The Challenges of Switching Therapies in an Evolving Multiple Biosimilars Landscape: A Narrative Review of Current Evidence

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ABSTRACT

With the increasing availability of biosimilars, the practice of switching therapies for non-medical reasons between an originator biologic and an analogous biosimilar has become more common. The evidence to support this practice mostly comes from single-switch randomized controlled trials (RCTs) and real-world (RW) evidence studies. However, as more biosimilars of the same originator enter the market, multiple switching events between originators and biosimilars is becoming a reality, despite limited evidence to support the efficacy and safety of such practice. Some countries have established guidelines, policies, or laws related to interchangeability and/or automatic substitution, whereas others have left these practices unregulated or controlled by other components of the healthcare system. Collectively, guidelines on single non-medical switching are often vague, with even less focus given to multiple non-medical switching, leaving this practice mostly unregulated. This narrative review will first discuss the current regulatory perspectives on non-medical switching and challenges associated with switching therapies, particularly with the availability of multiple biosimilars. We will then review the current evidence from RCTs and RW studies in the light of three different multiple-switch scenarios currently taking place in clinical practice: switching between an originator and a single biosimilar, switching between biosimilars of the same originator, and the clinical practice of switching back to the originator (i.e., switchbacks) after a failure of the initial non-medical switch to the analogous biosimilar.

Keywords: Biosimilar; Multiple switch; Non-medical switching; Originator; Switchback
The current evidence on the safety, efficacy, and immunogenicity of switching multiple times from an originator to the analogous biosimilar or from a biosimilar to another biosimilar is sparse, and comes from a limited number of randomized-controlled trials and real-world evidence studies.

More robust, well-designed, long-term studies are needed to investigate the consequences of multiple or biosimilar-to-biosimilar switching.

Any decision to switch therapies (single or multiple times) should be based on clinical judgement and made jointly between the patient and the treating physician.

INTRODUCTION

The availability of biosimilars has increased the practice of switching between originator biologics and analogous biosimilars for non-medical reasons in the treatment of immune-mediated inflammatory diseases [1–3]. In clinical practice, non-medical switching, defined as switching therapy for economic or other reasons not related to patient care, may include both switching from an originator to the analogous biosimilar and vice versa. Furthermore, as more biosimilars become available, switching between biosimilars of the same originator is a possibility. After the initial non-medical switch, changes in pharmaceutical pricing or administrative/reimbursement policies may trigger subsequent switches, leading to a complex multiple-switching environment [1]. A multiple switch can also occur when the initial non-medical switch from an originator to its biosimilar results in worsening of disease or tolerability issues, at which point the patient may be switched back to the originator for medical reasons [4]. In many countries, biologics are included as part of tenders and, with physicians unable to opt out, mandated treatment switches are likely to increase; in some cases, switching currently occurs as often as every 4 months [5]. Multiple switching for economic reasons has already occurred in Hungary, Sweden, and Norway [6–8], while in countries such as Australia where automatic substitution of certain biologics is allowed, patients can switch products as often as every month [9, 10]. Similar policies may also be introduced in other countries, e.g., in Germany, a new law—the Act for Greater Security in the Pharmaceutical Supply System—went into effect in 2019 and could provide a list of products approved for substitution by 2022, allowing pharmacists to substitute biologics with biosimilars (the framework and conditions for the new law are still being resolved). Overall, these policies are likely to increase the incidence of non-medical and multiple switching [11].

From a global perspective, although multiple switching between originator products and biosimilars already occurs, it is notable that both the quality and quantity of the evidence supporting this practice are limited. The majority of the non-medical switching studies conducted to date [randomized controlled trials (RCTs) and real-world (RW) studies] have assessed the safety and efficacy of single switches, not multiple, between the originator and one or more of its biosimilars. In addition, these studies do not meet the criteria for a robust, non-medical switching trial [1], and the results from these studies and systematic reviews of the data [2, 12] vary in their conclusions regarding the effect of multiple switching on efficacy and safety. Also, it is important when assessing the evidence to recognize that data from these trials should not be generalized to other originator–biosimilar combinations or to switching between biosimilars of the same originator [13]. Thus, the effect of multiple switching on efficacy, safety, and immunogenicity, as well as other issues (e.g., pharmacovigilance), remains largely unknown [13].

The first objective of this narrative review is to discuss the current regulatory policies and non-medical switching practices, as well as
discuss the evolving treatment landscape with multiple biosimilars. The second objective is to review the challenges and potential risks involved with multiple switching based on three different switching scenarios that already occur in clinical practice: multiple switching between an originator and a single biosimilar, switching between two or more biosimilars, and the clinical practice of switching back to the originator (i.e., switchbacks) after a failed non-medical switch to its biosimilar.

LITERATURE SEARCH

A literature search of databases, including Embase® and MEDLINE, was performed to identify multiple-switching studies. The search was limited to English language studies in human participants with publication dates from January 1, 2012, to February 17, 2020. Included studies involved one of the following three switching scenarios: multiple switching between originator and a single biosimilar, biosimilar-to-biosimilar switching, and switchbacks. Multiple switching was defined as > 1 switch between an originator and a single biosimilar for non-medical reasons (Fig. 1a). Biosimilar-to-biosimilar switching was defined as switching treatment between ≥ 2 different biosimilars of the same originator (Fig. 1b). Switchback was defined as switching treatment back to the originator for medical reasons after a failure of the initial non-medical switch from the originator to the analogous biosimilar (Fig. 1c).

