEREST

Dr. Bakalos is an employee of F. Hoffmann–La Roche Ltd. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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APPENDIX A. SUPPLEMENTARY DATA
Tables

Table S1. Literature search terms

Database searched	Search ID	Search terms	Filter
Pubmed	Search 1	(rituximab OR bevacizumab OR trastuzumab OR infliximab OR adalimumab) AND biosimilar AND (switch* OR transition*)	None
Pubmed	Search 2	biosimilar AND switch AND study	None
Pubmed	Search 3	(originator OR reference) AND biosimilar AND (switch* OR transition*)	None
EMBASE	Search 1	'nocebo effect'/exp AND 'biosimilar agent'/exp	None
Cochrane Library	Search 1	"nocebo effect" (MESH term) + "biosimilar"	None

Table S2. Congresses searched for switching studies

Congress	Search ID	Search terms
ACR/ARHP 2017	Search 1	Switch biosimilar
ACR/ARHP 2017	Search 2	Transition biosimilar
ASCO 2017	Search 1	Biosimilar
ASCO 2018	Search 1	Biosimilar
ASH 2017	Search 1	Switch biosimilar
ASH 2017	Search 2	Transition biosimilar
EHA 2017	Search 1	Switch biosimilar
EHA 2017	Search 2	Transition biosimilar
EHA 2018	Search 1	Switch biosimilar
EHA 2018	Search 2	Transition biosimilar
ESMO 2017	Search 1	Biosimilar
EULAR 2017	Search 1	Biosimilar
EULAR 2018	Search 1	Biosimilar
ICML 2017	Search 1	Biosimilar
SABCS 2017	Search 1	Biosimilar
ECCO 2018	Search 1	Switch biosimilar
ECCO 2018	Search 2	Transition biosimilar

Abbreviations: ACR/ARHP = American College of Rheumatology/Association of Rheumatology Professionals; ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; EHA = European Hematology Association; ECCO = European Crohn's and Colitis Organisation; ESMO = European Society for Medical Oncology; EULAR = European League Against Rheumatism; ICML = International Conference on Malignant Lymphoma; SABSC = San Antonio Breast Cancer Symposium.

Table S3. Overview of excluded interventional mAb switching studies

Reference	Originator mAb	Biosimilar product	Study[a]	Follow-up period after switch	Indication	Patients, n — switched & continued (cont.) treatment cohorts	Discontinuation rate, % (n) — switched vs. continued (cont.) treatment cohorts
Jorgensen 2017	Infliximab	CT-P13	NCT02148640/NOR-SWITCH, randomized, double-blind Phase 4 study	52 wks	CD, UC, SpA, PsA, Ps	Switch: 240 cont. originator: 241	Switch: 7.5% (18) cont. originator: 10.4% (25)
Goll 2017 ACR abst 2800	Infliximab	CT-P13	Open-label extension of randomized, double-blind Phase 4 study NCT02148640/ NOR-SWITCH	26 wks	CD, UC, SpA, PsA, Ps	Switch: 183 cont. biosimilar: 197	Not reported
Park 2017	Infliximab	CT-P13	NCT01571206, open-label extension of randomized, double-blind Phase 1 study NCT01220518/ PLANETAS	48 wks (wks 54—102 post treatment initiation)	AS	Switch: 86 cont. biosimilar: 88	Switch: 8.0% (7) cont. biosimilar: 10.5% (9)
Tanaka 2017	Infliximab	CT-P13	Open-label extension of a randomized, double-blind Phase 1/2 study in Japan	105 wks (wks 62—167 post treatment initiation)	RA	Switch: 33 cont. biosimilar: 38	Switch: 33.3% (11) cont. biosimilar: 15.8% (6)
Yoo 2017	Infliximab	CT-P13	NCT01571219, open-label extension of randomized, double-blind Phase 3 study NCT01217086/ PLANETRA	40 wks	RA	Switch: 144 cont. biosimilar: 158	Switch: 11.1% (16) cont. biosimilar: 15.8% (25)
Smolen 2018	Infliximab	SB2		23 wks (wks 54—78 post	RA	Switch: 94 cont.	Switch: 6.4% (6) cont. biosimilar:

(*continued on next page*)

Table S3. (*Continued*)

