Adv Ther (2018) 35:1295–1332
https://doi.org/10.1007/s12325-018-0742-9

REVIEW

Non-medical Switching from Originator Tumor Necrosis Factor Inhibitors to Their Biosimilars: Systematic Review of Randomized Controlled Trials and Real-World Studies

Syed Numan · Freddy Faccin

Received: May 14, 2018 / Published online: August 6, 2018

ABSTRACT

Tumor necrosis factor (TNF) inhibitors are widely used biologics for the treatment of several chronic inflammatory diseases. The launch of anti-TNF biosimilars has introduced the possibility of non-medical switching between originator biologics and their biosimilars. However, the potential clinical and patient-reported consequences of non-medical switching remain largely unknown, as much of the evidence comes from poorly or uncontrolled real-world evidence (RWE) studies that often have an element of bias and nonstandardized outcome measures. To appropriately evaluate the safety, efficacy, and immunogenicity of non-medical switching from an originator to its biosimilar, we propose that seven key study design elements should be considered when assessing the existing evidence: studies should be (1) randomized and double-blind, (2) adequately controlled, and (3) adequately powered; include (4) multiple switching, (5) an assessment of immunogenicity, and (6) adequate follow-up duration; and (7) report individual patient-level outcomes. This systematic review assessed the robustness and consistency of the current non-medical switching evidence, with a focus on TNF inhibitors. A comprehensive literature search (January 2012–February 2018) identified 98 publications corresponding to 91 studies (17 randomized controlled trials and 74 RWE studies) describing non-medical switching from a TNF inhibitor originator to its biosimilar. When assessing the totality of this evidence, none of the non-medical switching studies conducted to date were found to use all seven of the key design elements, and the absence of these elements dilutes the robustness of the data. Furthermore, discontinuation rates varied widely among studies (0–87%), suggesting heterogeneity and inconclusiveness of the current efficacy, safety, and immunogenicity evidence, particularly at an individual patient level. Therefore, patients should not be indiscriminately switched from an originator TNF inhibitor to its biosimilar for non-medical reasons. Switching decisions should remain between the treating physicians and their patients and be made on a case-by-case basis, relying upon robust scientific evidence.
Funding: AbbVie.

Enhanced digital features To view enhanced digital features for this article go to https://doi.org/10.6084/m9.figshare.6507722.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s12325-018-0742-9) contains supplementary material, which is available to authorized users.

S. Numan (✉)
AbbVie Inc., North Chicago, IL, USA
e-mail: syed.numan@abbvie.com

F. Faccin
AbbVie Inc., San Juan, PR, USA

Plain Language Summary: Plain language summary available for this article.

Keywords: Biologic therapy; Biosimilar; Immune-mediated inflammatory diseases; Non-medical switching; Research design; Switching study; TNF inhibitor

PLAIN LANGUAGE SUMMARY

Tumor necrosis factor (TNF) inhibitors are biologic therapies used for the treatment of several chronic inflammatory diseases. Biosimilars are biologics that are very similar to an approved biologic therapy (called an "originator") in terms of quality, clinical efficacy, and safety. Among patients taking TNF-inhibitor therapy, the availability of biosimilars has now made it possible to switch between TNF-inhibitor originators and corresponding biosimilars for economic or other non-medical reasons. However, the potential clinical consequences of non-medical switching remain largely unknown, since much of the evidence comes from studies that were not adequately designed to evaluate efficacy or safety after switching therapies. To evaluate the consequences of non-medical switching from an originator to its biosimilar, we propose seven key study design elements that should be considered when assessing the evidence. This article used these design elements to assess the strength and consistency of the current non-medical switching evidence, with a focus on studies evaluating TNF inhibitors. A comprehensive literature search identified 98 publications (91 studies) describing non-medical switching from a TNF-inhibitor originator to its biosimilar. None of these non-medical switching studies were found to use all seven key design elements, and the data from these studies were inconsistent and inconclusive, suggesting that the current evidence for non-medical switching may be weak. Therefore, patients should not be indiscriminately switched from an originator TNF inhibitor to its biosimilar for non-medical reasons. Decisions to switch therapies should remain between treating physicians and patients, be made on a case-by-case basis, and rely upon robust scientific evidence.

INTRODUCTION

Tumor necrosis factor (TNF) inhibitors are widely used biologics employed in the treatment of immune-mediated inflammatory diseases (IMIDs) such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and psoriasis (Ps) [1]. The launch of anti-TNF biosimilars is expected to provide cost savings and add to the economic sustainability of the healthcare system [2, 3]. Consequently, some payers and formulary decision makers in certain geographic regions are supporting practice of non-medical switching between originator products and their biosimilars [2–4]. Non-medical switching occurs when a patient whose current therapy is effective and well tolerated is switched between therapies, such as from an originator TNF inhibitor to its biosimilar, for economic or other non-medical reasons [3, 5, 6].

A biosimilar is a biologic product approved based on the totality of evidence demonstrating that it is highly similar to an approved biologic product (called the "originator" or "reference product") in terms of quality (i.e., physicochemical and biologic properties) and clinical efficacy and safety [7, 8]. Because biosimilars have many specific and unique considerations related to regulatory approval, specific guidelines for biosimilars have been developed by relevant authorities such as the European Medicines Agency (EMA), US Food and Drug Administration (FDA), and World Health Organization (WHO; Table 1) [7–9]. Although the various guidelines differ somewhat, all suggest a step-wise approach to demonstrate biosimilarity with an originator.

In the USA, a biosimilar can also receive a further designation of interchangeability. An interchangeable product is required to meet additional requirements that go beyond biosimilarity to demonstrate that it is expected to produce the same clinical result as the originator product in any given patient and, for products that are administered more than once, that no risks exist in terms of safety or decreased efficacy when alternating or switching between the originator and biosimilar products [10]. To date, no biosimilar has been designated as

Table 1 Definitions of biosimilarity

Agency	Definition
EMA [7]	A biologic medicinal product that contains a version of the active substance of an already authorized original biologic medicinal product
FDA [8]	A biologic product that is highly similar to the originator product, notwithstanding minor differences in clinically inactive components, and with no clinically meaningful differences between the biologic product and the reference product in terms of safety, purity, and potency
WHO [9]	A biotherapeutic product that is similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product

EMA European Medicines Agency, *FDA* US Food and Drug Administration, *WHO* World Health Organization

interchangeable [11]. Although the FDA designation of interchangeability provides assurance that a product is safe for substitution, individual US states are expected to legislate their own policies on automatic substitution [12]. In contrast, the EMA has no remit to formally designate two products as interchangeable and instead allows each member country to determine its own policies [13].

As mentioned above, the launch of biosimilars has introduced the possibility for non-medical switching between originator biologic products and their biosimilars, and this process has already been adopted or is being evaluated in several countries [14–17]. However, to properly evaluate the safety and efficacy of non-medical switching between an originator product and its biosimilar, we propose seven key study design elements that should be considered when assessing the existing evidence (Table 2). Comprehensive non-medical switching studies should be (1) randomized and double-blind, (2) adequately controlled, and (3) adequately powered with (4) multiple switching, including (5) an assessment of immunogenicity and (6) an adequate follow-up, and (7) report individual patient-level outcomes [3, 18–20]. The importance of each key study design element is detailed in Table 2. These elements are derived from the key evidentiary standards for an interchangeable product as per the definition adopted by the FDA [10].

Table 2 Design elements for a switching study [3, 10, 18–20]

Element	Reason
Randomized, double-blind trial	Ensures comparison between homogenous populations and reduces/controls bias
Adequately controlled	Allows the measurement of the impact of a single intervention that differs between study arms
Adequately powered	Allows for statistically supported inference of outcomes to the universe represented in the study population
Multiple switches	May elicit a prime boost response when the subject is exposed to different sets of epitopes (antigenic determinants)
Immunogenicity-related outcomes	Potential pathophysiologic and clinical response to "prime boost" effect from alternation
Adequate follow-up	Allows for the detection of late-onset, low-frequency immunogenicity
Individual patient-level outcomes	Allows for the study to apply to "any given patient"

For a non-medical switching study, switching is defined as when a prescriber exchanges one medicine for another medicine with the same therapeutic intent [123]. In contrast, automatic substitution is the practice of dispensing one medicine in place of another equivalent and interchangeable medicine at the pharmacy level (also known as pharmacy-level substitution) without consulting the prescriber [124]

As of 14 February 2018, nine TNF inhibitor biosimilars have been approved by the EMA [21] and six by the FDA [11] (Table S1). Since their

approval, numerous non-medical switching studies have been conducted with the intent to demonstrate safety and efficacy of switching from an originator to its biosimilar. However, these studies vary greatly not only in their study designs, but also in their results. The objective of this systematic review was to assess the robustness and conclusiveness of the current evidence on non-medical switching from an originator to its biosimilar with a focus on TNF inhibitors. All identified randomized controlled trials (RCTs) and real-world evidence (RWE) studies were assessed for (1) robustness of data, based on whether they fulfilled the seven key study design elements described above, and (2) consistency of the evidence across studies while considering the heterogeneity of the studies.

METHODS

This systematic literature review searched the following databases: BIOSIS Previews®, Derwent Drug File, Embase®, International Pharmaceutical Abstracts, MEDLINE®, and SciSearch®. The initial search was performed on 10 November 2017, with an updated search performed on 14 February 2018. Search terms included the following: biosimilar or biogeneric or "subsequent entry biologic" or "follow on biologic" or "GP 2015" or "CT P13" or SB2 OR SB4 or Remsima or Flixabi or Benepali or Brenzys or Inflectra; interchange* or switch* or transition* or substitute* or exchang* or replac* or crossover or alternat* or conversion or convert*; nocebo or "non immunogenic*" or nonimmunogenic* or nonmedical or "non medical"; humira or adalimumab or remicade or infliximab or Enbrel or etanercept or simponi or golimumab or cimzia or certolizumab; "tum*r necrosis factor blocker" or "tnf alpha blockade" or "anti tnf agent*". Full search terms and strategy are listed in Table S2. The search was limited to English language, humans and publication dates from 1 January 2012 to 14 February 2018.

All search results were manually screened by two reviewers for eligibility and to exclude duplicates and ineligible studies (Fig. 1). Full texts of all identified publications were further manually screened, and only studies that reported switching from an originator TNF inhibitor to its biosimilar were included. A congress abstract was excluded if the included data had been published in a full-length article by 14 February 2018. Bibliographies of the identified studies were also manually searched for additional publications that fit the eligibility criteria but had not been detected by the original search. The characteristics and design elements of each identified study were assessed and compared with the seven design elements of a robust switching study (Table 2). In addition, patient discontinuation rates from each study were collected to assess the consistency of evidence across studies while taking into consideration the heterogeneity of the studies.

For this publication, individual patient-level data were defined as individual data points that included, but were not limited to, immunogenicity markers that were separately reported for each individual participant in the publication of a clinical study; data reported separately for each individual study participant may also have included, for example, demographic characteristics, efficacy outcomes, and/or laboratory test results. 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.

RESULTS

The search identified 603 publications (Fig. 1). Eight duplicate records were excluded, and eight publications were identified through other sources. The resulting 603 publications were manually screened for eligibility, of which 426 publications did not meet the inclusion criteria and were excluded. The full articles or congress abstracts of the remaining 177 publications were manually reviewed to identify studies that reported switching from an originator TNF inhibitor to its biosimilar. Of these, 79 were excluded (reasons: congress abstract had been published as a full article, $n = 36$; did not report non-medical switching data, $n = 23$; not relevant or more recent data are available from the study, $n = 19$; case study, $n = 1$), and the remaining 98 publications (corresponding

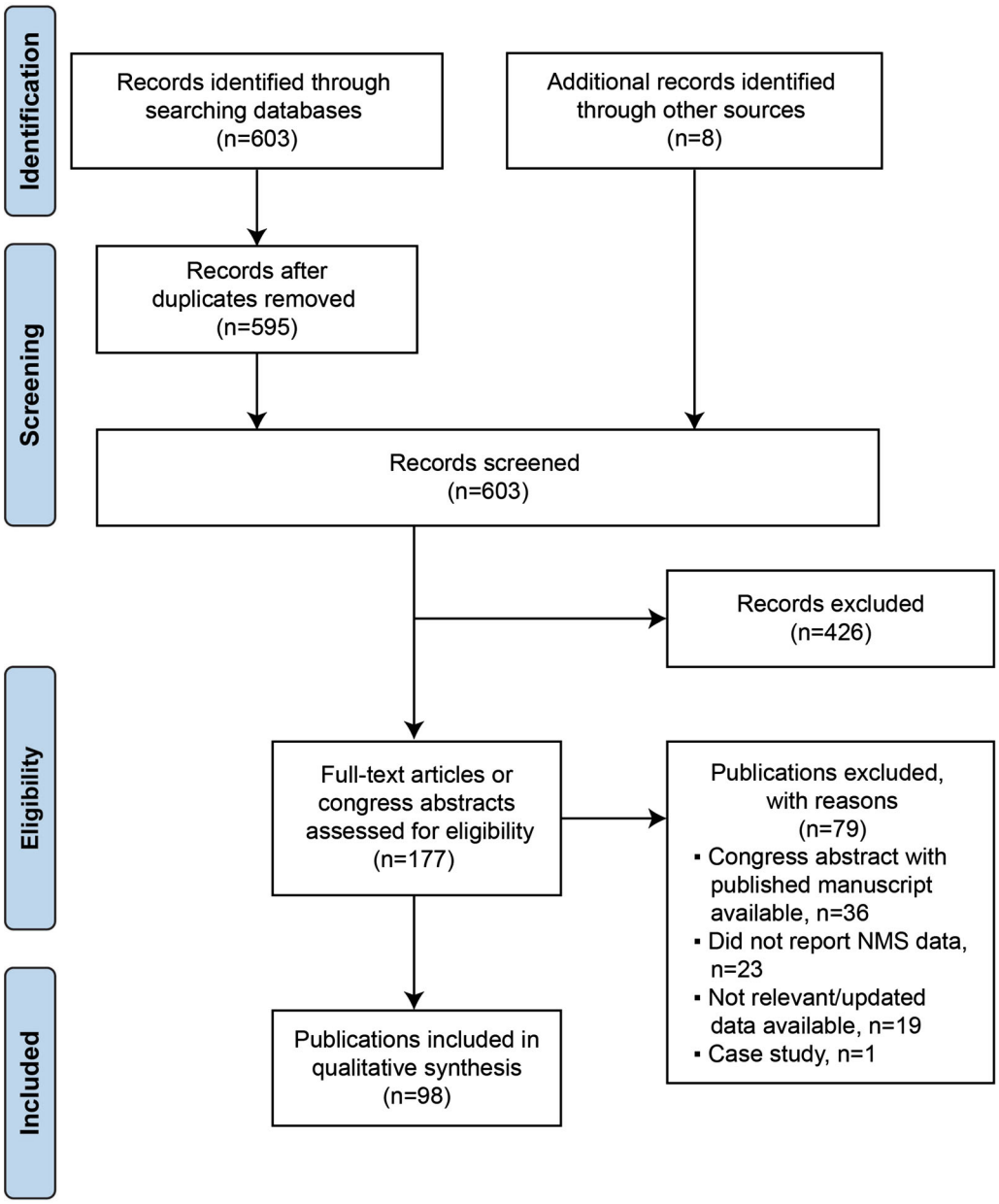

Fig. 1 Flow diagram for the selection of studies. *NMS* non-medical switching

to 91 studies) were included in this review (Fig. 1) [14–17, 22–115].