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.

REGULATORY PERSPECTIVES ON NON-MEDICAL SWITCHING

Specific guidelines related to biosimilars and/or interchangeability have been developed by regulatory authorities, such as the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), and Health Canada [1, 14–17].

The EMA does not include recommendations on interchangeability, and the decision-making authority related to substitution policies (including automatic substitution) rests within the EU member states [15]. According to an information guide prepared jointly by the EMA and the European Commission, interchangeability refers to the practice of changing one medicine for another that is expected to have the same clinical effect. This includes switching an originator product with the analogous biosimilar (or vice versa) or switching a biosimilar with another biosimilar, as well as automatic substitution [18]. Switching is carried out by the physician; automatic substitution may be carried out by a pharmacist (e.g., substitution for a generic) without the need for physician consultation [18].

Unlike the EMA, the FDA grants a designation of interchangeability separately from biosimilarity [19]. To support a demonstration of interchangeability, the FDA guidelines note that the product must first show biosimilarity to the originator product, as defined in the Biologics Price Competition and Innovation Act of 2009 [19]. The biosimilar product must also show that it can be expected to produce the same clinical result as the originator product in

![Fig. 1](image-url)
any given patient, and, for those biologics administered more than once, that the risk in terms of safety or diminished efficacy of alternating or switching between the originator and the biosimilar is not greater than the risk of using the originator product without such alternation or switch [19]. Furthermore, to demonstrate interchangeability, a switching study should employ a study design that alternates 1 treatment arm ≥ 2 times (i.e., ≥ 3 switches) between the originator and biosimilar product (i.e., to show the effect of multiple switching) while the other arm includes only the originator product (non-switching arm) [19]. Importantly, guidance from the FDA notes that multiple exposures in a switching study may potentially prime the immune system to recognize subtle structural differences between the 2 products, leading to an overall increased immune response [19]. Once a product is deemed interchangeable by the FDA, it can be substituted for the originator without intervention by the physician [19, 20]. Currently, no biosimilar has been granted interchangeability by the FDA [21]. However, even without a formal interchangeability designation, patients can be switched for non-medical reasons, and it is up to each state to determine policies on automatic substitution [19, 20].

Like the FDA, Health Canada’s authorization of interchangeability is independent of biosimilarity [17]. In Canada, the term interchangeability usually refers to the pharmacist’s ability to switch a patient from one drug to another equivalent drug without intervention from the prescribing physician. Health Canada’s authorization of a biosimilar is not a declaration of interchangeability, and the authority to declare two products interchangeable ultimately rests with each province and territory [17].

Globally, some countries have established guidelines, policies, or laws related to interchangeability and/or automatic substitution; in other countries, these practices remain unregulated or have been established by other components of the healthcare system [5, 10, 22–24]. Collectively, guidelines on non-medical switching are often vague, and even less focus has been given to multiple switching for non-medical reasons, leaving this practice mostly unregulated.

CHALLENGES WITH MULTIPLE SWITCHING

Although biosimilar products are deemed similar, regulatory agencies acknowledge that they are not structurally identical to the originator [14, 15]. Structural variations may arise from differences in post-translational modifications (such as glycosylation) or higher-order structure (such as protein folding) [14, 25]. When patients are switched from one product to another once or multiple times, these differences in the drug substance (i.e., structure) or the drug product (including process- or product-related impurities) raise the potential for negative outcomes, such as loss of efficacy (including by increasing the risk of immunogenicity) [26] and the emergence or worsening of adverse events (AEs). To better ensure the quality of biosimilars, the International Psoriasis Council suggests guidelines to standardize preclinical analytical assessments determining similarity between a biosimilar and its originator [27]. Of note, manufacturing changes can also lead to relevant quality differences within different batches of the originator product [28]; however, discussing these are beyond the scope for this paper. Also, it is important to note that, although scientific principles for biosimilarity comparability assessments are based on those that assess manufacturing changes for already approved biologics, both regulatory pathways are distinct and should not be confused or used in lieu of the other [14, 15].

Other potential challenges with multiple switching between products include complexity of pharmacovigilance (tracking and tracing) and patient-related challenges owing to differences in delivery devices, presentation, drug formulation, or dosage, and the availability and quality of patient-support programs. Because of these challenges, most global, regional, and national (including US) medical societies urge caution when considering non-medical switching, recommending that any decision to switch be made with the knowledge and consent of the

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prescribing physician and the patient [29–34]. Those same medical and scientific societies may not be in favor of [32–35] or specifically express opposition to [29–31, 36–38] multiple switching. We will next look at these challenges in more detail.