Reference	Originator mAb	Biosimilar product	Study[a]	Follow-up period after switch	Indication	Patients, n — switched & continued (cont.) treatment cohorts	Discontinuation rate, % (n) — switched vs. continued (cont.) treatment cohorts
			NCT01936181, randomized, double-blind Phase 3 study	treatment initiation)		biosimilar: 201 cont. originator: 101	7.5% (15) cont. originator: 5.0% (5)
Alten 2018 EULAR abst. FRI0137	Infliximab	PF-06438179 (candidate)	NCT02222493/ REFLECTIONS B537-02, randomized, double-blind Phase 3 study	24 wks (wks 30—54 post treatment initiation)	RA	Switch: 143 cont. biosimilar: 280 cont. originator: 143	Not reported
Papp 2017	Adalimumab	ABP 501	NCT01970488, randomized, double-blind Phase 3 study	36 wks (wks 16—52 post treatment initiation)	Ps	Switch: 77 cont. biosimilar: 152 cont. originator: 79	Switch: 11.7% (9) cont. biosimilar: 12.5% (19) cont. originator: 10.1% (8)
Cohen 2018	Adalimumab	BI 695501	NCT02137226/ VOLTAIRE-RA, randomized, double-blind Phase 3 study	24 wks (wks 24—48 post treatment initiation)	RA	Switch: 147 cont. biosimilar: 298 cont. originator: 148	Switch: 6.1% (9) cont. biosimilar: 5.7% (17) cont. originator: 5.4% (8)
Weinblatt 2018	Adalimumab	SB5	NCT02167139, randomized, double-blind Phase 3 study	28 wks (wks 24—52 post treatment initiation)	RA	Switch: 125 cont. biosimilar: 254 cont. originator: 129	Switch: 6.4% (8) cont. biosimilar: 2.4% (6) cont. originator: 3.9% (5)
Park 2017	Rituximab	CT-P10	NCT01873443, open-label extension of randomized, double-blind Phase 1 study NCT01534884/ Triad RA	32 wks (wks 72—104 post treatment initiation)	RA	Switch: 20 cont. biosimilar: 38	Switch: 15.0% (3) cont. biosimilar: 7.9% (3)
Cohen 2018	Rituximab	PF-05280586 (candidate)	NCT01643928/ REFLECTIONS	25 wks	RA		

Table S3. (*Continued*)

Reference	Originator mAb	Biosimilar product	Study[a]	Follow-up period after switch	Indication	Patients, n — switched & continued (cont.) treatment cohorts	Discontinuation rate, % (n) — switched vs. continued (cont.) treatment cohorts
			B328-04, blind extension of randomized, double-blind Phase 1/2 study NCT01526057			Switch: 126 cont. biosimilar: 59	Switch: 1.6% (2) cont. biosimilar: 10.2% (6)
Shim 2017 ACR abst. 2445	Rituximab	CT-P10	NCT02149121/CT-P10 3.2, randomized, double-blind Phase 3 study	24 wks (wks 48–72 post treatment initiation)	RA	Switch: 109 cont. biosimilar: 122 cont. originator: 64	Not reported
Tony 2017 ACR abst. 2795	Rituximab	GP2013	NCT02514772/ ASSIST-RT, randomized, double-blind Phase 3 study	24 wks	RA	Switch: 53 cont. originator: 54	Switch: 5.7% (3) cont. originator: 3.7% (2)
Von Minckwitz 2017 SABCS abst. P5-20-13	Trastuzumab	ABP 980	NCT01901146/LILAC, randomized, double-blind Phase 3 study	adjuvant period up to 1 year	eBC	Switch: 171 cont. originator: 171	Not Reported

Abbreviations: AS, ankylosing spondylitis; CD, Crohn's disease; CRA, chronic reactive arthritis; eBC, early breast cancer; N/R, not reported; Ps, psoriasis PsA, psoriatic arthritis; RA, rheumatoid arthritis; UC, ulcerative colitis.

[a] Studies were excluded during the literature appraisal based on the exclusion criteria "interventional study" and/or "blinded study".