Randomized Controlled Trials

A total of 17 RCTs (20 publications) were included (Table 3) [16, 22–40], of which 10 (59%) were in rheumatology, 4 (24%) in dermatology, 2 (12%) in gastroenterology, and 1 (6%) in multiple indications (Fig. 2a). Eight (47%) studies investigated a switch from originator infliximab to its biosimilar (CT-P13, SB2, or BOW015), seven (41%) studies from originator adalimumab to its biosimilar (ABP 501, SB5, BI 695501, GP2017, FKB327, or CHS-1420), and two (12%) studies from originator etanercept to its biosimilar (SB4 or GP2015). Follow-

Table 3 Summary of randomized controlled switching or transition trials

Study	Biosimilar (study name)	Population	Switch group	Control group	Follow-up duration post switch	Discontinuation rate (switch vs. control group)	Dose escalation allowed
Adalimumab biosimilars							
Blauvelt et al. 2017 [22]	GP2017 (ADACCESS)	Ps	Originator to GP2017 (n = 63)	Originator continuers (n = 127)[a]	34 weeks	16 (25%) vs. 23 (18%)[a]	NR
Cohen et al. 2017 [23]	BI 695501 (VOLTAIRE-RA)	RA	Originator to BI 695501 (n = 147)	Originator continuers (n = 148)[b]	24–34 weeks	9 (6%) vs. 8 (5%)[b]	NR
Cohen et al. 2016 [24]	ABP 501	RA	Originator to ABP 501 (n = 237)	ABP 501 continuers (n = 229)	46 weeks	30 (13%) vs. 25 (11%)[c]	NR
Genovese et al. 2017 [25]	FKB327 (ARABESC-OLE)	RA	Originator to FKB327 (n = 108)	Originator continuers (n = 213)[d]	76 weeks	NR	NR
Hodge et al. 2017 [26]	CHS-1420	Ps and PsA	Originator to CHS-1420 (n = 124)	Originator continuers (n = 129)[e]	8 weeks	NR	NR
Papp et al. 2017 [27]	ABP 501	Ps	Originator to ABP 501 (n = 77)	Originator continuers (n = 79)[f]	36 weeks	9 (12%) vs. 8 (10%)	NR
Weinblatt et al. 2017 [28, 29]	SB5	RA	Originator to SB5 (n = 125)	Originator continuers (n = 129)[g]	28 weeks	8 (6%) vs. 5 (4%)[g]	NR
Etanercept biosimilars							
Emery et al. 2017 [30]	SB4	RA	Originator to SB4 (n = 119)	SB4 continuers (n = 126)	48 weeks	6 (5%) vs. 7 (6%)	NR

Table 3 continued

Study	Biosimilar (study name)	Population	Switch group	Control group	Follow-up duration post switch	Discontinuation rate (switch vs. control group)	Dose escalation allowed
Griffiths et al. 2017 [31, 32]	GP2015 (EGALITY)	Ps	Originator to GP2015 (n = 96)	Originator continuers (n = 151)[h]	40 weeks	6 (6%) vs. 14 (9%)	NR
Infliximab biosimilars							
Jørgensen et al. 2017 [16, 33]	CT-P13 (NOR-SWITCH)	IMID	Originator to CT-P13 (n = 240)[i]	Originator continuers (n = 241)	78 weeks	18 (8%) vs. 25 (10%)[i]	NR
Kim et al. 2017 [34]	CT-P13	CD	Originator to CT-P13 (n = 55)	Originator continuers (n = 54)[j]	24 weeks	NR	NR
Park et al. 2017 [35]	CT-P13 (PLANETAS)	AS	Originator to CT-P13 (n = 86)	CT-P13 continuers (n = 88)	48 weeks	9 (10%) vs. 7 (8%)	No
Smolen et al. 2018 [36]	SB2	RA	Originator to SB2 (n = 94)	Originator continuers (n = 101)[k]	16 weeks	6 (6%) vs. 5 (5%)	Yes
Tanaka et al. 2017 [37]	CT-P13	RA	Originator to CT-P13 (n = 33)	CT-P13 continuers (n = 38)	105 weeks	11 (33%) vs. 6 (16%)	Yes
Taylor et al. 2016 [38]	BOW015	RA	Originator to BOW015 (n = 53)	BOW015 continuers (n = 104)	38 weeks	NR	No
Volkers et al. 2017 [39]	CT-P13 (SIMILAR)	IBD	Originator to CT-P13 (n = 15)	Originator continuers (n = 6)	30 weeks	NR	NR

Table 3 continued

Study	Biosimilar (study name)	Population	Switch group	Control group	Follow-up duration post switch	Discontinuation rate (switch vs. control group)	Dose escalation allowed
Yoo et al. 2017 [40]	CT-P13 (PLANETRA)	RA	Originator to CT-P13 (n = 144)	CT-P13 continuers (n = 158)	48 weeks	16 (11%) vs. 25 (16%)	No

AS ankylosing spondylitis, *IBD* inflammatory bowel disease, *IMID* immune-mediated inflammatory diseases, *NR* not reported, *Ps* psoriasis, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis

[a] Adalimumab originator to GP2017, n = 63; GP2017 to adalimumab originator, n = 63; originator continuers, n = 127; GP2017 continuers, n = 126; discontinuation rates available from results posted on ClinicalTrials.gov (NCT02016105)

[b] Adalimumab originator to BI 695501, n = 147 (full-analysis set) or n = 146 (safety set); originator continuers, n = 148; BI 695501 continuers, n = 298; discontinuation rates available from results posted on ClinicalTrials.gov (NCT02137226)

[c] Discontinuation rates available from results posted on ClinicalTrials.gov (NCT02114931)

[d] Treatment groups from weeks 0 to 28 of open-label extension: originator to FKB327, n = 108; originator continuers, n = 213; FKB327 continuers, n = 216; FKB327 to originator, n = 108; thereafter, all patients received FKB327 to week 76

[e] Adalimumab originator to CHS-1420, n = 124; originator continuers, n = 129; CHS-1420 continuers, n = 250

[f] Adalimumab originator to ABP 501, n = 77; originator continuers, n = 79; ABP 501 continuers, n = 152

[g] Adalimumab originator to SB5, n = 125; originator continuers, n = 129; SB5 continuers, n = 254; discontinuation rates available from results posted on ClinicalTrials.gov (NCT02167139)

[h] Etanercept originator to GP2015, n = 96; originator continuers, n = 151; GP2015 continuers, n = 150; GP2015 to etanercept originator, n = 100; each switch group underwent a sequence of three treatment switches at 6-week intervals

[i] 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. Reported discontinuation rates correspond to the end of the 52-week main study, not the 78-week extension study

[j] Infliximab originator to CT-P13, n = 55; CT-P13 to infliximab originator, n = 55; originator continuers, n = 54; CT-P13 continuers, n = 56

[k] Infliximab originator to SB2, n = 94; originator continuers, n = 101; SB2 continuers, n = 201

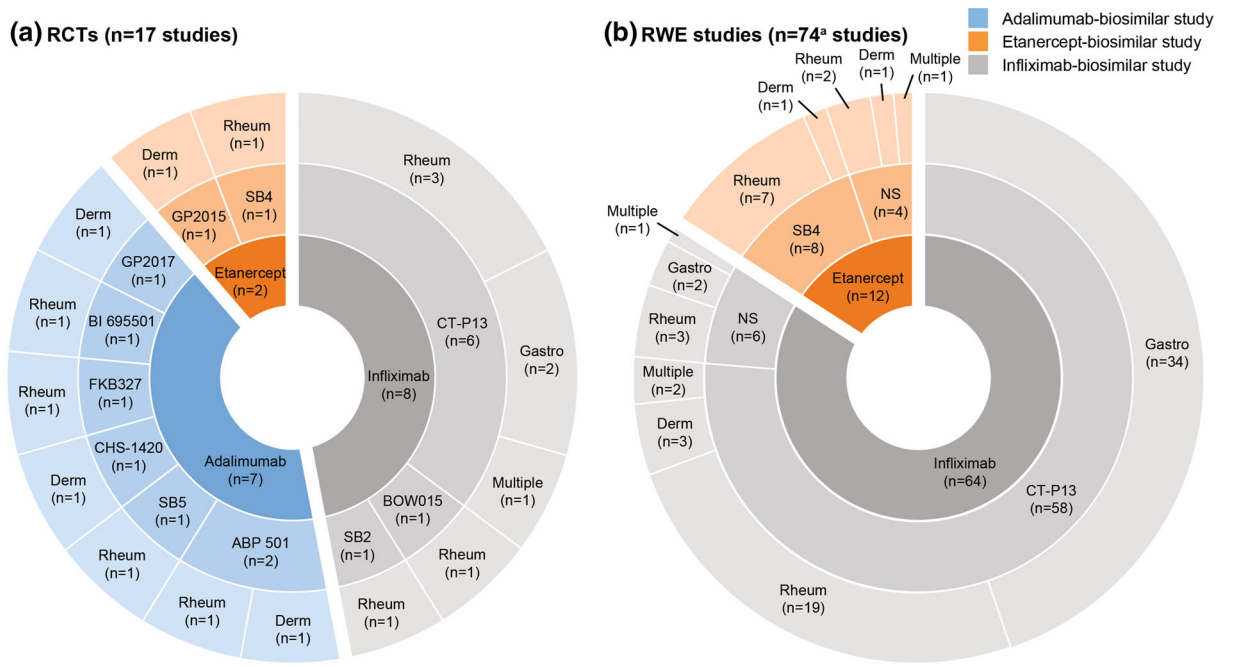

Fig. 2 Summary of originators (inner ring), biosimilars (middle ring), and therapeutic areas (outer ring) investigated in published RCTs and RWE studies reporting non-medical switching of TNF inhibitor originator to biosimilar. *Derm* dermatologic diseases, *Gastro* gastroenterologic diseases, *Multiple* multiple indications, *NS* not specified, *RCT* randomized controlled trial, *Rheum* rheumatic diseases, *RWE* real-world evidence, *TNF* tumor necrosis factor. [a]Etanercept-biosimilar and infliximab-biosimilar aspects of the De Cock et al. [17] and Egeberg et al. [44] studies are each counted separately

up durations post switch ranged from 8 to 105 weeks (Fig. 3a). All studies included a comparison group, which, in 11 (65%) studies, consisted of randomized patients continuing treatment with the originator; in the remaining 6 (35%) studies, the control group consisted of biosimilar continuers.

Overall, none of the studies fulfilled all the design elements for a robust switching study (Table 4 and Fig. 4a). Only two (12%) studies (NOR-SWITCH [16] and ARABESC-OLE [25]) met five of the seven design elements, and three (18%) studies (ADACCESS [22], EGALITY [31, 32], and ARABESC-OLE) included multiple switches. Furthermore, in all of the studies except NOR-SWITCH, ADACCESS, and EGALITY, the switching component was part of the extension periods. In the three-period ADACCESS and EGALITY studies, the multiple switching phase (period 2) was preceded by a two-arm, head-to-head period (at the end of which the primary end points were assessed) and, after the last switch between treatments, concluded with a follow-up period. The single-switch non-crossover NOR-SWITCH study was the only study powered to detect differences in the rate of disease worsening between the switch and control groups. However, because it assessed multiple indications, NOR-SWITCH was powered at a pooled, and not individual, indication level [16]. None of the RCTs have reported individual patient-level outcomes, and only three (18%) RCTs included follow-up periods of $\geq$ 12 months' duration post switch (Table 4 and Fig. 4a).