**Treatment Failures and Discontinuations**

Treatment failure, particularly at the individual patient level, is a concern following a non-medical switch, and discontinuation rates ranging from 0 to 87% have been reported in single-switch RW studies [1, 39–41]. One reason for treatment failures after switching is tolerability issues and the emergence of new or worsening AEs, potentially caused by unanticipated differences in safety between the 2 products [39, 41, 42]. Treatment failures can also occur due to loss of efficacy when the biosimilar is not clinically functioning the same way as the originator product, potentially because of subtle drug- or product-related differences. Most importantly, these effects may be amplified in the context of multiple switches. Of note, it is important to clarify that, when a patient’s disease is controlled, there is generally no expectation for improvement when switching from an originator to a biosimilar; however, based upon the current evidence, switching for non-medical reasons may carry risks such as treatment failure/discontinuation of therapy [1, 39, 40, 42]. Overall, considering the large variation in discontinuation rates across the current single-switch studies, and because none of the studies meet the minimum requirements for a robust switching study, the evidence on the occurrence of treatment failures following single or multiple non-medical switches remains inconclusive [1].

**Immunogenicity Concerns**

Immunogenicity, mostly defined by the development of anti-drug antibodies (ADAs), is another concern when switching therapies because of a possible immune response against the different antigens (not detected during or after biosimilar development) that may be present across products, both at the drug substance and at the drug product level [43–46]. Although ADAs can be transient and without consequences, the persistence of ADAs can have negative effects, including loss of response, type I and type III hypersensitivity, worsening of disease, increased drug toxicity, and tolerability issues, such as injection-site or infusion reactions [42, 43, 47]. Several challenges and gaps remain in the assessment of immunogenicity [48]. In vitro testing and animal studies cannot fully predict immune response in humans, and empiric data from clinical trials are needed to demonstrate whether ADAs are altering the pharmacokinetic and pharmacodynamic properties of a product, thereby affecting clinical outcome, including possible treatment failure [48–52]. An equally important consideration is the variability and heterogeneity present in ADA detection, which should be taken into account when developing ADA assays [50]. Although current RCTs show no difference in immunogenicity after a single-switch from originator to its biosimilar [53–56], the patient populations in these studies were limited and post-switch follow-up durations were short, suggesting that the studies may not be robust enough to reveal conclusive immunogenicity profiles. In RW studies, 2–14% of patients have discontinued therapy due to “ADAs” or “ADAs and inefficacy” after a single non-medical switch [41, 57–61]. However, because most RW studies conducted to date either do not report immunogenicity data or give no specific reasons for discontinuation (including whether loss of efficacy or AEs that led to discontinuation were ADA driven), the data are currently inconclusive. Thus, the concern of immunogenicity exists and is amplified when a switch is carried out multiple times between products [57]. Longer-term data from studies with ≥ 1 year follow-up are needed to assess immunogenicity that may not be detected for some time following drug administration or treatment switches [1, 14, 62, 63].
The Nocebo Effect

Treatment failures following a non-medical switch can also occur because of the nocebo effect, defined as a negative outcome or failure of treatment resulting from a patient’s negative expectations [41, 64–66]. Nocebo response is a problem in both clinical trials and real-life practice. In clinical switching trials, nocebo response may affect both trial outcomes and interpretation, while in clinical practice, nocebo response could lead to higher relapse rates, which have the potential to increase healthcare costs and the number of additional therapies needed to manage individual patients. Although the nocebo response is a well-characterized phenomenon [64–66], the current evidence regarding a role in treatment failure following a non-medical switch between biologics and their biosimilars is limited and based on studies that lack adequate design or do not collect all the necessary data to assess it properly [41]. Despite these limitations, a few studies have suggested that some treatment failures following a non-medical switch can be attributed to the nocebo response [7, 67–69]. In contrast, a retrospective study that included a blinded control group did not find any evidence of a nocebo response following a non-medical switch [70]. However, some limitations must be noted with this study; namely that no direct comparison of data for patients who knew about the switch (n = 24) versus those who did not (n = 60) was reported [70]. Thus, the frequency and impact of nocebo response following a non-medical switch remains inconclusive.

Pharmacovigilance Concerns

Subsequent to drug approval, pharmacovigilance systems continuously assess the risk–benefit profile of an agent to detect new safety signals and to minimize risks [71, 72]. Switching between an originator and biosimilars, especially multiple times and sometimes at intervals of only a few weeks, has the potential to complicate the accurate assessment and traceability of AEs. One reason for this is the delay that may occur between starting a biologic drug and the occurrence and identification of AEs, due to the relatively long latency in the development of some of these adverse reactions, including those related to immunogenicity [72–75]. Traceability is likely to get more complicated when automatic substitution and non-medical switching become more widely used. Pharmacy-level substitution of originators/biosimilars is already possible in some EU countries (Czech Republic, Latvia, Turkey, Poland, Serbia, and Estonia) and in Australia, although physicians can opt out from the practice in each country. In addition, non-medical switching is allowed in 12 EU countries without the treating physician’s consent [5, 9, 10]. To add complexity, biosimilars are mostly given the same non-proprietary name as their originator product, and the lack of a unique identifier may lead to AEs being inappropriately attributed to the wrong product [71, 72]. One potential solution is to generate unique identifiers, or qualifiers, for the originator and corresponding biosimilars to distinguish them from one another [72, 76]. To monitor AEs and to attribute them to the correct product, improved pharmacovigilance efforts are still largely needed in the era of biosimilars, although some advances have been made [77]. Accordingly, a number of medical societies have proposed requirements for postmarketing surveillance, registries, and traceability [30, 32, 33, 78, 79].