Figures

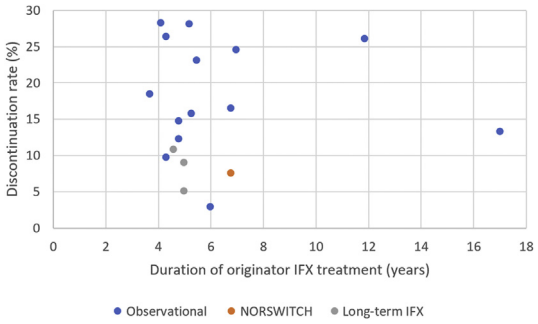

Figure S1. **CT-P13 discontinuation rate vs. duration of pre-switch treatment with originator infliximab.** IFX = infliximab; Observational = 14 observational studies identified by the literature search; NORSWITCH = 52-week, randomized double-blind study involving a switch from originator infliximab to CT-P13; Long-term IFX = observational and registry studies of long-term originator infliximab use. Where identified observational studies reported multiple durations of pre-switch originator IFX treatment (according to therapeutic indication), the mean duration is presented.

Congress Abstract Summaries

Congress abstract S1:

Switching from RA originator to biosimilar in routine clinical care: Early Data from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis.

De Cock D, Kearsley-Fleet L, Watson K et al.

Abstr. 2439, American College of Rheumatology/ Association of Rheumatology Professionals annual meeting. 2017.

Products:

- Originator infliximab and biosimilar CT-P13 sourced from the EU (Remsima) and the US (Inflextra)
- Originator etanercept and biosimilar SB4 (Benepali)

Study design and patients:

- Observational study of 1165 patients with rheumatoid arthritis initiating biosimilar treatments available in the UK.
- Patients were recruited from 03/08/2015 to 10/05/2017, the majority with low disease activity (median DAS28 2.7 (IQR 2.0−3.8)).
- 59% of recruited patients (691/1165) were treatment experienced and switched from the originator product to a respective biosimilar (74% Benepali, 9% Inflectra, 17% Remsima).
- Median (IQR) time on originator treatment before biosimilar switch: 5.3 (2.7−8.8) years.
- Endpoints: disease activity, occurrence of adverse events, changes to treatment.

Results (6-months post-switch)

	Benepali	Inflectra	Remsima
Disease activity			
6 months follow-up data available, n (%)	29 (6%)	38 (61%)	32 (27%)
DAS28 at 6 months	3.1 (2.4; 3.8)	2.6 (2.1; 3.7)	3.2 (2.5; 4.1)
DAS28 change at 6 months	0.0 (−0.3; 0.8)	0.0 (−0.8; 0.4)	0.0 (−0.2; 0.8)
Changes to treatment			
Continued biosimilar	25 (86%)	36 (95%)	23 (72%)
Switched back to originator	1 (3%)	2 (5%)	4 (13%)
Switched to another infliximab biosimilar	—	0 (0%)	4 (13%)
Stopped or switched to alternative treatment	3 (10%)	0 (0%)	1 (3%)

All data presented are median (IQR) or number (%).

- Reasons for switching back to originator: inefficacy (3 patients) and adverse events (2 patients), with 2 reasons missing.
- Only one serious adverse event was reported (drug hypersensitivity reaction in a Remsima treated patient).

Congress abstract S2:

Efficacy, safety and economic impact of the switch to biosimilar of infliximab in inflammatory bowel disease patients in clinical practice: results of one year.

Rodríguez Glez G.E, Díaz Hernández L, Morales Barrios J.A et al.

Abstr. P629, European Crohn's and Colitis Organisation annual congress. 2017.

Products:

- Originator infliximab
- CT-P13, infliximab biosimilar

Study design:

- 12 month observational and retrospective study to assess the impact of switching from originator infliximab to CT-P13 in 72 patients with inflammatory bowel disease (IBD).
- Mean time on originator infliximab before switch: 51 ± 38.83 months.
- Endpoints: disease activity at switching time, 6- and 12- month post-switching (Harvey Bradshaw index for Crohn's disease; partial Mayo score for ulcerative colitis); safety; treatment discontinuation rate.

Disease activity results:

- At time of switch: 86% of patients (62/72) in clinical remission.
- 12 months post-switch:
  - 80.5% of patients (58/72) in clinical remission.
  - 9 patients required steroid treatment.
  - 10 patients required treatment intensification.
  - 8 patients required urgent surgery.