Real-World Evidence Studies

A total of 74 RWE studies (78 publications) were included (Table 5) [14, 15, 17, 41–115], of which 36 (49%) were in gastroenterology, 30 (41%) in rheumatology, 4 (5%) in dermatology, and 4 (5%) in multiple indications (Fig. 2b). Most studies (n = 64; 86%) investigated a switch from

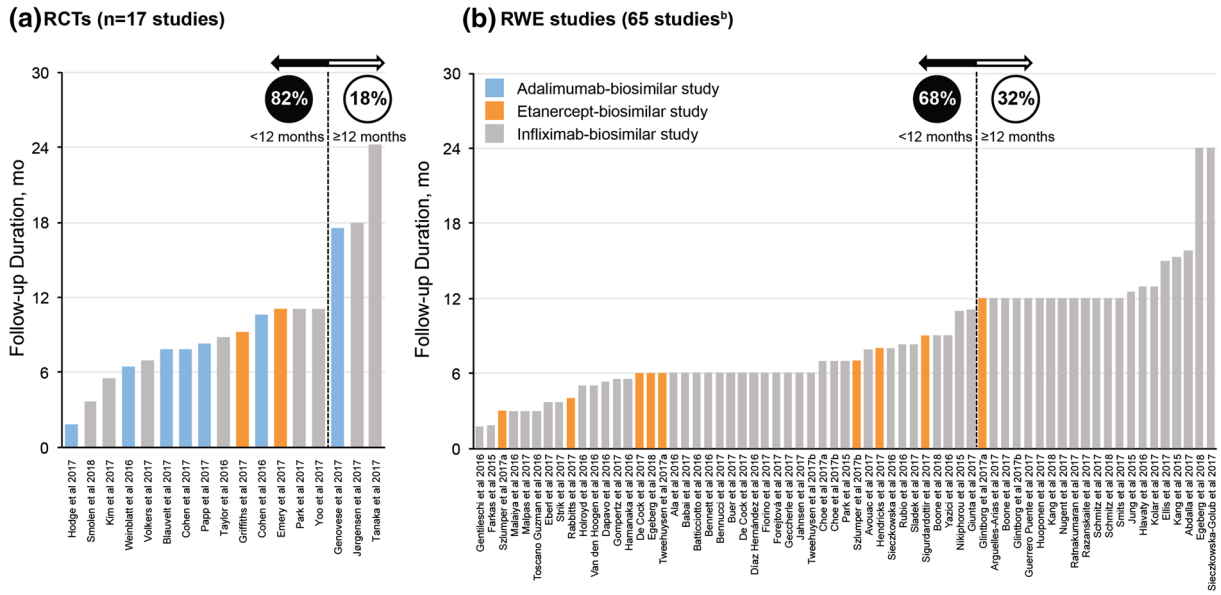

Fig. 3 Follow-up duration[a] post switch reported in published RCTs and RWE studies reporting non-medical switching from TNF inhibitor originator to biosimilar. Proportions of studies with < 12 and ≥ 12 months of follow-up are displayed within each graph. *RCT* randomized controlled trial; *RWE* real-world evidence; *TNF* tumor necrosis factor. [a]For conversion of follow-up duration reported in months or years, conversion factors of 4.33 weeks/month and 52 weeks/year, respectively, were used. If a range of follow-up duration was provided, the maximum provided value was graphed. [b]Of the 74 RWE studies, 65 reported follow-up duration. Etanercept-biosimilar and infliximab-biosimilar aspects of the De Cock et al. [17] and Egeberg et al. [44] studies are each displayed separately

infliximab originator to its biosimilar, and only 12 (16%) studies investigated a switch from etanercept to its biosimilar (percentages do not add to 100% because 2 studies each reported data for both infliximab and etanercept) [17, 44]. As of 14 February 2018, no published RWE studies have investigated a non-medical switch from adalimumab originator to its biosimilars, likely because no adalimumab biosimilars were commercially available as of that date. A historical comparison cohort or a parallel control group consisting of patients who had continued originator therapy was included in only 12 (16%) studies (Tables 5, 6), and 18 (24%) studies included a control group consisting of treatment-naive patients initiating biologic therapy with the biosimilar. Of the 72 studies that reported the number of patients who switched from originator to biosimilar, most ($n = 52$; 72%) were relatively small, with fewer than 100 patients who switched in each study.

Similar to the RCTs, and as anticipated, none of the RWE studies fulfilled all the design elements for a robust switching study (Tables 2, 6). All of the RWE studies investigated a single switch from originator therapy to its biosimilar, and none were randomized at the time of the switch (Fig. 4b). However, 26 (35%) studies did report a switch-back from biosimilar to originator therapy among patients who had reported worsened outcomes or who had requested to switch back to the originator therapy for other reasons [15, 17, 41–43, 46, 48, 51, 52, 57, 58, 63, 71, 75, 77, 83, 86, 90–92, 95, 100, 103, 104, 113, 115]. Furthermore, most studies did not report whether they were powered to detect differences in efficacy or safety after the switch, although several multiple cohort studies did provide some statistical comparisons, albeit with divergent results [14, 44, 45, 51, 73, 88, 95, 99, 100, 115]. Twenty-five (34%) studies reported immunogenicity data, and three (4%) studies reported individual patient-level immunogenicity outcomes. In the 65 (88%) studies that reported follow-up duration post switch, follow-up

Table 4 Characteristics and design elements of randomized controlled trials

Study	Randomized at time of switch	Control group (originator continuers)	Powered to detect differences in efficacy after switch	Multiple switch	Immunogenicity data reported	Follow-up ≥ 12 months after switch	Individual patient-level outcomes[a] reported
Adalimumab biosimilars							
Blauvelt et al. 2017 [22]	Yes	Yes	No	Yes	Yes	No	No
Cohen et al. 2017 [23]	Yes	Yes	No[b]	No	Yes	No	No
Cohen et al. 2016 [24, 125]	No[c]	No	No[b]	No	Yes	No	No
Genovese et al. 2017 [25]	Yes	Yes	NR	Yes	Yes	Yes	No
Hodge et al. 2017 [26, 126]	Yes[d]	Yes	No[b]	No	Yes	No	No[e]
Papp et al. 2017 [27, 127]	Yes	Yes	No[b]	No	Yes	No	No[e]
Weinblatt et al. 2017 [28, 29]	Yes	Yes	No[b]	No	Yes	No	No
Etanercept biosimilars							
Emery et al. 2017 [30, 128]	No[c]	No	No[b]	No	Yes	No	No[e]
Griffiths et al. 2017 [31, 32]	Yes	Yes	No[b]	Yes	Yes	No	No[e]
Infliximab biosimilars							
Jørgensen et al. 2017 [16]	Yes	Yes	Yes[f]	No	Yes	Yes	No[e]

Table 4 continued

Study	Randomized at time of switch	Control group (originator continuers)	Powered to detect differences in efficacy after switch	Multiple switch	Immunogenicity data reported	Follow-up ≥ 12 months after switch	Individual patient-level outcomes[a] reported
Kim et al. 2017 [34]	Yes	Yes	No	No	Yes	No	No
Park et al. 2017 [35, 129]	No[c]	No	No[b]	No	Yes	No	No[e]
Smolen et al. 2018 [36]	Yes	Yes	No[b]	No	Yes	No	No
Tanaka et al. 2017 [37, 130]	No[c]	No	No	No	Yes	Yes	No[e]
Taylor et al. 2016 [38]	No[c]	No	No	No	No	No	No
Volkers et al. 2017 [39]	Yes	Yes	No	No	No	No	No[e]
Yoo et al. 2017 [40, 131]	No[c]	No	No[b]	No	Yes	No	No[e]

[a] Individual patient-level data defined as individual data points that included, but were not limited to, immunogenicity markers that were separately reported for each individual participant in the publication of a clinical study; data reported separately for each individual study participant may also have included, for example, demographic characteristics, efficacy outcomes, and/or laboratory test results

[b] Powered to detect differences in efficacy in pre-switch analysis

[c] Study was an open-label extension of a randomized controlled study; patients remained blinded to their original treatment at the time of the switch

[d] Randomization details available from study design as posted on ClinicalTrials.gov (NCT02489227)

[e] Reports patient-reported outcome measures

[f] Powered at pooled, but not at individual, indication level for disease worsening

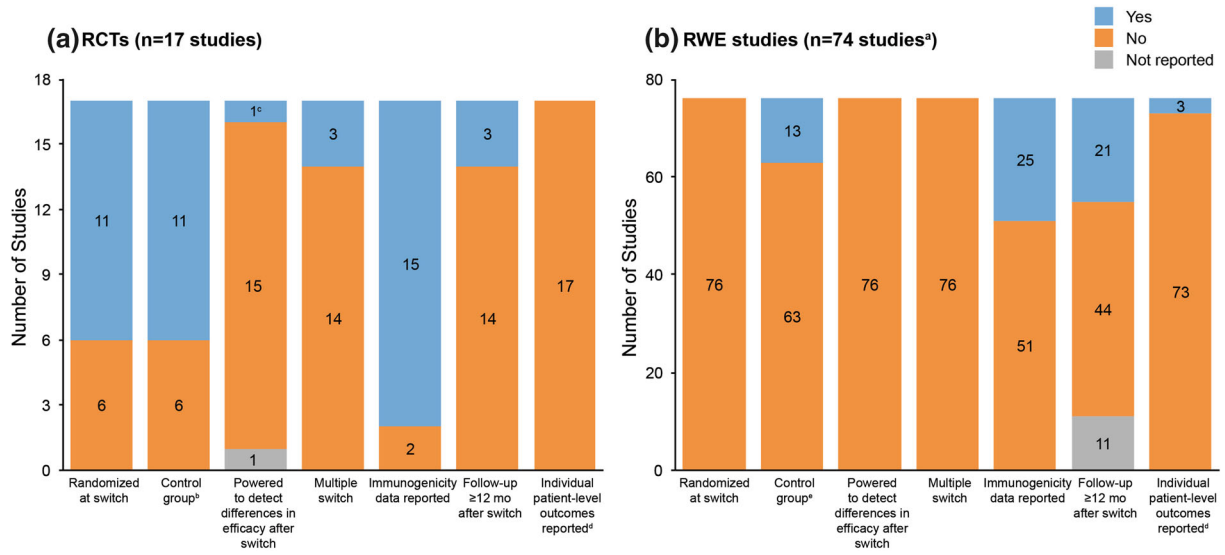

Fig. 4 Fulfillment of the seven switching study design elements in published RCTs and RWE studies reporting non-medical switching from TNF inhibitor originator to biosimilar. *RCT* randomized controlled trial, *RWE* real-world evidence, *TNF* tumor necrosis factor. [a]Etanercept-biosimilar and infliximab-biosimilar aspects of the De Cock et al. [17] and Egeberg et al. [44] studies are each counted separately. [b]Refers only to originator continuers. [c]Powered at pooled, but not at individual, indication level for disease worsening. [d]Individual patient-level data defined as individual data points that included, but were not limited to, immunogenicity markers that were separately reported for each individual participant in the publication of a clinical study; data reported separately for each individual study participant may also have included, for example, demographic characteristics, efficacy outcomes, and/or laboratory test results. [e]Excludes any comparison group consisting of naive patients or patients previously treated with other biologics

duration ranged from 1.7 months to 2 years (Table 5 and Fig. 3b), with only 21 studies (32%) following patients post switch for ≥ 12 months (Table 6).

Discontinuation Rate Post Switch in Randomized Controlled Trials

Of the 17 RCTs, discontinuation rates were reported for 12 (71%) studies (Fig. 5). Overall discontinuation rates ranged from 5% to 33% in the switch groups and from 4% to 18% in the comparison groups (Table 3). In general, discontinuation rates were divergent; they were slightly numerically higher among the switchers in some studies and higher in the control group in other studies. Most notably, the discontinuation rate demonstrated for the switch group in the Tanaka et al. study (33%) was considerably higher than that for the continuers group (16%) [37].