Other Patient-Related Concerns

Several additional concerns are relevant when patients are switched for non-medical reasons, including the availability and quality of patient-support programs, which may differ between originator and biosimilars or not be available at all with some products. Differences in patient-support programs can affect how patients are educated on the use and acceptance of the biologic; it is suggested that patient-support programs from the biosimilar should be just as good (i.e., in terms of patient offerings, drug-use training, disease education, etc.) as those programs offered by the originator product [80]. Switching patients once or multiple times
between therapies can also lead to concerns related to product delivery devices and injection-site reactions because the biosimilar may not use the same delivery device, formulation, dosage, or dosing interval as the originator [81–84]. Differences in formulation may also influence patient satisfaction and adherence [81]. Of note, fewer injection-site reactions were reported with biosimilar etanercept SB4 (3.7%) compared with the originator etanercept (17.2%) in a phase 3 RCT in biologic-naive patients with rheumatoid arthritis [85]. The authors concluded that the only difference in drug formulation between the products was the absence of L-arginine in SB4 [85]. Although they noted that L-arginine has not been associated with an increased risk of injection-site reactions, the authors could not exclude this difference in formulation as the cause of injection-site reactions [85]. Issues related to product delivery devices can also lead to increased healthcare utilization if patients need to be reeducated after each switch or critical handling errors when patients are not trained in the use of or confuse the different devices [81]. Such issues can also reduce treatment adherence and thereby compromise disease control and increase the toll on healthcare services [81, 83].

MULTIPLE SWITCHING BETWEEN ORIGINATOR AND A SINGLE BIOSIMILAR (SCENARIO 1)

As previously described, the act of non-medical switching from an originator product to a biosimilar or vice versa is mandated in multiple jurisdictions in select countries driven by economic reasons [6, 7, 67]. This provides the framework whereby constant fluctuations in pharmaceutical pricing and changes in reimbursement policies can lead to patients being switched multiple times between an originator and the analogous biosimilar (Fig. 1a). This has already happened in the EU, and data from two RW multiple-switch observational studies in clinical settings are available [6, 7]. In Hungary, biosimilar infliximab was mandated in 2014 to patients naive to tumor necrosis factor antagonists or those with a ≥ 1-year drug holiday. However, all patients underwent a mandated reverse switch from the biosimilar to the originator in 2017 because of changes in the National Health Insurance Fund policy [6]. In Sweden, patients who were switched from the etanercept originator to its biosimilar in 2016 were later switched back to the originator based upon pricing considerations [7]. Although in both of these studies efficacy was maintained after the switches, these studies evaluated only short-term outcomes and included small numbers of patients or patients who had been on drug holiday for an extended time before the first switch (Table 1) [6, 7].

Often, non-medical switching policies have been implemented in clinical practice based on a few single-switch studies concluding that switching from a tumor necrosis factor inhibitor originator to a biosimilar was safe and efficacious [54–56]. However, to date, only a few RCTs have assessed the safety and efficacy of multiple non-medical switches (Table 1) [86–89]. Importantly, none of these studies meet the criteria for a robust switching trial as defined by the FDA [1, 19].

One such study (ADACCESS) compared the efficacy and safety of adalimumab originator with its biosimilar, GP2017, in patients with moderate-to-severe plaque psoriasis [86]. Patients were initially randomized to receive either GP2017 or the originator adalimumab for 17 weeks, after which patients were sequentially switched 4 times between the 2 products (switch groups) or continued the originator or GP2017 (non-switch groups) for an additional 34 weeks. The study showed similar efficacy (defined by a Psoriasis Area and Severity Index 75 response), immunogenicity, and safety in the switch groups compared with the non-switch groups over time. However, although the study was powered to assess biosimilarity, it was not powered to assess the effect of treatment switching; therefore, no meaningful insights on the effect of multiple switches can be extrapolated from this study [86]. Another limitation of the study was the relatively short follow-up duration (16 weeks) after the last switch.

Another study performed in patients with moderate-to-severe rheumatoid arthritis compared the efficacy and safety of originator
Table 1 Multiple switching and biosimilar-to-biosimilar switching studies