Treatment discontinuation (12 months post-switch):

- Treatment withdrawn in 9.72% of patients (7/72).
- Loss of secondary response reported as the reason for discontinuation in 4/7 patients.

Safety:

- 13.8% of patients (10/72) reported adverse events, mostly infections.
- No treatment withdrawals or modifications due to the reported adverse events.

Congress abstract S3:

Efficacious transition from reference product infliximab to the biosimilar in daily practice.

Layegh Z, Ruwaard J, Hebing R.C et al.

Abstr. AB1279, European League against Rheumatology Annual European Congress of Rheumatology. 2018. https://doi.org/10.1136/annrheumdis-2018-eular.5241

Products:

- Originator infliximab
- CT-P13, infliximab biosimilar

Study design and patients:

- Observational study to assess the impact of switching from originator infliximab to CT-P13 in 45 patients with rheumatoid arthritis (RA) or psoriatic arthritis (PsA) followed at the Amsterdam Rheumatology and immunology Center, Reade.
- Patients were informed by letter about transitioning from originator infliximab to a biosimilar. A nurse or the pharmacist subsequently contacted patients for additional questions and to confirm their agreement. In case of doubts, patients were also advised to contact their treating rheumatologist.
- Patients were switched between July 2015 and June 2016 and followed until January 2018.
- Biosimilar administration followed the same dosage and interval as initial treatment with originator infliximab.
- Median time on originator infliximab before switch: 17 ± 11 years.
- 31% of patients received concomitant methotrexate.
- Endpoints: Treatment discontinuation and reasons (primary), disease activity at 12 months (secondary).

Treatment discontinuation after switch:

- 3 patients switched back to originator infliximab due to subjective reasons (increased disease activity was not objectified by the rheumatologist).
- 1 patient switched to another biologic due to lack of effect.
- 2 patients stopped biologic treatment due to malignancy.

Disease activity:

- Comparable mean disease activity score in 28 joints using erythrocyte sedimentation rate (DAS28-ESR) before and approximatively 12 months after the switch: 2.34 ± 1.02 vs 2.31 ± 1.11, respectively.

Congress abstract S4:

Long-Term Safety and Efficacy of Biosimilar Infliximab (CTP13) after Switching from Originator Infliximab: Results from the 26-Week Open Label Extension of a Randomized Norwegian Trial

Goll G.L, Jørgensen K.K, Sexton J et al.

Abstr. 2800, American College of Rheumatology/Association of Rheumatology Professionals annual meeting.

Products:

- Originator infliximab
- CT-P13, infliximab biosimilar

Study design:

- 26-week open-label extension of a 52-week randomized, non-inferiority, double-blind Phase 4 study (NCT02148640/NOR-SWITCH) to assess the safety and efficacy of switching from originator infliximab to biosimilar CT-P13 in patients with immune-mediated inflammatory diseases (rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and chronic plaque psoriasis).

- Weeks 1−52:
  - Between October 2014 and July 2016, 481 patients with inflammatory diseases on stable treatment with originator infliximab were randomized 1:1 to continue with their treatment (n = 241) or to switch to CT-P13 (n = 240).
  - Results showed non-inferiority of the biosimilar treatment vs. continued originator infliximab treatment.

- Weeks 53−78 (extension period):
  - 183 patients still on originator infliximab at week 52 were switched to the biosimilar (switch group).
  - 197 patients already on CT-P13 continued with the biosimilar treatment (maintenance group: CT-P13 treatment over the full 78-week study period).
  - Mean ongoing infliximab treatment duration: 6.7 ± 3.8 years in the maintenance group vs. 6.4 ± 3.5 years in the switch group.

- Endpoints of extension period: treatment efficacy, safety and immunogenicity, disease worsening, treatment discontinuation.

Disease activity (extension period, per protocol set (maintenance group, n = 190; switch group n = 173)):

- Disease worsening in 16.8% of patients from the maintenance group vs. 11.6% of patients from the switch group.

Immunogenicity (extension period, full analysis set):

- Anti-drug antibodies detected in 3/197 patients from the maintenance group vs. 5/183 patients from the switch group.

Adverse events (extension period):

- Comparable frequencies of reported adverse events in both treatment arms.