Discontinuation Rate Post Switch in Real-World Evidence Studies

In the 74 RWE studies, discontinuation rates in the switch groups showed greater variation compared with those rates in the RCTs, ranging from 0% to 87% in the infliximab studies and from 8% to 17% in the etanercept studies (Table 5 and Fig. 6). Discontinuation rates were similarly variable across studies regardless of the patient population (gastroenterology, 0–50%; rheumatology, 3–87%). Only 8 (11%) studies (5 in rheumatologic conditions, 2 in IBDs, and 1 in multiple indications) compared overall raw discontinuation rates between the switch group and the historical/parallel originator continuer group, with divergent results [14, 15, 51, 71, 88, 95, 100, 115]. In three studies, discontinuation rates were slightly numerically lower for continuers versus switchers (8% vs. 10% [51], 14% vs. 16% [14],

Table 5 Summary of real-world studies

Study	Biosimilar (study name)	Population	Patient number (switch vs. control group)	Control group[a]	Follow-up duration post switch	Discontinuation rate (switch vs. control group)	Dose escalation allowed
Etanercept biosimilars							
Alten et al. 2017a [41]	NS	Any	1899 vs. 2576	Naive	NR	10% vs. 9%[b]	NR
Alten et al. 2017b [42]	NS	Rheum	2938 vs. 1845	Naive	NR	11%[b] vs. NR	NR
De Cock et al. 2017 [17]	SB4	RA	511[c]	No	6 months[c]	4/29 (14%)[c]	NR
Dyball et al. 2017 [43]	SB4	RA	38	No	NR	6/36 (17%)	No
Egeberg et al. 2018 [44]	SB4 (DERMBIO)	Ps	517 (switch + nonswitch)	Historical cohort	6 months	HR, 0.46 (95% CI 0.11–1.98; $P = 0.297$)[d]	Yes
Glintborg et al. 2017a [45]	SB4 (DANBIO)	Rheum	1623 vs. 407	Originator continuers	1 year	276 (17%) vs. NR	Yes
Hendricks et al. 2017 [46]	SB4	Rheum	85	No	8 months	7 (8%)	NR
Rabbitts et al. 2017 [47]	SB4	Rheum	70 vs. 13	Naive	4 months	5/44 (11%) vs. NR	No
Sigurdardottir et al. 2017 [48][e]	SB4	Rheum	147	No	9 months	21 (14%)	NR
Szlumper et al. 2017a [49]	NS	Ps	17	No	3 months	NR	NR
Szlumper et al. 2017b [50]	NS	Rheum	103	No	7 months	NR	NR

Table 5 continued

Study	Biosimilar (study name)	Population	Patient number (switch vs. control group)	Control group[a]	Follow-up duration post switch	Discontinuation rate (switch vs. control group)	Dose escalation allowed
Tweehuysen et al. 2017a [51]	SB4 (BIOSPAN)	Rheum	625 vs. 600	Historical cohort	6 months	60 (10%) vs. 46 (8%); HR, 1.57 (95% CI 1.05–2.36)	NR
Infliximab biosimilars							
Abdalla et al. 2017 [52]	CT-P13	Rheum	34	No	Mean: 15.8 months	5 (15%)	NR
Akrout et al. 2017 [53]	NS	Rheum	90	No	NR	14 (16%)	Yes
Ala et al. 2016 [54]	CT-P13	CD	20	No	6 months	4 (20%)	NR
Arguelles-Arias et al. 2017 [55, 56]	CT-P13	IBD	98 vs. 22	Naive[f]	12 months	12 (12%) vs. NR[f]	NR
Avouac et al. 2017 [57]	CT-P13	IMID	260	No	Mean: 34 weeks	59 (23%)	NR
Babai et al. 2017 [58]	NS	SpA	53	No	6 months	12 (23%)	NR
Batticciotto et al. 2016 [59]	CT-P13	SpA	36	No	6 months	2 (6%)	NR
Bennett et al. 2016 [60]	CT-P13	IBD	104	No	6 months	19 (18%)	NR
Bennucci et al. 2017 [61]	CT-P13	SpA	41	No	6 months	1 (2%)[g]	NR
Boone et al. 2017 [62]	NS	IBD	65	No	52 weeks	8 (12%)	NR
Boone et al. 2018 [63]	NS	IMID	125	No	9 months	23 (18%)	NR
Buer et al. 2017 [64]	CT-P13	IBD	143	No	6 months	5 (3%)	Yes

Table 5 continued

Study	Biosimilar (study name)	Population	Patient number (switch vs. control group)	Control group[a]	Follow-up duration post switch	Discontinuation rate (switch vs. control group)	Dose escalation allowed
Choe et al. 2017a [65]	CT-P13	IBD	32 vs. 42	Naive	30 weeks	NR	NR
Choe et al. 2017b [66]	CT-P13	CD	204 (switch + naive)	Naive	30 weeks	NR	NR
Chung et al. 2016 [67]	CT-P13	IBD	64	No	NR	7 (11%)	NR
Dapavo et al. 2016 [68]	CT-P13	Ps	30 vs. 5	Naive	Median: 23 weeks	NR	NR
De Cock et al. 2017 [17]	CT-P13	RA	180[c]	No	6 months[c]	11/70 (16%)[c]	NR
Díaz Hernández et al. 2016 [69]	NS	IBD	72	No	6 months	3 (4%)	NR
Eberl et al. 2017 [70]	CT-P13	IBD	78	No	16 weeks	NR	Yes
Egeberg et al. 2018 [44]	CT-P13 (DERMBIO)	Ps	296 (switch + nonswitch)	Historical cohort	2 years	HR, 1.64 (95% CI, 0.69–3.89; $P = 0.264$)[d]	Yes
Ellis et al. 2017 [71]	CT-P13	RA	92 vs. 605	Originator continuers	Mean: 15 months	80 (87%) vs. NR[h]	NR
Farkas et al. 2015 [72][e]	CT-P13	IBD	3 vs. 36	Naive	8 weeks	1 (33%) vs. 1 (3%)	No
Fiorino et al. 2017 [73, 74]	CT-P13 (PROSIT-BIO)	IBD	97 vs. 450	Naive	Mean: 6 months	5 (5%) vs. 40 (9%)[i]	No
Forejtová et al. 2017 [75]	CT-P13	AS	38	No	6 months	1 (3%)	NR

Table 5 continued

Study	Biosimilar (study name)	Population	Patient number (switch vs. control group)	Control group[a]	Follow-up duration post switch	Discontinuation rate (switch vs. control group)	Dose escalation allowed
Geccherle et al. 2017 [76]	CT-P13	IBD	5 vs. 37	Naive[j]	6 months	NR	NR
Gentileschi et al. 2016 [77]	CT-P13	Rheum	23	No	Mean: 1.7 months	7 (30%)	NR
Giunta et al. 2017 [78][e]	CT-P13	Ps	46 vs. 17	Naive	48 weeks	NR	No
Glintborg et al. 2017b [14]	CT-P13 (DANBIO)	Rheum	802 vs. 1121	Historical cohort	1 year	132 (16%) vs. NR (14%) HR 1.31 (95% CI 1.02–1.68; $P = 0.03$)	Yes
Gompertz et al. 2017 [79][e]	CT-P13	IBD	30	No	24 weeks	NR	Yes
Guerrero Puente et al. 2017 [80]	CT-P13	IBD	36	No	12 months	4 (11%)	Yes
Hamanaka et al. 2016 [81]	CT-P13	IBD	3 vs. 17	Naive	24 weeks	0 vs. 0	NR
Hlavaty et al. 2016 [82]	CT-P13	IBD	12 vs. 13	Naive	56 weeks	2 (17%) vs. 3 (23%)	Yes
Holroyd et al. 2016 [83][e]	CT-P13	Rheum	56	No	5 months	4 (7%)	NR
Huoponen et al. 2017 [84]	CT-P13	IBD	56	No	1 year	NR	NR
Jahnsen et al. 2017 [85]	CT-P13	IBD	56	No	6 months	NR	NR
Jung et al. 2015 [86]	CT-P13	IBD	36 vs. 74	Naive	54 weeks	5 (14%) vs. NR	Yes
Kang et al. 2015 [87]	CT-P13	IBD	9 vs. 8	Naive	9–66 weeks	1 (11%) vs. 0	No

Table 5 continued

Study	Biosimilar (study name)	Population	Patient number (switch vs. control group)	Control group[a]	Follow-up duration post switch	Discontinuation rate (switch vs. control group)	Dose escalation allowed
Kang et al. 2018 [88]	CT-P13	IBD	38 vs. 36	Originator continuers	1 year	3 (8%) vs. 5 (14%)	Yes
Kolar et al. 2017 [89]	CT-P13	IBD	74 vs. 119	Naive	56 weeks	4 (5%) vs. 13 (11%)	Yes
Malaiya et al. 2016 [90][e]	CT-P13	Rheum	30	No	3 months	2 (7%)	NR
Malpas et al. 2017 [91]	NS	RA and axSpA	62	No	3 mo	3 (5%)[b]	NR
Nikiphorou et al. 2015 [92]	CT-P13	Rheum	39	No	Median: 11 months	11 (28%)	NR
Nugent et al. 2017 [93][e]	CT-P13 (EIR SWITCH)	IBD	35	No	1 year	6 (17%)	NR
Park et al. 2015 [94]	CT-P13	IBD	60 vs. 113	Naive	30 weeks	NR	Yes
Phillips et al. 2017 [95][e]	CT-P13	Any	136 vs. 1388	Originator continuers	NR	13/1000PY vs. 2/1000PY HR 5.53 (95% CI 4.01–7.63)	NR
Plevris et al. 2017 [96]	CT-P13	IBD	109	No	NR	NR	Yes
Presberg et al. 2017 [97]	CT-P13	Rheum	89	No	NR	6 (7%)	NR
Rahmany et al. 2016 [98]	CT-P13	IBD	78	No	NR	5 (6%)	Yes
Ratnakumaran et al. 2017 [99]	CT-P13	IBD	191 vs. 19	Originator continuers	12 months	NR	NR

Table 5 continued

Study	Biosimilar (study name)	Population	Patient number (switch vs. control group)	Control group[a]	Follow-up duration post switch	Discontinuation rate (switch vs. control group)	Dose escalation allowed
Razanskaite et al. 2017 [100]	CT-P13	IBD	143 vs. 120	Historical cohort	12 months	41 (29%) vs. 31 (26%); $P = 0.94$	NR
Rubio et al. 2016 [101]	CT-P13	Rheum	53 vs. 25	Naive	Mean: 8.3 months	5 (9%) vs. 6 (24%)	NR
Schmitz et al. 2017 [102]	CT-P13	Rheum	27	No	12 months	7 (26%)	NR
Schmitz et al. 2018 [103]	CT-P13	IBD	133	No	1 year	35 (26%)	Yes
Sheppard et al. 2016 [104]	CT-P13	Rheum	25	No	NR	5 (20%)	NR
Sieczkowska et al. 2016 [105]	CT-P13	IBD	39	No	Mean: 8 months	15 (38%)	Yes
Sieczkowska-Golub et al. 2017 [106, 107]	CT-P13	CD	16	No	2 years	8 (50%)	NR
Sladek et al. 2017 [108]	CT-P13	IBD	45	No	24–36 weeks	3 (7%)	NR
Smits et al. 2017 [109, 110]	CT-P13	IBD	83	No	52 weeks	15 (18%)	Yes
Strik et al. 2017 [111]	CT-P13 (SECURE)	CD	44	No	16 weeks	NR	NR
Toscano Guzman et al. 2016 [112]	CT-P13	UC	25	No	3 months	NR	NR
Tweehuysen et al. 2017b [15]	CT-P13 (BIO-SWITCH)	Rheum	192 vs. 19	Originator continuers	6 months	47 (24%) vs. 1 (5%)	NR

Table 5 continued

Study	Biosimilar (study name)	Population	Patient number (switch vs. control group)	Control group[a]	Follow-up duration post switch	Discontinuation rate (switch vs. control group)	Dose escalation allowed
Van den Hoogen et al. 2016 [113]	CT-P13	Rheum	136	No	5 months	23 (17%)	NR
Vergara-Dangond et al. 2017 [114]	CT-P13	Rheum	7 vs. 6	Originator continuers	4 cycles	1 (14%) vs. 0 [g]	Yes
Yazici et al. 2016 [115]	CT-P13	RA	148 vs. 2870	Originator continuers	Mean: 9 months	121 (82%) vs. 1089 (38%)	NR

AS ankylosing spondylitis, *axSpA* axial spondyloarthritis, *CD* Crohn's disease, *CI* confidence interval, *HR* hazard ratio, *IBD* inflammatory bowel disease, *IMID* immune-mediated inflammatory disease, *NR* not reported, *NS* not specified, *Ps* psoriasis, *PY* person-year, *RA* rheumatoid arthritis, *Rheum* rheumatic diseases, *SpA* spondyloarthritis, *TNF* tumor necrosis factor, *UC* ulcerative colitis

[a] Naive patients defined as those who received induction therapy with the biosimilar regardless of previous treatment history (including biologic naive, TNF inhibitor naive, and others who may have been previously treated with TNF inhibitors and/or originator product)

[b] Switched back to originator, no other discontinuation data provided

[c] Study is ongoing, with follow-up data to be captured every 6 months for 3 years and annually thereafter; at time of publication, 6-month data were available for 29 patients taking etanercept biosimilar and for 70 patients taking infliximab biosimilar

[d] HR is for patients who were well treated with the originator but switched from originator to biosimilar compared with nonswitchers

[e] Publication identified outside the systematic literature search via other sources

[f] Data for naive patients were only reported until month 6; at 6 months, discontinuation rates were 7 (7%) for the switch group and 3 (14%) for the control group

[g] The only discontinuations reported were those due to adverse events

[h] The authors are unclear which of the two discontinuation rates (19% or 34%) listed by the publication for the originator continuer control group was accurate

[i] The only discontinuation rates reported were those due to serious adverse events or infusion reactions

[j] Switch group consisted of patients with $\geq$ 12 months of clinical remission; control group consisted of anti-TNF-naive patients, infliximab-naive patients, and patients previously treated with infliximab

Table 6 Characteristics and design elements of published real-world evidence studies

Study	Randomized at time of switch	Comparison group[a]	Powered to detect differences in efficacy after switch	Multiple switch	Immunogenicity data reported	Follow-up ≥ 12 months	Individual patient-level outcomes[b] reported
Etanercept biosimilars							
Alten et al. 2017a [41]	No	No	No	No	No	NR	No
Alten et al. 2017b [42]	No	No	No	No	No	NR	No
De Cock et al. 2017 [17]	No	No	No	No	No	No	No
Dyball et al. 2017 [43]	No	No	No	No	No	NR	No[c]
Egeberg et al. 2018 [44]	No	Yes	No	No	No	No	No
Glintborg et al. 2017a [45]	No	Yes	No	No	No	Yes	No
Hendricks et al. 2017 [46]	No	No	No	No	No	No	No
Rabbitts et al. 2017 [47]	No	No	No	No	No	No	No
Sigurdardottir et al. 2017 [48]	No	No	No	No	No	No	No
Szlumper et al. 2017a [49]	No	No	No	No	No	No	No
Szlumper et al. 2017b [50]	No	No	No	No	No	No	No
Tweehuysen et al. 2017a [51]	No	Yes	No	No	No	No	No[c]