| Study               | Type | Disease | Follow-up duration | Switch from: originator/biosimilar(s) | Discontinuations | Disease activity | ADA positive | Limitations                                                                 |
|---------------------|------|---------|--------------------|---------------------------------------|------------------|-----------------|--------------|-----------------------------------------------------------------------------|
| Multiple switch studies |      |         |                    |                                       |                  |                 |              |                                                                             |
| Blauvelt et al.      | RCT  | Psoriasis| 34 weeks           | Adalimumab/ GP2017                    | Switch groups: 16% and 17%Non-switch groups: 13% and 17% | Similar between switched and non-switched groups | Switch groups: 39% and 47%Non-switch groups: 36% and 45% | Not powered to assess treatment effect after switching, short follow-up duration after first switch |
| Genovese et al.      | RCT  | RA      | 76 weeks           | Adalimumab/ FKB327                    | NR               | Comparable for all treatment groups | No differences in ADA profiles between treatment groups | No originator–biosimilar–originator switch or continuous originator treatment groups were included |
| Alten et al.         | RCT  | Psoriasis| 40 weeks           | Etanercept/ GP2015                    | Switched groups: 6% and 12%Non-switch groups: 9% and 12% | Comparable between pooled switched and pooled continued groups | During treatment period 2 (18 weeks), no patients were positive for ADAs after switching | Data pooled for switch and non-switch groups, short follow-up duration after first switch |
| Gerdes et al.        | RCT  | Psoriasis| 40 weeks           | Infliximab/ CT-P13                    | n/N: NR/18c      | No difference in the proportion of patients in clinical remission | ADA positive at baseline and week 16: n/N, 2/14 (14%) at both time points | Short follow-up duration, 12-month drug holiday between last dose of originator and first treatment switch |
| Griffiths et al.     | RW   | IBD     | 24 weeks           | Infliximab/ CT-P13                    |                  |                 |              |                                                                             |
| Study                          | Type | Disease | Follow-up duration \(^a\) | Switch from: originator/biosimilar(s) | Discontinuations | Disease activity | ADA positive | Limitations                                      |
|-------------------------------|------|---------|--------------------------|---------------------------------|------------------|-----------------|--------------|-------------------------------------------------|
| Sigurdardottir and Svärd 2018 [7] | RW   | Rheum   | 636 days\(^d\)          | Etanercept/ SB4                 | 48/145 (33\%)    | No significant change in disease activity or inflammatory markers\(^c\) | NR           | Small numbers of patients, no safety or immunogenicity data reported |
| Cunningham et al. 2019 [93]   | RW   | NR      | 37 months               | Infliximab/ NR                  | NR               | NR              | NR           | No information on disease, disease activity or discontinuations were given |
| Fautrel et al. 2019 [94]      | RW   | RA, PsA, AS | 12 months              | Infliximab/ CT-P13, SB2         | 4/81 (4.9%)      | No significant change in disease score | NR           | Interim analysis reporting pooled data for patients switched from originator infliximab or biosimilar CT-P13 to SB2 |
| Gisondi et al. 2019 [95]      | RW   | Ps      | 6 months                | NA/CT-P13, SB2                  | NR              | No significant change in disease score | NR           | Small population, short follow-up duration |
| Harris et al. 2019 [96]       | RW   | IBD     | 16/18 weeks             | NA/CT-P13, SB2                  | 18/133 (13.5%)   | No significant change in disease activity, disease control, or drug persistence | NR           | Small population, short follow-up, no control group of matched/adjusted non-switchers for disease activity, disease control assessments |

\(^a\) Follow-up duration; \(^b\) Switch from: originator/biosimilar(s); \(^c\) Disease activity; \(^d\) ADA positive; \(^e\) Limitations.
| Study | Type | Disease | Follow-up duration* | Switch from: originator/biosimilar(s) | Discontinuations | Disease activity | ADA positive | Limitations |
|-------|------|---------|---------------------|--------------------------------------|------------------|----------------|-------------|-------------|
| Lauret et al. 2019 [97] | RW | ID | 3 years | Infliximab/Infliximab biosimilars | n/N: 111/265 (41.9%) | NR | n/N, 20/236 (8%) | Pooled indications and no control group of matched/adjusted non-switchers |
| Petit et al. 2019 [98] | RW | RA, SpA, PsA | 34 weeks | NA/CT-P13, SB2 | n/N: 6/18 (33.3%) | NR | NR | Small population, short follow-up duration, no efficacy or safety data |

* Follow-up duration after first switch

ADA anti-drug antibody, AS ankylosing spondylitis, IBD inflammatory bowel disease, ID inflammatory diseases, NA not applicable, NR not reported, Ps psoriasis, PsA psoriatic arthritis, RA rheumatoid arthritis, RCT randomized controlled trial, Rheum rheumatology, RW real-world, SpA spondyloarthritis

a Discontinuation data are calculated using the number of patients who did not complete the extension period as numerator and the number of patients who entered treatment period 2 as denominator; not all patients who completed treatment period 2 entered the extension period, but no reason was given
b 18 patients previously exposed to the originator infliximab had been on a drug holiday for ≥ 12 months before the initiation of infliximab biosimilar. The patients were switched back to the originator infliximab because of economic reasons and were followed up for 24 weeks. Proportion of patients in clinical remission 8 weeks before switch, at switch baseline, and at weeks 16 and 24 after switchback to the originator were 87%, 100%, 94%, and 93%, respectively
c Patients were switched from the originator etanercept to its biosimilar SB4 during days 0–543. On day 544, a mandated reverse switchback to the originator was initiated. Discontinuation data were reported only before the second mandated switch (days 0–543). Efficacy data were reported until day 636
adalimumab with the biosimilar FKB327 [87]. Patients were initially randomized to receive either the originator or FKB327, rerandomized either to switch therapies or continue treatment during the first part of an open-label extension phase, and randomized again to receive FKB327 during the second part of the open-label extension [87]. As a result, one group experienced a multiple switch, from FKB327 to the originator adalimumab and back to FKB327; 2 groups experienced a single switch; and 1 group received FKB327 throughout the study. An interim analysis at week 30 showed that safety and efficacy profiles were similar for all treatment groups; however, this study was not adequately powered to show statistical differences between treatments [87]. Limitations included that this was an open-label extension study and no originator–biosimilar–originator switch or continuous–originator treatment groups were included for comparison. Definitive interpretation of the findings from this study is pending publication of the final results.