Congress abstract S5:

Efficacy, safety and immunogenicity from week 30 to week 54 in a randomised, double-blind phase III study comparing a proposed infliximab biosimilar (PF-06438179/GP1111) with reference infliximab

Alten R, Tseluyko V, Hala T et al

Abstr. FRI0137, European League against Rheumatology Annual European Congress of Rheumatology. 2018

Products:

- Originator infliximab sourced from the EU

- PF-06438179/GP1111, infliximab biosimilar candidate

Study design:

- Randomized, double-blind, parallel-group, Phase 3 clinical study (NCT02222493/REFLECTIONS B537-02) in biologic-naïve patients with moderate-to-severe active rheumatoid arthritis receiving a stable dose of methotrexate.
  - Treatment period 1 (TP1), Weeks 0−30: comparison of treatment efficacy, safety and immunogenicity in patients treated with either EU-infliximab or biosimilar candidate PF-06438179.

- Treatment period 2 (TP2), Weeks 30–54: patients on EU-infliximab were re-randomized 1:1 to switch to PF-06438179 or continue with EU-infliximab.

- Switching study (TP2): 566 of the 650 initially-randomized patients entered TP2.
  - 280 patients continued with the biosimilar treatment (total treatment of 54 weeks).
  - 143 patients continued with EU-infliximab treatment (total treatment of 54 weeks).
  - 143 patients switched from EU-infliximab to the biosimilar candidate.

- Endpoints from TP2: long-term efficacy, safety and immunogenicity.

Disease activity (TP2):

- Comparable ACR20 rates and DAS28-CRP scores across all groups at all TP2 visits.

Adverse Events (TP2):

- Comparable incidence of treatment-emergent adverse events: 36.8% in the continued biosimilar candidate group, 33.6% in the continued EU-infliximab group, and 37.8% in the switching group.

- Similar incidence of serious adverse events: 4.6% in the continued biosimilar candidate group, 7.7% in the continued EU-infliximab group and 2.8% in the switching group.

- Comparable rates of infusion-related reactions: 3.2% in the continued biosimilar candidate group, 8.4% in the continued EU-infliximab group and 4.2% in the switching group.

Immunogenicity (TP2):

- Pre-dose anti-drug antibody (ADA) rates at Week 30: 47.1% in the continued biosimilar candidate group, 53.8% in the continued EU-infliximab group and 45.5% in the switching group.

- Comparable post-dose ADA rates: 52.1% in the continued biosimilar candidate group, 60.1% in the continued EU-infliximab group and 58.0% in the switching group.

Congress abstract S6:

Efficacy and Safety of Rituximab Biosimilar, CT-P10, after a Single Switch from Innovator Rituximabs in Patients with Rheumatoid Arthritis: Results from Phase 3 Randomized Controlled Trial over 72 Weeks

Shim S.C, Majstorovic L.B, Kasay A.B et al.

Abstr. 2445, American College of Rheumatology/ Association of Rheumatology Professionals annual meeting. 2017.

Products:

- Originator rituximab sourced from the EU (EU-rituximab) and the US (US-rituximab)

- CT-P10, rituximab biosimilar

Study design:

- 24-week extension period of a 48-week randomized, double-blind, Phase 3 study (NCT02149121/CT-P10 3.2) in patients with rheumatoid arthritis.
  - Weeks 1–48 (main period): to compare pharmacokinetic parameters, efficacy and safety of CT-P10 and originator rituximab.
  - Weeks 48–54 (extension period): to assess the impact of switching from originator rituximab to CT-P10.

- Extension period: included 295 patients who had completed the first 48 weeks of the clinical study.
  - Patients who had received CT-P10 or EU-rituximab in the main period received CT-P10, and patients who had received US-rituximab were randomized 1:1 to receive CT-P10 or continue US-rituximab.
  - 122 patients continued CT-P10 treatment.

- 64 patients randomized for continued US-rituximab treatment.
- 62 patients randomized to switch from US-rituximab to CT-P10.
- 47 patients switched from EU-rituximab to CT-P10.

- Endpoints: efficacy, pharmacodynamics, safety and immunogenicity.

Efficacy:

- Similar mean changes of DAS28 from week 1 (main period) and ACR response rate across all groups.
- Comparable and maintained B-cell depletion after the first infusion and until the end of the extension period across all groups.