Table 6 continued

Study	Randomized at time of switch	Comparison group[a]	Powered to detect differences in efficacy after switch	Multiple switch	Immunogenicity data reported	Follow-up ≥ 12 months	Individual patient-level outcomes[b] reported
Infliximab biosimilars							
Abdalla et al. 2017 [52]	No	No	No	No	No	Yes	No[c]
Akrout et al. 2017 [53]	No	No	No	No	No	NR	No
Ala et al. 2016 [54]	No	No	No	No	No	No	No[c]
Arguelles-Arias et al. 2017 [55, 56]	No	No	No	No	No	Yes	No[c]
Avouac et al. 2017 [57]	No	No	No	No	No	No	No[c]
Babai et al. 2017 [58]	No	No	No	No	No	No	No
Batticciotto et al. 2016 [59]	No	No	No	No	No	No	No[c]
Bennett et al. 2016 [60]	No	No	No	No	Yes	No	No
Bennucci et al. 2017 [61]	No	No	No	No	Yes	No	No[c]
Boone et al. 2017 [62]	No	No	No	No	Yes	Yes	No
Boone et al. 2018 [63]	No	No	No	No	Yes	No	No
Buer et al. 2017 [64]	No	No	No	No	Yes	No	No[c]

Table 6 continued

Study	Randomized at time of switch	Comparison group[a]	Powered to detect differences in efficacy after switch	Multiple switch	Immunogenicity data reported	Follow-up ≥ 12 months	Individual patient-level outcomes[b] reported
Choe et al. 2017a [65]	No	No	No	No	No	No	No
Choe et al. 2017b [66]	No	No	No	No	No	No	No
Chung et al. 2016 [67]	No	No	No	No	No	NR	No
Dapavo et al. 2016 [68]	No	No	No	No	No	No	No
De Cock et al. 2017 [17]	No	No	No	No	No	No	No
Díaz Hernández et al. 2016 [69]	No	No	No	No	No	No	No[c]
Eberl et al. 2017 [70]	No	No	No	No	Yes	No	No[c]
Egeberg et al. 2018 [44]	No	Yes	No	No	No	Yes	No
Ellis et al. 2017 [71]	No	Yes	No	No	No	Yes	No
Farkas et al. 2015 [72]	No	No	No	No	Yes	No	No[c]
Fiorino et al. 2017 [73, 74]	No	No	No	No	Yes	No	No[c]
Forejtová et al. 2017 [75]	No	No	No	No	No	No	No[c]
Geccherle et al. 2017 [76]	No	No	No	No	No	No	No

Table 6 continued

Study	Randomized at time of switch	Comparison group[a]	Powered to detect differences in efficacy after switch	Multiple switch	Immunogenicity data reported	Follow-up ≥ 12 months	Individual patient-level outcomes[b] reported
Gentileschi et al. 2016 [77]	No	No	No	No	No	No	No
Giunta et al. 2017 [78]	No	No	No	No	No	No	No[c]
Glintborg et al. 2017b [14]	No	Yes	No	No	No	Yes	No[c]
Gompertz et al. 2017 [79]	No	No	No	No	Yes	No	No
Guerrero Puente et al. 2017 [80]	No	No	No	No	Yes	Yes	No[c]
Hamanaka et al. 2016 [81]	No	No	No	No	No	No	No[c]
Hlavaty et al. 2016 [82]	No	No	No	No	No	Yes	No[c]
Holroyd et al. 2016 [83]	No	No	No	No	No	No	No[c]
Huoponen et al. 2017 [84]	No	No	No	No	No	Yes	No[c]
Jahnsen et al. 2017 [85]	No	No	No	No	No	No	No[c]
Jung et al. 2015 [86]	No	No	No	No	No	Yes	No[c]
Kang et al. 2015 [87]	No	No	No	No	No	Yes	No[c]

Table 6 continued

Study	Randomized at time of switch	Comparison group[a]	Powered to detect differences in efficacy after switch	Multiple switch	Immunogenicity data reported	Follow-up ≥ 12 months	Individual patient-level outcomes[b] reported
Kang et al. 2018 [88]	No	Yes	No	No	Yes	Yes	No[c]
Kolar et al. 2017 [89]	No	No	No	No	Yes	Yes	No[c]
Malaiya et al. 2016 [90]	No	No	No	No	No	No	No[c]
Malpas et al. 2017 [91]	No	No	No	No	No	No	No[c]
Nikiphorou et al. 2015 [92]	No	No	No	No	Yes	No	No[c]
Nugent et al. 2017 [93]	No	No	No	No	Yes	Yes	No
Park et al. 2015 [94]	No	No	No	No	No	No	No[c]
Phillips et al. 2017 [95]	No	Yes	No	No	No	NR	No
Plevris et al. 2017 [96]	No	No	No	No	Yes	NR	No
Presberg et al. 2017 [97]	No	No	No	No	Yes	NR	No[c]
Rahmany et al. 2016 [98]	No	No	No	No	No	NR	No[c]
Ratnakumaran et al. 2017 [99]	No	Yes	No	No	Yes	Yes	No

Table 6 continued

Study	Randomized at time of switch	Comparison group[a]	Powered to detect differences in efficacy after switch	Multiple switch	Immunogenicity data reported	Follow-up ≥ 12 months	Individual patient-level outcomes[b] reported
Razanskaite et al. 2017 [100]	No	Yes	No	No	Yes	Yes	No[c]
Rubio et al. 2016 [101]	No	No	No	No	No	No	No
Schmitz et al. 2017 [102]	No	No	No	No	Yes	Yes	Yes[c]
Schmitz et al. 2018 [103]	No	No	No	No	Yes	Yes	Yes
Sheppard et al. 2016 [104]	No	No	No	No	No	NR	No
Sieczkowska et al. 2016 [105]	No	No	No	No	No	No	No[c]
Sieczkowska-Golub et al. 2017 [106, 107]	No	No	No	No	Yes	Yes	No[c]
Sladek et al. 2017 [108]	No	No	No	No	Yes	No	No
Smits et al. 2017 [109, 110]	No	No	No	No	Yes	Yes	Yes[c]
Strik et al. 2017 [111]	No	No	No	No	Yes	No	No[c]
Toscano Guzman et al. 2016 [112]	No	No	No	No	No	No	No
Tweehuysen et al. 2017b [15]	No	Yes	No	No	Yes	No	No[c]

Table 6 continued

Study	Randomized at time of switch	Comparison group[a]	Powered to detect differences in efficacy after switch	Multiple switch	Immunogenicity data reported	Follow-up ≥ 12 months	Individual patient-level outcomes[b] reported
Van den Hoogen et al. 2016 [113]	No	No	No	No	No	No	No
Vergara-Dangond et al. 2017 [114]	No	Yes	No	No	No	NR	No[c]
Yazici et al. 2016 [115]	No	Yes	No	No	No	No	No

[a] Excludes comparison group consisting of naive patients or patients previously treated with other biologics

[b] Individual patient-level data defined as individual data points that included, but were not limited to, immunogenicity markers that were separately reported for each individual participant in the publication of a clinical study; data reported separately for each individual study participant may also have included, for example, demographic characteristics, efficacy outcomes, and/or laboratory test results

[c] Reports patient-reported outcome measures

and 26% vs. 29% [100], respectively), whereas in one study discontinuation rates were slightly numerically higher for continuers versus switchers (14% vs. 8% [88]). In contrast, in four studies, the differences between the continuer and switcher groups were more pronounced (34% vs. 87% [71], 2 vs. 13 per 1000 patient-years [95], 5% vs. 24% [15], and 38% vs. 82% [115]). In three studies, hazard ratios showed that patients who switched from an originator to its biosimilar were significantly more likely to discontinue treatment than the historical/parallel continuer cohorts [14, 51, 95], whereas similar analyses in two studies showed no significant differences (Table 5) [44, 100].

Similarly, only six (8%) studies compared overall discontinuation rates between switch and treatment-naive groups [72, 81, 82, 87, 89, 101]. In three studies, rates were higher for the naive group versus switchers (23% vs. 17% [82], 11% vs. 5% [89], and 24% vs. 9% [101]), whereas in two studies rates were lower for the naive group versus switchers and differences between the groups were more pronounced (3% vs. 33% [72] and 0% vs. 11% [87]); however, the numbers of patients in these studies were small (Table 5). In one study, discontinuation rates were 0% for both groups [81].

DISCUSSION

This systematic review assessed the robustness and conclusiveness of the current evidence of non-medical switching from an originator TNF inhibitor to its biosimilar as reported in RCTs and RWE studies published between 1 January 2012 and 14 February 2018. The results of this review confirm that, when assessing the totality of the evidence, no single non-medical switching RCT or RWE study has been identified in which all seven key design elements of a robust switching study have been comprehensively incorporated and analyzed. Furthermore, among the 91 studies (98 publications) identified, discontinuation rates varied widely, suggesting that the current evidence is inconclusive and that more data from properly designed studies are needed to bridge the knowledge gap.

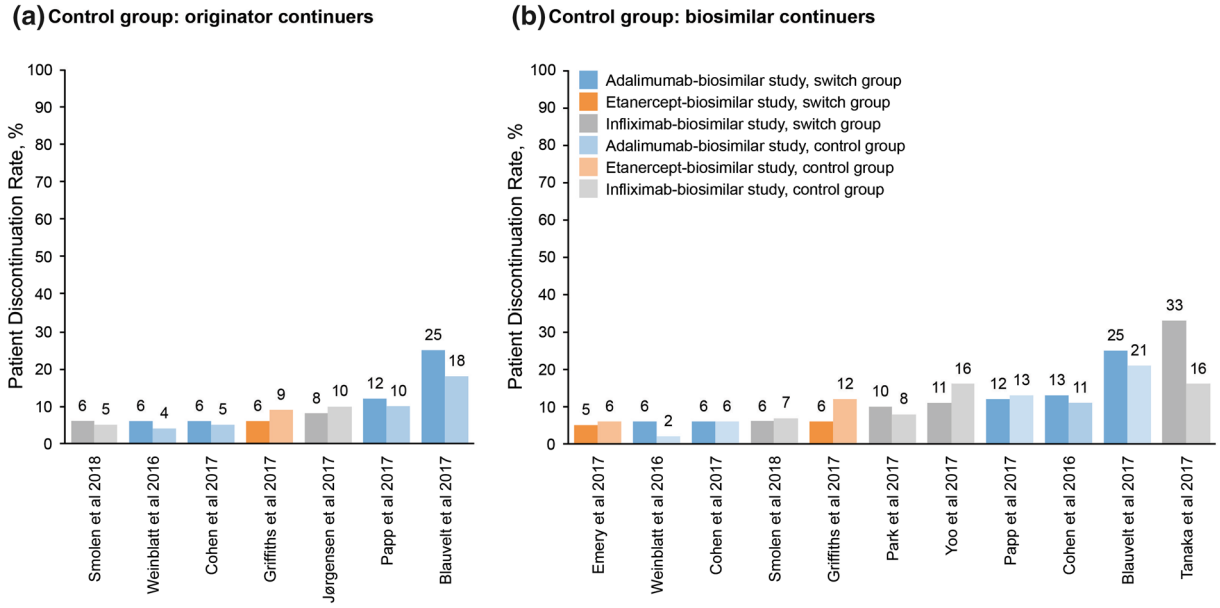

Fig. 5 Patient discontinuation rates reported in published RCTs reporting non-medical switching from TNF inhibitor originator to biosimilar. *RCT* randomized controlled trial, *TNF* tumor necrosis factor

Switching from originator biologic therapies to their biosimilars is becoming more attractive because of the potential cost savings [3, 4]. However, caution is needed when switching patients who are stable on their current therapy. A recent systematic review of 29 US-based studies (each ≥ 25 patients) examining a total of 253,795 patients treated with a variety of medications (e.g., TNF inhibitors, antihypertensives, antidepressants, insulin, and statins) demonstrated that negative or neutral effects were more commonly associated with non-medical switching than positive effects [116], an observation that was especially apparent among stable patients with well-controlled disease. Thus, more robust studies are needed to assess the outcomes of non-medical switching, particularly on an individual patient level. The results of this systematic review support this concept and demonstrate that the current evidence on the safety and efficacy of non-medical switching from the originator biologic to its biosimilar is inconclusive and inconsistent. In general, non-medical switching evidence should come from long-term, randomized, controlled, adequately powered studies that use multiple switches between the originator and its biosimilar (Table 2) [3, 10]. In addition to safety and efficacy outcomes, these studies should collect immunogenicity and individual patient-level outcomes.