A third multiple-switching study is the EGALITY trial that evaluated multiple switching between originator etanercept and the biosimilar GP2015 in patients with moderate-to-severe chronic plaque-type psoriasis [88, 89]. Patients were initially randomized either to receive the etanercept originator or GP2015 for 12 weeks, then rerandomized to continue the same treatment or undergo 3 treatment switches during the 18-week treatment period 2, followed by a 22-week extension period [88]. A prespecified analysis was performed to evaluate the effect of multiple switches compared with continued treatment in pooled treatment arms, and the study showed no difference in efficacy in the pooled switch and non-switch groups [89]. However, limitations of the study included a short follow-up duration after the last switch and pooling of the study data for the switch and non-switch groups, complicating the interpretation of the efficacy and safety results [89].

As mentioned above, immunogenicity is another concern that should be evaluated, because single or multiple switching could trigger an immune response to different antigenic determinants that might be present between an originator product and analogous biosimilars [43–46]. Only one of the two RW studies evaluated immunogenicity, and it was limited to 16 weeks and assessment of 14 patients (Table 1) [6]. In contrast, all three RCTs assessed the development of ADAs (Table 1). In the ADACCESS study, 39% and 47% of patients in the switch groups developed ADAs versus 36% and 45% in the non-switch groups by week 51, of which 100%, 75%, 86%, and 85%, respectively, were neutralizing ADAs [86]. In the FKB327 biosimilar study, 54% of patients in the multiple-switch group (from biosimilar to originator adalimumab back to biosimilar) had ADAs at week 78 compared with 51% in the treatment continuation group, and 43% and 48% in the single-switch groups; the authors concluded that long-term immunogenicity was comparable between the products but provided no statistical comparison [90]. In the 52-week EGALITY study, 1.9% (5/267) of patients in the group that continued treatment with originator etanercept had confirmed positive non-neutralizing ADAs within the first 4 weeks of treatment, and an additional patient (1/90) in the group that switched from originator etanercept was positive for non-neutralizing ADAs at week 36; no other confirmed ADAs were observed, and all respective patients with previous positive ADAs were ADA-negative at all subsequent visits [88]. It is worth noting, however, that etanercept has historically presented with a low rate of immunogenicity [91, 92], which raises questions regarding the relevance of the reported ADA rates to clinical practice. Overall, the follow-up duration in these studies varied and might not have been long enough to detect immune reactions or all AEs, which can have implications on pharmacovigilance as well [73].

Overall, the evidence regarding the efficacy, safety, and immunogenicity of multiple switching from an originator to a single biosimilar is currently based on two RW studies [6, 7] and three multiple-switch RCT studies, none of which were powered to show a difference between switchers and non-switchers and were limited in their follow-up durations after the last switch [86–89]. Furthermore, to our knowledge, no study to date has investigated the potential implications of the differences in patient-support programs, devices, or drug
formulations in a single- or multiple-switch scenario. Thus, until more robust, longer-term RCTs, supported by well-designed RW studies, are conducted, any decision to switch, especially multiple times, should be made by the treating physician based on clinical judgment and with informed patient consent.

SWITCHING FROM BIOSIMILAR TO BIOSIMILAR (SCENARIO 2)

With an array of biosimilars entering the market, the prospect of single or multiple switches between biosimilars of the same originator is already a reality that is likely to increase in the future (Fig. 1b) [1, 93–98]. However, comparability studies for product registration are performed between a biosimilar and its originator product and not between biosimilars, which raises the potential for broader differences between biosimilars of the same originator product [1, 99, 100]. As such, for any given comparison, each biosimilar could be on different portions of the similarity or equivalence margin as defined for the specific originator product and, at least theoretically, there is a chance that the products would not meet a comparability standard if both biosimilars were compared head-to-head (Fig. 2) [101]. For this reason, data from switching studies with an originator and the analogous biosimilar are unique to those particular products and should not be generalized to other switching scenarios between the originator and its biosimilars or between different biosimilars of the same originator. Importantly, the FDA guidelines clearly stipulate that interchangeability is defined only against the originator product and not against another biosimilar of the same reference product [19]. Therefore, the similarity between two biosimilars of the same originator product is currently unknown.

To our knowledge, only five RW studies have evaluated switching between two biosimilars of the same originator product on efficacy or safety, and one additional study has evaluated the immunogenic effect of such a switch (Table 1) [93–98]. The first study conducted in the United Kingdom assessed clinical outcomes in 133 patients with inflammatory bowel disease who agreed to transition from infliximab...
biosimilar, CT-P13 (mean treatment duration of 3 years), to infliximab biosimilar, SB2 [96]. The results demonstrated that disease activity did not significantly change after 16 or 18 weeks with SB2 nor were there any significant difference in drug persistence between a historical CT-P13 cohort and the SB2 switch group. Eighteen patients (14%) stopped treatment after the switch (therapeutic failure, n = 7; adverse drug reactions, n = 6; withdrew consent, n = 2; lost to follow-up, n = 2; withdrew for other reasons, n = 1). The limitations of this study include short follow-up duration, lack of a matched or adjusted control group of non-switchers for comparison of disease activity, and lack of immunogenicity or safety data.