Safety (extension period):

- Comparable safety profiles across all groups.
- Most frequently-reported infections: upper respiratory and urinary tract infections.
- Infusion-related reactions: all of grade 1 or 2 intensity.
- No report of malignancy, progressive multifocal leukoencephalopathy or death.

Immunogenicity (extension period):

- No remarkable change in immunogenicity profile observed following switch.
- 2 patients developed anti-drug antibodies after the first extension infusion: one from the continued US-rituximab group, one from the US-rituximab-to-CT-P10 group.

Congress abstract S7:

Comparison of Switching from the Originator Rituximab to the Biosimilar Rituximab GP2013 or Re-Treatment with the Originator Rituximab in Patients with Active Rheumatoid Arthritis: Safety and Immunogenicity Results from a Multicenter, Randomized, Double-Blind Study

Tony HP, Schulze-Koops H, Krüger K et al

Abstr. 2795, American College of Rheumatology/ Association of Rheumatology Professionals annual meeting. 2017.

Products:

- Originator rituximab
- GP2013, rituximab biosimilar

Study design:

- 24-week, randomized, double-blind, parallel-group, multicenter Phase 3 clinical study (NCT02514772/ ASSIST-RT) in patients with active rheumatoid arthritis to assess the impact of switching from originator rituximab to GP2013.
- 107 patients who had received the last originator rituximab treatment 6 to 18 months prior to randomization and requiring re-treatment were randomized 1:1 to receive GP2013 (switch group, n = 53) or to continue with originator rituximab (control group, n = 54).
- Treatment: 1000 mg intravenous infusions of originator rituximab or GP2013 on days 1 and 15; methotrexate and folic acid as before randomization.
- Endpoints: safety parameters, such as hypersensitivity, adverse events, immunogenicity, infusion-related and anaphylactic reactions.

Study completion:

- 94.3% of patients from the switch group and 96.3% of patients from the control group completed the study

Safety:

- Hypersensitivity: similar incidence in both treatment arms (9.4% in the switch group vs. 11.1% in the control group).
- Infusion-related reactions: comparable incidence in both treatment arms (11.3% in the switch group vs. 18.5% in the control group).
- Anaphylactic reaction: reported in one patient from the control group within 24 hours of originator rituximab infusion.
- Immunogenicity:
  - No patient with anti-drug antibodies (ADAs) at the start of the study
  - Only one patient from the control group developed ADAs after the first study infusion (ADAs present in all subsequent visits)
  - No patient had neutralizing ADAs
- Adverse events (AEs):
  - Similar AE rate in both groups (69.8% in the switch group vs. 51.9% in the control group)
  - Occurrence of 3 serious AEs in the control group, none in the switch group

Congress abstract S8:

Biosimilar ABP 980 in patients with early breast cancer: Results of single switch from trastuzumab to ABP 980

von Minckwitz G, Turdean M, Zhang N et al

Abstr. P5-20-13, San Antonio Breast Cancer Symposium. 2017.

Products:

- Originator trastuzumab
- ABP 980, trastuzumab biosimilar

Study design:

- Randomized, double-blind, active-controlled, parallel-group, multicenter, Phase 3 study (NCT01901146/LILAC) in women with HER2-positive early breast cancer (eBC).
  - Neoadjuvant phase: 725 patients with eBC were randomized 1:1 to receive originator trastuzumab (n = 361) or ABP 980 (n = 364).
  - Adjuvant phase:
  - Patients who had received ABP 980 continued with the biosimilar.
  - 342/361 patients who had received originator trastuzumab in the neoadjuvant phase entered the switch study and were randomized to either continue with originator trastuzumab (n = 171) or to switch to ABP 980 (n = 171).
  - Follow-up period of up to 1 year following the first dose of originator trastuzumab or biosimilar in the neoadjuvant period.
- Endpoints: safety and immunogenicity (data presented were collected at the first post-surgery clinical visit).

Adverse Events (AEs):

- No frequency or severity increase of AEs, and no detection of unexpected safety signals after switching.
- AEs reported in 52.0% (89/171) of patients from the continued originator trastuzumab group vs. 57.3% (98/171) of patients from the switched group.
- Grade $\geq$3 AEs in 10 patients from each group (5.8%).