Although the RCTs and RWE studies conducted to date fulfill some of these requirements and provide valuable information on safety and efficacy consequences after non-medical switching, several additional factors need to be considered when analyzing the totality of the evidence. First, although most of the identified RCTs were powered to detect differences in efficacy and safety during the head-to-head comparison phase of originator versus biosimilar, none were powered to detect these differences after the switch from originator to biosimilar. The only exception to this was the NOR-SWITCH study, which, as highlighted above, was powered at a pooled, but not individual, indication level to compare rates of disease worsening between switchers and continuers [16]; in addition to the pooling of indications, the NOR-SWITCH study had several other important methodologic limitations that have been examined elsewhere [19]. Second,

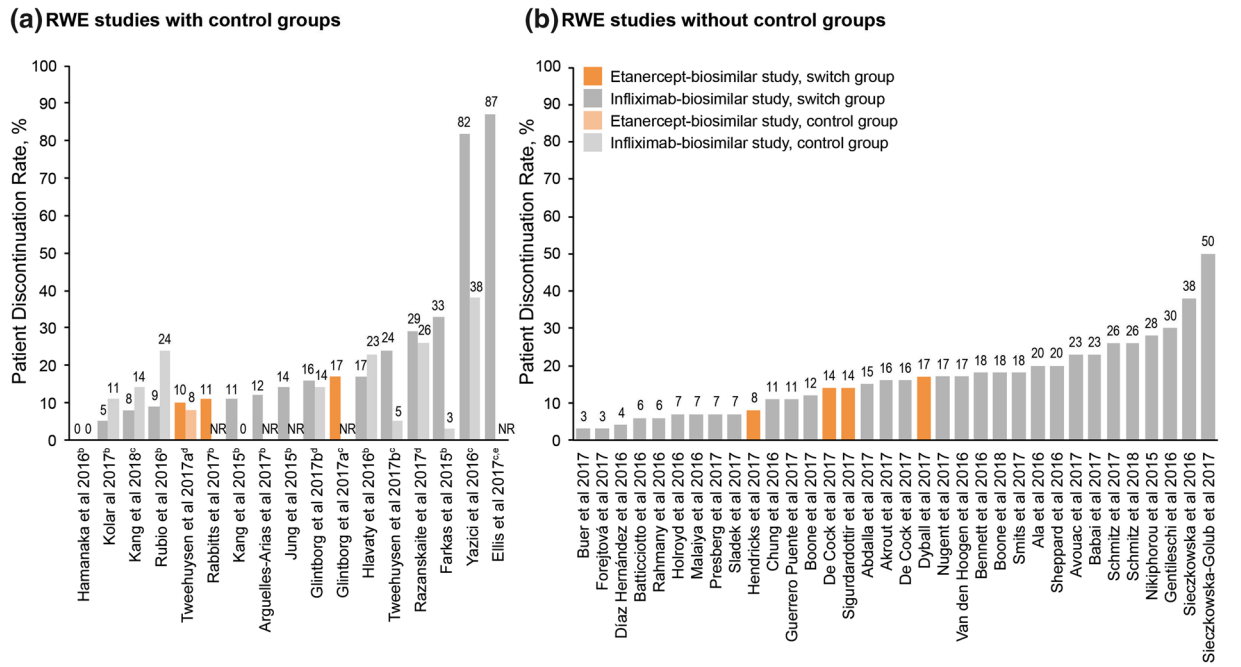

Fig. 6 Patient discontinuation rates reported in published RWE studies reporting non-medical switching from TNF inhibitor originator to biosimilar. *NR* not reported; *RWE* real-world evidence; *TNF* tumor necrosis factor. [a]Of the 74 RWE studies, 51 reported discontinuation rates. Etanercept-biosimilar and infliximab-biosimilar aspects of the De Cock et al. study [17] are each displayed separately. [b]Control group consisted of naive patients (defined as those who received induction therapy with the biosimilar regardless of previous treatment history, including biologic naive, TNF-inhibitor naive, and others who may have been previously treated with TNF inhibitors and/or originator product). [c]Control group consisted of originator continuers. [d]Control group consisted of historical cohort. [e]The authors are unclear which of the two discontinuation rates (19% or 34%) listed by the publication for the originator continuer control group was accurate

although all RCTs included a comparison group, only 11 (65%) studies followed a group of randomized patients continuing on the originator [16, 22, 23, 25–29, 31–34, 36, 39], and only 3 (18%) studies (ADACCESS [22], EGALITY [31, 32], and ARABESC-OLE [25]) investigated multiple switches between the originator and its biosimilar. Finally, the current publications for most of the RCTs lacked long-term follow-up data and all lacked individual patient-level data.

At the time of this review, the bulk of the non-medical switching evidence comes from RWE studies (particularly among patients switching from infliximab originator to biosimilar) and, although they play an important role in the continuous evaluation of therapies such as biosimilars, RWE studies should not supersede well-designed RCTs in the investigation of non-medical switching from an originator to its biosimilar [3, 10, 117]. Similar to the RCTs and as anticipated, none of the currently published RWE studies met all of the design elements for a robust switching study; the patient populations were generally small and widely heterogeneous, the follow-up periods were mostly short, and most studies lacked control groups and immunogenicity and/or individual patient-level analyses. Furthermore, although some of the multiple-cohort RWE studies provided some statistical comparisons [14, 44, 45, 51, 73, 88, 95, 99, 100, 115], none of them were powered to detect differences in efficacy or safety after the switch.

The diverse outcomes observed across the RCTs and RWE studies are most likely a consequence of the variability of the study designs as well as a lack of the seven key design elements.

This was evident in particular across the RWE studies that included elements such as grouping of indications, enrolling heterogeneous patient populations that varied in duration of disease and time on current therapy, and mixing treatment-naive and stable patient populations while lacking other elements such as defining disease stability pre-switch, identifying concomitant medications pre- and post switch, and describing dose intensification details post switch. These are typical characteristics for RWE studies; however, because of the heterogeneous results across the studies, the data need to be assessed with caution, especially for decision-making purposes.

To assess the consistency of the current non-medical switching data across studies, we examined the post-switch rates of therapy discontinuation across studies. Discontinuation data can provide a marker of treatment efficacy and tolerability and can also provide insight into clinical and patient-reported consequences of non-medical switching [118]. The overall discontinuation rates in the RCTs ranged from 5% to 33% in the switch groups, with even larger variation noted among the RWE studies (0–87%). This high level of variation is concerning, especially when considering that some studies included non-medically switched patients with chronic diseases who may have been in long-term disease remission before the switch. Although discontinuation rates were the only outcome examined here, outcomes reported by the RCTs are also limited in that they did not perform statistical analyses on switch groups. Of the RCT non-medical switching studies published to date, only ADACCESS, EGALITY, and NOR-SWITCH performed statistical analyses on switch groups rather than simply reporting descriptive numerical data. Future studies should evaluate in more detail the specific reasons for, as well as consequences of, therapy discontinuation following a non-medical switch from an originator to its biosimilar.

As the US regulatory guidance currently stands, FDA approvals of biosimilars are entirely based on head-to-head trials versus the originator. However, depending on the clinical experience, additional evaluation(s) may be needed in certain patient subgroups to assess potential risks in terms of immunogenicity, hypersensitivity, or other reactions that may arise following a single switch from originator to the proposed biosimilar product [119]. Therefore, owing to the limited, inconclusive, and heterogeneous nature of the currently available data, non-medical switching from an originator to a biosimilar not designated as interchangeable in the USA should be an evidence-based decision made between the physician and the patient [120]. Currently, no biosimilar has yet been deemed interchangeable with its originator product in the USA [11], but this may change in the future and at least one trial with the apparent objective of demonstrating interchangeability with the originator adalimumab has already commenced: the VOLTAIRE-X study with BI 695501 [121, 122].

Based on the current literature, the amount of data describing switching from infliximab to CT-P13 by far outweighs the amount of data for any other originator-biosimilar pair, but it is important to note that these data should not be transferred to other biosimilars. With increasing numbers of biosimilars coming to market for each originator product, it is likely that switching will also occur between multiple biosimilars of the same originator product and that individual patients will experience multiple switches. Because biosimilars are evaluated against the originator product but not against other biosimilars, any similarity between two biosimilars of the same originator product is unknown [123]. Currently, and to the best of the authors' knowledge, no studies have been published that primarily examine the consequences of switching between different biosimilars of the same originator product. Furthermore, none of the RWE studies published to date have examined multiple switches between an originator and its biosimilar. Therefore, further research is needed to evaluate patient efficacy, safety, and immunogenicity after multiple switches or when switching between different individual biosimilars of the same originator. These data should come from well-controlled clinical trials, as suggested by the FDA, and not solely from registry studies [117].

In this systematic review, the use of discontinuation rates as an outcome, especially in the RWE studies, is limited by the fact that discontinuation rates are cumulative and all of the RWE studies varied in length. Other limitations included potential publication bias, limited focus on secondary outcomes that were included in some trials (such as quality-of-life assessments), and variability in the methodology used by individual studies. In addition, many of the studies were descriptive in nature and were not powered or designed to detect differences post switch; as a result, it was not possible to pool the studies for a meta-analysis of either safety or efficacy end points. Finally, the proposed benchmark of seven key study design elements is limited by having been derived from regulatory requirements and expert opinion rather than all possible elements of study design that might have bearing on non-medical switching, for reasons of practicality.

CONCLUSIONS

Based on the totality of the published data and the prevailing evidence gaps, conclusive safety and efficacy of non-medical switching from an originator TNF inhibitor therapy to its biosimilar has yet to be fully demonstrated. To properly assess the safety and efficacy of non-medical switching, future studies should incorporate all of the seven key study design elements discussed in this review. Furthermore, systematic collection of switching data using validated registries and medical records is essential to gather the totality of clinical evidence needed to inform clinical decision-making on the safety and efficacy of non-medical switching from an originator to a biosimilar. In parallel, continued pharmacovigilance is important to identify and monitor rare and long-term safety events. Overall, in patients who are doing well on their current biologic treatment, such as TNF inhibitors, switching for non-medical reasons should be approached with caution, as data describing non-medical switching for currently marketed biosimilars are not robust and are inconclusive regarding any potential impact on efficacy, safety, and immunogenicity, particularly at the individual patient level. Decisions to switch should remain between the treating physician and the patient and be made on a case-by-case basis relying on scientific evidence.

ACKNOWLEDGEMENTS

Funding. AbbVie funded this review, was involved in the collection, analysis, and interpretation of the data, and in the writing, review, and approval of the publication. Article processing charges were funded by AbbVie. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Medical Writing, Editorial and Other Assistance. Literature search support was provided by Sherry Kim of AbbVie, Inc. Editorial and medical writing support was provided by Maria Hovenden, PhD, and Morgan C. Hill, PhD, of Complete Publication Solutions, LLC, North Wales, PA, USA, and was funded by AbbVie.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given approval for this version to be published.

Disclosures. Syed Numan is a full-time employee of AbbVie and may own AbbVie stock or stock options. Freddy Faccin is a full-time employee of AbbVie and may own AbbVie stock or stock options.

Compliance with Ethics Guidelines. 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.

Data Availability. This manuscript has no associated data.

REFERENCES

1. Silva LC, Ortigosa LC, Benard G. Anti-TNF-alpha agents in the treatment of immune-mediated inflammatory diseases: mechanisms of action and pitfalls. Immunotherapy. 2010;2:817–33.

2. Braun J, Kudrin A. Switching to biosimilar infliximab (CT-P13): evidence of clinical safety, effectiveness and impact on public health. Biologicals. 2016;44:257–66.

3. Moots R, Azevedo V, Coindreau JL, et al. Switching between reference biologics and biosimilars for the treatment of rheumatology, gastroenterology, and dermatology inflammatory conditions: considerations for the clinician. Curr Rheumatol Rep. 2017;19:37.

4. Singh SC, Bagnato KM. The economic implications of biosimilars. Am J Manag Care. 2015;21:s331–40.

5. Reger A, Dube N. Non-medical switching of medications. Hartford, CT: Connecticut General Assembly, Office of Legislative Research; January 12, 2017. 2017-R-0008.

6. Reynolds A, Koenig AS, Bananis E, Singh A. When is switching warranted among biologic therapies in rheumatoid arthritis? Expert Rev Pharmacoecon Outcomes Res. 2012;12:319–33.

7. European Medicines Agency. Guideline on similar biological medicinal products (Revision). CHMP/437/04 Rev 1. London, UK: 2014.

8. US Department of Health and Human Services, US Food and Drug Administration. Guidance for industry scientific considerations in demonstrating biosimilarity to a reference product. Rockville, MD: US Dept of Health and Human Services; 2015.

9. World Health Organization. Guidelines on evaluation of similar biotherapeutic products (SBPs). http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf. Accessed 28 March 2018.

10. US Food and Drug Administration. Considerations in demonstrating interchangeability with a reference product Bethesda, MD: US Department of Health and Human Services. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf. Accessed 10 April 2018.

11. List of licensed biological products with (1) reference product exclusivity and (2) biosimilarity or interchangeability evaluations to date. Center for Drug Evaluation and Research. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM560162.pdf. Accessed 10 April 2018.

12. National Conference of State Legislatures. State laws and legislation related to biologic medications and substitution of biosimilars. July 2015. http://www.ncsl.org/documents/summit/summit2015/onlineresources/BiologicsreportLS15newmedicines.pdf. Accessed 10 April 2018.

13. Kurki P, van Aerts L, Wolff-Holz E, Giezen T, Skibeli V, Weise M. Interchangeability of biosimilars: a European perspective. BioDrugs. 2017;31:83–91.

14. Glintborg B, Sorensen IJ, Loft AG, et al. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. Ann Rheum Dis. 2017;76:1426–31.

15. Tweehuysen L, van den Bemt BJF, van Ingen IL, et al. Subjective complaints as the main reason for biosimilar discontinuation after open-label transition from reference infliximab to biosimilar infliximab. Arthritis Rheumatol. 2018;70:60–8.

16. Jørgensen KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. Lancet. 2017;389:2304–16.

17. De Cock D, Kearsley-Fleet L, Watson K, Hyrich KL. Switching from RA originator to biosimilar in routine clinical care: early data from the British Society for Rheumatology biologics register for rheumatoid arthritis. Arthritis Rheumatol. 2017;69:3489–91.

18. Levin KA. Study design VII. Randomised controlled trials. Evid Based Dent. 2007;8:22–3.

19. Faccin F, Tebbey P, Alexander E, Wang X, Cui L, Albuquerque T. The design of clinical trials to support the switching and alternation of biosimilars. Expert Opin Biol Ther. 2016;16:1445–53.