The second study (PERFUSE) investigated the efficacy and safety of switching from CT-P13 to SB2 in patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis across 6 clinical practices in France [94]. The interim results demonstrated no clinically meaningful differences in disease activity from baseline to month 6 (n = 96) or 12 (n = 67) in patients previously treated with infliximab originator or CT-P13 (only pooled data were reported). SB2 persistence at 12 months ranged from 92 to 100%. Four serious AEs were reported (no details on treatment history were reported for these patients). Limitations of the study include a small patient population and pooling of the data.

The third study investigated the safety and efficacy of cross-switching from CT-P13 to SB2 in 24 patients with psoriasis in Italy [95]. The mean (SD) previous exposure to CT-P13 was 23.2 (7.5) months. No difference in efficacy was observed 6 months post-switch and only 4 AEs were reported. However, the lack of immunogenicity data and a control group, as well as the small patient population and short follow-up duration, are limitations of this study.

The fourth study, conducted in France, March–May 2018, reported retention rate for 18 patients switching from CT-P13 to SB2 [98]. Data were compared with 45 patients switching from originator infliximab to SB2 during the same time period at the same rheumatology department. The retention rate after switching from CT-P13 to SB2 was 12/18 (66.7%), suggesting that 6 (33.3%) patients discontinued after the switch. In comparison, the retention rate following a switch from originator infliximab to SB2 was 41/45 (91.1%) with a median follow-up of 34 weeks. No efficacy, safety or immunogenicity data were reported and the study was limited by a small patient population and short follow-up duration.

The fifth study was a descriptive analysis by the US Department of Veterans Affairs of outpatients receiving infliximab and switched to/from the originator or one of two biosimilars between January 2016 and January 2019 [93]. Of the 607 patients who switched from biosimilar to biosimilar, 138 (23%) patients had at least one AE, and 22 (4%) had at least one hospitalization. Among all single switchers, 335/1024 (33%) and 69/1024 (7%) patients had at least one AE or hospitalization compared with 172/666 (26%) and 38/666 (6%) multiple switchers, respectively, during the same time period. No details on disease, disease activity, discontinuation, or immunogenicity were reported.

The only study reporting immunogenicity data included 265 patients with chronic inflammatory diseases receiving maintenance treatment with infliximab in France [97]. The patients were switched to an initial infliximab biosimilar in October/December 2015; of these, 140 patients were switched to a second infliximab biosimilar starting in December 2017, 26 remained on the first biosimilar, and 55 switched back to the originator. At the end of the 3-year observation period, the biosimilar retention rate was 58% (154/265; 131 receiving the second biosimilar and 23 receiving the first biosimilar). During the study, 29 patients had ADAs at baseline; of the 236 patients without ADAs, 20 developed ADAs during the observation period, corresponding to an immunogenicity rate of 3/100 patient-years. Of these 20 patients, 4 were switched back to the originator at the time of ADA detection, 10 were exposed only to the first biosimilar, and 6 to the second. Although the risk of treatment discontinuation was significantly higher among patients who were ADA positive at baseline or during follow-up, a Kaplan–Meier analysis showed that immunogenicity was not influenced by the
number of infliximab biosimilars received. However, as above, these results are based on a single study with no control group of matched or adjusted non-switchers, and data were pooled from multiple indications. Because only six studies conducted to date have assessed the efficacy, safety, or immunogenicity of biosimilar-to-biosimilar switches and because none were powered to detect differences or investigated pharmacokinetic parameters, no definite conclusions can be drawn about the potential risks of such switches. Furthermore, concerns regarding pharmacovigilance, patient-support programs, and other patient-related concerns remain unknown. In cases in which ≥2 biosimilars are added into the scenario, these concerns are amplified because patients can be switched multiple times between several different products, and each switch may be associated with different delivery systems, drug dosages, dosing intervals, and formulations. Until more evidence is available, patients should not be forced to undergo a biosimilar-to-biosimilar switch, and patients and their physicians should be fully informed and allowed to opt out of such switches.

**SWITCHBACK (SCENARIO 3)**

As stated above, numerous studies have investigated the safety and efficacy of a single non-medical switch from an originator to a biosimilar [1, 39, 40]. Although many of these studies showed that such a switch is generally feasible and well-tolerated, 0–87% of patients discontinued therapy after the switch. Those patients for whom the switch fails and who discontinue treatment are sometimes allowed to switch back to the originator product, leading to a multiple-switch scenario. A meta-analysis of 62 RW studies (with almost half of the studies reporting switchback data) showed an annualized (95% confidence interval) switchback rate of 14% (10–17%) among all non-medical switchers and 62% (44–80%) among those who discontinue therapy, suggesting that switchback is occurring in a considerable number of patients who are initially switched from originator to a biosimilar for non-medical reasons [4]. However, no details were reported on the success of switchback in this analysis.