Immunogenicity:

- No increase in the incidence of Anti-drug antibody (ADA) development after switching.

- Development of binding, non-neutralizing ADAs in one patient from the switch group during the adjuvant phase.

Disease activity

- Rate of disease progression or recurrence or death: 5.3% in the continued originator trastuzumab group vs. 2.9% in the switched group.
  - Hazard ratio = 0.48; 90% CI: [0.181, 1.292].
- Similar event-free survival rate between treatment groups.

Congress abstract S9:

One-Year Clinical Outcomes in 1623 Patients with Inflammatory Arthritis Who Switched from Originator to Biosimilar Etanercept – an Observational Study from the Danish Danbio Registry

Glintborg B, Omerovic E, Danebod K et al

Abstr. 1550, American College of Rheumatology/ Association of Rheumatology Professionals annual meeting. 2017.

Products:

- Originator etanercept
- SB4, etanercept biosimilar

Study design:

- Prospective Observational study of patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthrits (SpA) who were included in the Danish DANBIO registry and who switched to SB4 or continued treatment with originator etanercept following a nation-wide, non-medical switch.
- 2030 originator etanercept-treated patients, of which 1623 (80%) switched to SB4 in April 2016, were followed for approximately 1 year [median follow-up: 316 (254–345) days].
- Median time on originator etanercept treatment prior to switching: 6.1 (3.7–8.8) years in RA patients, 4.5 (3.0–7.5) years in PsA patients, 4.7 (2.9–6.9) years in SpA patients.
- Endpoints: 1-year treatment retention rate; reasons for withdrawal.

Treatment discontinuation:

- 18% of patients in the switch group (276/1623) stopped biosimilar treatment during the 1-year follow-up.
- Main reasons for discontinuation: lack of effect (45%), adverse events (28%).
- For patients with RA and PsA, withdrawal was associated with higher patient's global scores.

Congress abstract S10:

Higher acceptance and persistence rates after biosimilar transitioning in patients with a rheumatic disease after employing an enhanced communication strategy.

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Abstr. FRI02009, European League against Rheumatology Annual European Congress of Rheumatology. 2017.

Products:

- Originator infliximab and biosimilar CT-P13
- Originator etanercept and biosimilar SB4

Study design:

- Observational study to assess the impact of sequential switching from originator infliximab to biosimilar CT-P13 (BIO-SWITCH study in 2015) and from originator etanercept to biosimilar SB4 (BIO-SPAN study in 2016) in patients with

rheumatic diseases using different communication strategies.

- Communication strategy:
  - Patients treated with originator infliximab or etanercept were informed by letter about the switch to a biosimilar, then subsequently contacted by telephone to confirm their agreement to the switch.
  - Enhanced communication was used for patients switching from originator etanercept to SB4 only.
    - Patients informed all at the same time, directly followed by a national media item.
    - Reasons for switching explained: lower cost as well as previously-demonstrated fewer injection site reactions with SB4 vs. originator etanercept.
    - Soft skills training provided to rheumatology and pharmacy staff about: 1) how to ease patient concerns about biosimilars; 2) how to act if a patient has objective or subjective health complaints, including discussing possible nocebo effects and incorrect causal attribution.
- Endpoints: switch acceptance rate, treatment persistence rate, disease activity and AEs during a 6-month follow-up period.

Results:

- 88% of originator infliximab treated patients and 99% of originator etanercept treated patients transitioned to CT-P13 and SB4, respectively; up to January 1st 2017, 75% patients gave informed consent for the BIO-SPAN study.
- Baseline characteristics were similar, with the exception of disease duration and originator treatment duration, which were both shorter in the BIO-SPAN vs. BIO-SWITCH cohort ($p<0.01$).
- Over 84 person-years, 47 patients discontinued CT-P13 (56/100 person-years; 26% due to inefficacy, 74% due to AEs).
- Over 230 person-years, 36 patients discontinued SB4 (16/100 person-years; 53% due to inefficacy, 42% due to AEs and 5% due to remission).
- No 'group think effects' occurred during SB4 treatment (due to individual subcutaneous administration as opposed to group intravenous administration).

Conclusions:

- Enhanced communication and the absence of group think effects improved drug survival and patient acceptance.