20. European Medicines Agency policy on publication of clinical data for medicinal products for human use. EMA/240810/2013. October 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500174796.pdf. Accessed 10 April 2018.

21. European Medicines Agency. European Public Assessment Reports (Biosimilars). http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fmedicines%2Flanding%2Fepar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&alreadyLoaded=true&isNewQuery=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&keyword=Enter+keywords&searchType=name&taxonomyPath=&treeNumber=&searchGenericType=biosimilars&genericsKeywordSearch=Submit. Accessed 10 April 2018.

22. Blauvelt A, Lacour JP, Fowler J, et al. Long-term efficacy, safety and immunogenicity results from a randomized, double-blind, phase III confirmatory efficacy and safety study comparing GP2017, a proposed biosimilar, with reference adalimumab [abstract]. Arthritis Rheumatol. 2017;69:abstr2440.

23. Cohen SB, Alonso-Ruiz A, Klimiuk PA, et al. Biosimilar candidate BI 695501 and adalimumab reference product have similar efficacy and safety in patients with moderately-to-severely active rheumatoid arthritis (RA): 1-year results from a phase III study. Arthritis Rheumatol. 2017;69:3495–7.

24. Cohen S, Pablos JL, Zhang N, et al. ABP 501 long-term safety/efficacy: interim results from an open-label extension study. Arthritis Rheumatol. 2016;68:808–9.

25. Genovese MC, Glover J, Matsunaga N, Chisholm D, Alten R. Efficacy, safety and immunogenicity in randomized, double-blind (DB) and open-label extension (OLE) studies comparing FKB327, an adalimumab biosimilar, with the adalimumab reference product (Humira®; RP) in patients (pts) with active rheumatoid arthritis (RA). Arthritis Rheumatol. 2017;69:abstr2799.

26. Hodge J, Tang H, O'Connor P, Finck B. Switching from adalimumab to CHS-1420: a randomized, double-blind global clinical trial in patients with psoriasis and psoriatic arthritis. Arthritis Rheumatol. 2017;69:abstr2879.

27. Papp K, Bachelez H, Costanzo A, et al. Clinical similarity of the biosimilar ABP 501 compared with adalimumab after single transition: long-term results from a randomized controlled, double-blind, 52-week, phase III trial in patients with moderate-to-severe plaque psoriasis. Br J Dermatol. 2017;177:1562–74.

28. Weinblatt M, Baranauskaite A, Ghil J, Cheong SY, Hong E. Minimal and comparable radiographic progression by disease activity states in patients with rheumatoid arthritis who continued SB5 or reference adalimumab and who switched to SB5. Arthritis Rheumatol. 2017;69:abst2446.

29. Weinblatt M, Baranauskaite A, Ghil J, Cheong SY, Hong E. Sustained efficacy and comparable safety and immunogenicity after transition to SB5 (an adalimumab biosimilar) vs. continuation of SB5 or reference adalimumab (Humira®) in patients with rheumatoid arthritis: results of phase III study. Arthritis Rheumatology. 2016;68:790–2.

30. Emery P, Vencovsky J, Sylwestrzak A, et al. Long-term efficacy and safety in patients with rheumatoid arthritis continuing on SB4 or switching from reference etanercept to SB4. Ann Rheum Dis. 2017;76:1986–91.

31. Griffiths CEM, Thaci D, Gerdes S, et al. The EGALITY study: a confirmatory, randomized, double-blind study comparing the efficacy, safety and immunogenicity of GP2015, a proposed etanercept biosimilar, vs. the originator product in patients with moderate-to-severe chronic plaque-type psoriasis. Br J Dermatol. 2017;176:928–38.

32. Gerdes S, Thaci D, Griffiths CEM, et al. Multiple switches between GP2015, an etanercept biosimilar, with originator product do not impact efficacy, safety and immunogenicity in patients with chronic plaque-type psoriasis: 30-week results from the phase 3, confirmatory EGALITY study. J Eur Acad Dermatol Venereol. 2018;32:420–7.

33. Goll G, Jørgensen KK, Sexton J, et al. Long-term safety and efficacy of biosimilar inliximab (CTP13) after switching from originator infliximab: results from the 26-week open label extension of a randomized Norwegian trial. Arthritis Rheumatol. 2017;69:abstr2800.

34. Kim Y, Ye BD, Pesegova M, et al. Phase III randomized controlled trial to compare biosimilar infliximab (CT-P13) with innovator infliximab in patients with active Crohn's disease: 1-year maintenance and switching results. United Eur Gastroenterol J. 2017;5:1139–40.

35. Park W, Yoo DH, Miranda P, et al. Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance of CT-P13 in ankylosing spondylitis: 102-week data from the PLANETAS extension study. Ann Rheum Dis. 2017;76:346–54.

36. Smolen JS, Choe JY, Prodanovic N, et al. Safety, immunogenicity and efficacy after switching from reference infliximab to biosimilar SB2 compared with continuing reference infliximab and SB2 in patients with rheumatoid arthritis: results of a randomised, double-blind, phase III transition study. Ann Rheum Dis. 2018;77:234–40.

37. Tanaka Y, Yamanaka H, Takeuchi T, et al. Safety and efficacy of CT-P13 in Japanese patients with rheumatoid arthritis in an extension phase or after switching from infliximab. Mod Rheumatol. 2017;27:237–45.

38. Taylor P, Wyand M, Knight A, Costantino C, Lassen C. Efficacy of the biosimilar BOW015, compared to originator infliximab, initiated at moderate and severe disease activity thresholds in rheumatoid arthritis. Ann Rheum Dis. 2016;75:488–9.

39. Volkers A, Jansen J. SIMILAR trial—efficacy of infliximab-biosimilar compared to infliximab-biological in patients with inflammatory bowel disease in remission—a randomized, controlled, double blind, phase 4 noninferiority trial. United Eur Gastroenterol J. 2017;5:A307.

40. Yoo DH, Prodanovic N, Jaworski J, et al. Efficacy and safety of CT-P13 (biosimilar infliximab) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Ann Rheum Dis. 2017;76:355–63.

41. Alten R, Jones HE, Singh E, et al. Preliminary real world data on switching between etanercept and its recently marketed biosimilar counterpart. Value Health. 2017;20:A230.

42. Alten R, Neregard P, Jones H, et al. Preliminary real world data on switching patterns between etanercept, its recently marketed biosimilar counterpart and its competitor adalimumab, using Swedish prescription registry. Arthritis Rheumatol. 2017;69:488.

43. Dyball S, Hoskins V, Christy-Kilner S, Haque S. Effectiveness and tolerability of Benepali in rheumatoid arthritis patients switched from Enbrel. Arthritis Rheumatol. 2017;69:3505–6.

44. Egeberg A, Ottosen MB, Gniadecki R, et al. Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. Br J Dermatol. 2018;178:509–19.

45. Glintborg B, Omerovic E, Danebod K, et al. 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 [abstract]. Arthritis Rheumatol. 2017;69:abstr1550.

46. Hendricks O, Hørslev-Petersen K. When etanercept switch fails—clinical considerations. Arthritis Rheumatol. 2017;69:3570–1.

47. Rabbitts R, Jewell T, Marrow KL, Herbison C, Laversuch C. Switching to biosimilars: an early clinical review. Rheumatology. 2017;56:132.

48. Sigurdardottir VR, Husmark T, Svärd A. Switching from reference product to the biosimilar SB4 in a real life setting: 12 month follow up of 146 patients. Ann Rheum Dis. 2017;76:835.

49. Szlumper C, Laftah Z, Smith C, et al. Switching to biosimilar etanercept in clinical practice: a prospective cohort study. Br J Dermatol. 2017;177:62.

50. Szlumper C, Topping K, Blackler L, et al. Switching to biosimilar etanercept in clinical practice. Rheumatology. 2017;56:ii139.

51. Tweehuysen L, Huiskes VJB, Van Den Bemt BJF, et al. Open label transitioning from originator etanercept to biosimilar SB4 compared to continuing treatment with originator etanercept in a historical cohort in rheumatic diseases in daily practice. Arthritis Rheumatol. 2017;69:abstr2438.

52. Abdalla A, Byrne N, Conway R, et al. Long-term safety and efficacy of biosimilar infliximab among patients with inflammatory arthritis switched from reference product. Open Access Rheumatol. 2017;9:29–35.

53. Akrout W, Bosycot A, Levet-Labry R, Gazaix-Fontaine E, Paul M, Claudepierre P. Transition from ongoing infliximab reference product to its biosimilar: can we talk about a failure? Rheum Dis. 2017;76:1301–2.

54. Ala K, Avery P, Wilson R, et al. Early experience with biosimilar infliximab at a district general hospital for an entire Crohn's disease patient cohort switch from Remicade to Inflectra. Gut. 2016;65:A81.

55. Arguelles-Arias F, Guerra Veloz MF, Perea Amarillo R, et al. Switching from reference infliximab to CT-P13 in patients with inflammatory bowel disease: 12 months results. Eur J Gastroenterol Hepatol. 2017;29:1290–5.

56. Arguelles-Arias F, Guerra Veloz MF, Perea Amarillo R, et al. Effectiveness and safety of CT-P13 (biosimilar infliximab) in patients with inflammatory bowel disease in real life at 6 months. Dig Dis Sci. 2017;62:1305–12.

57. Avouac J, Molto A, Abitbol V, et al. Systematic switch from innovator infliximab to biosimilar infliximab in inflammatory chronic diseases in daily clinical practice: the experience of Cochin

University Hospital, Paris, France. Semin Arthritis Rheum. 2018;47:741–8.

58. Babai S, Akrout W, Le-Louet H. Reintroduction of reference infliximab product in patients showing inefficacy to its biosimilar. Drug Saf. 2017;40:1027–8.

59. Batticciotto A, Antivalle M, Li Gobbi F, et al. Safety and efficacy of switching from originator to CT-P13 infliximab biosimilar in patients affected by spondyloarthritis. A 6-month observational study. Arthritis Rheumatol. 2016;68:957–8.

60. Bennett KJ, Heap GA, Hawkins S, Ahmad T. Prospective evaluation of the safety and efficacy of switching stable patients with inflammatory bowel disease from Remicade™ to biosimilar infliximab (IFX). Gut. 2016;65:A146.

61. Benucci M, Gobbi FL, Bandinelli F, et al. Safety, efficacy and immunogenicity of switching from innovator to biosimilar infliximab in patients with spondyloarthritis: a 6-month real-life observational study. Immunol Res. 2017;65:419–22.

62. Boone N, Lui L, Romberg M, et al. Transition study of biosimilar infliximab in patients with inflammatory bowel disease. Clin Ther. 2017;39:e9.

63. Boone NW, Liu L, Romberg-Camps MJ, et al. The nocebo effect challenges the non-medical infliximab switch in practice. Eur J Clin Pharmacol. 2018;74:655–61.

64. Buer LC, Moum BA, Cvancarova M, Warren DJ, Medhus AW, Hoivik ML. Switching from Remicade® to Remsima® is well tolerated and feasible: a prospective, open-label study. J Crohns Colitis. 2017;11:297–304.

65. Choe YH, Yang HR, Moon JS, et al. Effectiveness and safety of CT-P13 under routine care in paediatric patients with inflammatory bowel disease. Gastroenterology. 2017;152:S396.

66. Choe YH, Lee SH, Park DI, et al. Effectiveness and safety in Crohn's disease patients who were treated with CT-P13. Gastroenterology. 2017;152:S406.

67. Chung L, Arnold B, Johnson R, Lockett MJ. Making the change: switching to infliximab biosimilars for IBD at North Bristol NHS trust. Gut. 2016;65:A22–3.

68. Dapavo P, Vujic I, Fierro MT, Quaglino P, Sanlorenzo M. The infliximab biosimilar in the treatment of moderate to severe plaque psoriasis. J Am Acad Dermatol. 2016;75:736–9.

69. Díaz Hernández L, Rodríguez González GE, Vela González M, et al. Efficacy and safety of switching between originator and biosimilar infliximab in patients with inflammatory bowel disease in practical clinic: results to 6 months [abstract P449]. J Crohn's Colitis. 2016;10:S327.

70. Eberl A, Huoponen S, Pahikkala T, Blom M, Arkkila P, Sipponen T. Switching maintenance infliximab therapy to biosimilar infliximab in inflammatory bowel disease patients. Scand J Gastroenterol. 2017;52:1348–53.

71. Ellis LA, Simsek I, Xie L, et al. Analysis of real-world treatment patterns in a matched sample of rheumatology patients with continuous infliximab therapy or switched to biosimilar infliximab. Arthritis Rheumatol. 2017;69:abstr455.

72. Farkas K, Rutka M, Balint A, et al. Efficacy of the new infliximab biosimilar CT-P13 induction therapy in Crohn's disease and ulcerative colitis—experiences from a single center. Expert Opin Biol Ther. 2015;15:1257–62.

73. Fiorino G, Manetti N, Armuzzi A, et al. The PROSIT-BIO cohort: a prospective observational study of patients with inflammatory bowel disease treated with infliximab biosimilar. Inflamm Bowel Dis. 2017;23:233–43.

74. Fiorino G, Radice S, Gilardi D, et al. Switching from infliximab originator to CT-P13 is not related to increased immunogenicity in IBD patients: a prospective case-control study. J Crohns Colitis. 2017;11:S320.

75. Forejtová S, Zavada J, Szczukova L, Jarosova K, Philipp T, Pavelka K. A non-medical switch from originator infliximab to biosimilar CT-P13 in 36 patients with ankylosing spondylitis: 6-months clinical outcomes from the Czech biologic registry Attra. Arthritis Rheumatol. 2017;69:2198–201.

76. Geccherle A, Tessari R, Variola A, Massella A, Capoferro E, Zuppini T. A single-center experience with biosimilar infliximab: clinical, pharmacological and economic aspects. Tech Coloproctol. 2017;21:834.

77. Gentileschi S, Barreca C, Bellisai F, et al. Switch from infliximab to infliximab biosimilar: efficacy and safety in a cohort of patients with different rheumatic diseases. Response to: Nikiphorou E, Kautiainen H, Hannonen P, et al. Clinical effectiveness of CT-P13 (infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. Expert Opin Biol Ther. 2015;15:1677–1683. Expert Opin Biol Ther. 2016;16:1311–2.

78. Giunta A, Manfreda V, Del-Duca E, Vollono L, Di-Raimondo C, Bianchi L. A comparative study evaluating efficacy and safety of the biosimilar of

infliximab in psoriatic patients: naive to biosimilar versus patients previously treated with the originator. Presented at: European Academy of Dermatology and Venereology; September 13–17, 2017; Geneva, Switzerland.

79. Gompertz M, Alfaro L, Ricart E, et al. Infliximab biosimilar CT-P13 in inflammatory bowel disease patients that require intensification treatment. J Crohn's Colitis. 2017;11:S427–8.

80. Guerrero Puente L, Iglesias Flores E, Benitez JM, et al. Evolution after switching to biosimilar infliximab in inflammatory bowel disease patients in clinical remission. Gastroenterol Hepatol. 2017;40:595–604.

81. Hamanaka S, Nakagawa T, Koseki H, et al. Infliximab biosimilar in the treatment of inflammatory bowel disease: a Japanese single cohort observational study. J Crohn's Colitis. 2016;10:S260.

82. Hlavaty T, Krajcovicova A, Sturdik I, et al. Biosimilar infliximab CT-P13 treatment in patients with inflammatory bowel diseases—a one-year, single-centre retrospective study. Gastroenterol Hepatol. 2016;70:27–36.

83. Holroyd C, Parker L, Bennett S, et al. Switching to biosimilar infliximab: real-world data from the Southampton biologic therapies review service. Rheumatology. 2016;55:i60–1.

84. Huoponen S, Eberl A, Räsänen P, et al. Switching maintenance-infliximab to biosimilar-infliximab does not lead to significant changes in health-related quality of life and clinical outcomes in inflammatory bowel disease patients. Value Health. 2017;20:A545.

85. Jahnsen J, Jørgensen KK. Experience with biosimilar infliximab (Remsima®) in Norway. Dig Dis. 2017;35:83–90.

86. Jung YS, Park DI, Kim YH, et al. Efficacy and safety of CT-P13, a biosimilar of infliximab, in patients with inflammatory bowel disease: a retrospective multicenter study. J Gastroenterol Hepatol. 2015;30:1705–12.

87. Kang YS, Moon HH, Lee SE, Lim YJ, Kang HW. Clinical experience of the use of CT-P13, a biosimilar to infliximab in patients with inflammatory bowel disease: a case series. Dig Dis Sci. 2015;60:951–6.

88. Kang B, Lee Y, Lee K, Choi YO, Choe YH. Long-term outcomes after switching to CT-P13 in pediatric-onset inflammatory bowel disease: a single-center prospective observational study. Inflamm Bowel Dis. 2018;24:607–16.

89. Kolar M, Duricova D, Bortlik M, et al. Infliximab biosimilar (Remsima) in therapy of inflammatory bowel diseases patients: experience from one tertiary inflammatory bowel diseases centre. Dig Dis. 2017;35:91–100.

90. Malaiya R, McKee Z, Kiely P. Infliximab biosimilars—switching Remicade to Remsima in routine care: patient acceptability and early outcome data. Rheumatology. 2016;55:abstr158.

91. Malpas A, Steel L, Mills K, Pathak H, Gaffney K. Switching from Remicade to biosimilar infliximab: an evaluation of efficacy, safety and patient satisfaction. Rheumatology. 2017;56:ii69.

92. Nikiphorou E, Kautiainen H, Hannonen P, et al. Clinical effectiveness of CT-P13 (infliximab biosimilar) used as a switch from Remicade (infliximab) in patients with established rheumatic disease. Report of clinical experience based on prospective observational data. Expert Opin Biol Ther. 2015;15:1677–83.

93. Nugent S, Nugent M, Mullane D, Kelly C. EirSwitch echoes of NorSwitch: switching biosimilar therapy in an IBD cohort an Irish experience. J Crohn's Colitis. 2017;11:S295.

94. Park SH, Kim YH, Lee JH, et al. Post-marketing study of biosimilar infliximab (CT-P13) to evaluate its safety and efficacy in Korea. Expert Rev Gastroenterol Hepatol. 2015;9:35–44.

95. Phillips K, Juday T, Zhang Q, Keshishian A. Economic outcomes, treatment patterns, and adverse events and reactions for patients prescribed infliximab or CT-P13 in the Turkish population. Ann Rheum Dis. 2017;76:SAT0172.

96. Plevris N, Deekae A, Jones GR, et al. A novel approach to the implementation of biosimilar infliximab CT-P13 for the treatment of IBD utilising therapeutic drug monitoring: The Edinburgh experience. Gastroenterology. 2017;152:S385.

97. Presberg Y, Foltz V, L'Amour C, et al. THU0646 Interchangeability from infliximab originator to infliximab biosimilar: efficacy and safety in a prospective observational study on 89 patients. Ann Rheum Dis. 2017;76:450.

98. Rahmany S, Cotton S, Garnish S, et al. In patients with IBD switching from originator infliximab (remicade) to biosimilar infliximab (CT-P13) is safe and effective. Gut. 2016;65:A89.

99. Ratnakumaran R, To N, Gracie D, et al. Efficacy and tolerability of initiating, or switching to, infliximab biosimilar CT-P13 in inflammatory bowel disease (IBD): a large single-centre experience. United Eur Gastroenterol J. 2017;5:A524.

100. Razanskaite V, Bettey M, Downey L, et al. Biosimilar infliximab in inflammatory bowel disease: outcomes of a managed switching programme. J Crohns Colitis. 2017;11:690–6.

101. Rubio E, Ruiz A, López J, et al. Prospective study of 78 patients treated with infliximab biosimilar Remsima®. Ann Rheum Dis. 2016;75:1006.

102. Schmitz EMH, Benoy-De Keuster S, Meier AJL, et al. Therapeutic drug monitoring (TDM) as a tool in the switch from infliximab innovator to biosimilar in rheumatic patients: results of a 12-month observational prospective cohort study. Clin Rheumatol. 2017;36:2129–34.

103. Schmitz EMH, Boekema PJ, Straathof JWA, et al. Switching from infliximab innovator to biosimilar in patients with inflammatory bowel disease: a 12-month multicentre observational prospective cohort study. Aliment Pharmacol Ther. 2018;47:356–63.

104. Sheppard M, Hadavi S, Hayes F, Kent J, Dasgupta B. Preliminary data on the introduction of the infliximab biosimilar (CT-P13) to a real world cohort of rheumatology patients. Ann Rheum Dis. 2016;75:1011.

105. Sieczkowska J, Jarzebicka D, Banaszkiewicz A, et al. Switching between infliximab originator and biosimilar in paediatric patients with inflammatory bowel disease: preliminary observations. J Crohns Colitis. 2016;10:127–32.

106. Sieczkowska-Golub J, Jarzebicka D, Dadalski M, Meglicka M, Oracz G, Kierkus J. Maintenance biosimilar infliximab therapy in Crohn's disease pediatric patients after switching from original molecule. J Pediatr Gastroenterol Nutr. 2017;65:S23.

107. Sieczkowska J, Jarzębicka D, Oracz G, Meglicka M, Dadalski M, Kierkus J. Immunogenicity after switching from reference infliximab to biosimilar in children with Crohn disease. J Pediatr Gastroenterol Nutr. 2016;62:354.

108. Sladek M, Vultaggio A, Ghione S, et al. Efficacy, safety and immunogenicity of CT-P13 following transition from reference infliximab (Remicade) in children with established inflammatory bowel disease: a multi-centre prospective, observational study. J Pediatr Gastroenterol Nutr. 2017;64:52.

109. Smits LJT, Grelack A, Derikx L, et al. Long-term clinical outcomes after switching from Remicade® to biosimilar CT-P13 in inflammatory bowel disease. Dig Dis Sci. 2017;62:3117–22.

110. Smits LJ, Derikx LA, de Jong DJ, et al. Clinical outcomes following a switch from Remicade® to the biosimilar CT-P13 in inflammatory bowel disease patients: a prospective observational cohort study. J Crohns Colitis. 2016;10:1287–93.

111. Strik AS, Van De Vrie W, Megen Y, Minekus J, Rispens T, D'Haens GR. Unchanged infliximab serum concentrations after switching from the originator infliximab to the biosimilar CT-P13 in patients with quiescent Crohn's disease: a prospective study. Gastroenterology. 2017;152:S66.

112. Toscano Guzmán MD, Sierra Torres MI, Flores Moreno S, Avila Carpio AD, Romero Gomez M, Bautista Paloma FJ. Effectiveness and safety of biosimilar infliximab in ulcerative colitis. Eur J Hosp Pharm. 2016;23:A152.

113. van den Hoogen FHJ, Tweehuysen L. Introduction of biosimilars in a rheumatological practice: first findings. Nederlands Tijdschrift voor Dermatologie en Venereologie. 2016;26:135–6.

114. Vergara-Dangond C, Saez Bello M, Climente Marti M, Llopis Salvia P, Alegre-Sancho JJ. Effectiveness and safety of switching from innovator infliximab to biosimilar CT-P13 in inflammatory rheumatic diseases: a real-world case study. Drugs R D. 2017;17:481–5.

115. Yazici Y, Xie L, Ogbomo A, et al. A descriptive analysis of real-world treatment patterns in a Turkish rheumatology population that continued innovator infliximab (Remicade) therapy or switched to biosimilar infliximab [abstract SAT0175]. Arthritis Rheumatol. 2016;68:2903–6.

116. Nguyen E, Weeda ER, Sobieraj DM, Bookhart BK, Piech CT, Coleman CI. Impact of non-medical switching on clinical and economic outcomes, resource utilization and medication-taking behavior: a systematic literature review. Curr Med Res Opin. 2016;32:1281–90.

117. Fleischmann R. Therapy: biosimilars in rheumatology—why, how and when in 2017. Nat Rev Rheumatol. 2017;13:701–3.

118. Souto A, Maneiro JR, Gomez-Reino JJ. Rate of discontinuation and drug survival of biologic therapies in rheumatoid arthritis: a systematic review and meta-analysis of drug registries and health care databases. Rheumatology (Oxford). 2016;55:523–34.

119. US Food and Drug Administration. Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Accessed 3 April 2018.

120. McKinnon RA, Cook M, Liauw W, et al. Biosimilarity and interchangeability: principles and evidence: a systematic review. BioDrugs. 2018;32:27–52.

121. The VOLTAIRE-X trial looks at the effect of switching between Humira® and BI 695501 in patients with plaque psoriasis. https://clinicaltrials.gov/ct2/show/NCT03210259. Accessed 30 Jan 2018.

122. Boehringer Ingelheim Press Release. Boehringer Ingelheim starts clinical study on interchangeability between its adalimumab biosimilar candidate and HUMIRA® [press release]. https://www.boehringer-ingelheim.com/press-release/interchangeability-study-bi-695501-vs-humira. Accessed 3 April 2018.

123. Considerations for physicians on switching decisions regarding biosimilars. European Biopharmaceutical Enterprises; European Federation of Pharmaceutical Industries and Associations; International Federation of Pharmaceutical Manufacturers and Associations. https://www.ebe-biopharma.eu/wp-content/uploads/2017/04/considerations-for-switching-decisions_biosimilars-and-rbps-final-branded-1.pdf. Accessed 3 April 2018.

124. European Medicines Agency, European Commission. Biosimilars in the EU. Information guide for healthcare professionals. London, UK: European Medicines Agency, European Commission; 2017. http://www.ema.europa.eu/docs/en_GB/document_library/Leaflet/2017/05/WC500226648.pdf. Accessed 3 April 2018.

125. Cohen S, Genovese MC, Choy E, et al. Efficacy and safety of the biosimilar ABP 501 compared with adalimumab in patients with moderate to severe rheumatoid arthritis: a randomised, double-blind, phase III equivalence study. Ann Rheum Dis. 2017;76:1679–87.

126. Comparison of CHS-1420 versus Humira in subjects with chronic plaque psoriasis (PsOsim). https://clinicaltrials.gov/ct2/show/NCT02489227. Accessed 3 April 2018.

127. Papp K, Bachelez H, Costanzo A, et al. Clinical similarity of biosimilar ABP 501 to adalimumab in the treatment of patients with moderate to severe plaque psoriasis: a randomized, double-blind, multicenter, phase III study. J Am Acad Dermatol. 2017;76:1093–102.

128. Emery P, Vencovsky J, Sylwestrzak A, et al. A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis. 2017;76:51–7.

129. Park W, Hrycaj P, Jeka S, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis. 2013;72:1605–12.

130. Takeuchi T, Yamanaka H, Tanaka Y, et al. Evaluation of the pharmacokinetic equivalence and 54-week efficacy and safety of CT-P13 and innovator infliximab in Japanese patients with rheumatoid arthritis. Mod Rheumatol. 2015;25(6):817–24.

131. Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis. 2013;72:1613–20.