To assess this further, we identified 57 RW studies that reported switchback to the originator treatment after a non-medical switching failure (Table 2) [7, 58, 68–70, 93, 102–152]. The switchback rate varied widely between studies, with 1–72% of patients switching back after biosimilar failure either due to loss of efficacy, AEs, assumed nocebo effect, or subjective reasons. Only 24 studies reported outcomes following the switchback with the majority of patients (50–100%) regaining disease control following reinstitution of the originator treatment [58, 68, 70, 104, 107, 109, 115, 118–120, 123, 124, 128, 129, 133, 134, 138–140, 143–146, 148]. However, most of these studies do not provide an objective, blinded assessment of treatment failure after the switch or regaining response after switchback, and therefore it is important to note that there is a potential for bias in these studies.

In a few of these studies, the authors speculated that a nocebo effect was one explanation for treatment failure and the subsequent switchback success [7, 58, 67–69, 124]. However, this assumption may be unwarranted because none of the studies were adequately designed to test this hypothesis [41]. Furthermore, efforts to reduce the nocebo effect, such as patient education, have produced inconsistent results, and treatment failures have been observed even after patients were informed and educated before switching [41].

As mentioned previously, because patients may regain disease control after switching back to the originator, switchbacks can be considered a viable alternative compared with switching to another biologic within the same therapeutic class or a different drug class altogether (Table 2). However, it is important to note that all treatment failures and discontinuations carry a risk to the patient (including those resulting from the nocebo effect), and not all patients were successfully switched back to the originator treatment in these studies. Thus, treatment failure remains a concern.

Importantly, unlike the two other multiple-switching scenarios, switchbacks should be
| Study                 | Product                                | Follow-up duration | Switchback overall n/N (%) | Switchback success n/N (%) | Immunogenicity n/N (%) |
|----------------------|----------------------------------------|--------------------|-----------------------------|-----------------------------|------------------------|
| Abdalla et al. 2017  | Infliximab                             | Mean, 15.8 months | 1/34 (3) NR NR NR           |                             |                        |
| Ali et al. 2019      | Etanercept/infliximab                  | 3 months           | 3/102 (3) NR NR NR          |                             |                        |
| Alkoky et al. 2019   | Etanercept                             | 3–6 months         | 14/158 (9) 14/14 (100) NR   |                             |                        |
| Alten et al. 2019    | Etanercept                             | 11 months          | 937/4471 (21) NR NR NR      |                             |                        |
| Avouac et al. 2018   | Infliximab                             | Mean, 34 weeks     | 47/260 (18) NR NR           |                             |                        |
| Babai et al. 2017    | Infliximab                             | 6 months           | 12/53 (23) Yes: 7/12 (58) Unk: 3/12 (25) | NR | |
| Baganz et al. 2019   | Etanercept                             | 1 year             | 9/102 (9) NR NR NR          |                             |                        |
| Binkhorst et al. 2018| Infliximab                             | 2 infusions        | 7/197 (4) Yes: 4/7 (57) Unk: 1/7 (14) | ~ 7% at week 0; ~ 3% at week 16; 2/197 (1) after switching |
| Boone et al. 2018    | Infliximab                             | 9 months           | 16/125 (13) 16/16 (100) 5/125 (4) at week 0 4 |                             |                        |
| Cunningham et al. 2019| Infliximab                              | 37 months          | 105/666 (16) NR NR          |                             |                        |
| Dahanayake et al. 2019| Etanercept                              | 20 months          | 27/202 (13) NR NR           |                             |                        |
| Davies et al. 2019   | Etanercept and infliximab              | 23 months          | 71/966 (7) NR NR            |                             |                        |
| De Cock et al. 2017  | Etanercept and infliximab              | 6 months           | 7/99 (7) NR NR NR           |                             |                        |
| De Cock et al. 2018  | Etanercept and infliximab              | 2 years            | 1/9 (11) NR NR NR           |                             |                        |
| Dyball et al. 2017   | Etanercept                             | NR                 | 5/36 (14) NR NR NR          |                             |                        |
| Felis-Giemza et al. 2019| Etanercept                             | 6 months           | 24/162 (15) 23/24 (96) NR   |                             |                        |
| Study                        | Product     | Follow-up duration | Switchback overall n/N (%) | Switchback success n/N (%) | Immunogenicity n/N (%) |
|------------------------------|-------------|--------------------|-----------------------------|-----------------------------|------------------------|
| Fernandez et al. 2019 [116] | Etanercept  | 9 months           | 11/117 (9)                  | NR                          | NR                     |
| Forejtová et al. 2017 [117] | Infliximab  | 6 months           | 1/38 (3)                    | NR                          | NR                     |
| Gentileschi et al. 2016 [118]| Infliximab  | Mean, 1.7 months   | 7/23 (30)                   | 5/7 (71)                    | NR                     |
| Germain et al. 2018 [119]   | Infliximab  | Median, 120 weeks  | 1/89 (1)                    | 1/1 (100)                   | NR                     |
| Glintborg et al. 2019 [68]  | Etanercept  | 1 year             | 120/1621 (7)                | Yes: 104/120 (87)           | Unk: 16/120 (13)       |
| Hendricks et al. 2017 [120] | Etanercept  | 8 months           | 5/85 (6)                    | 5/5 (100)                   | NR                     |
| Holroyd et al. 2016 [121]   | Infliximab  | 5 months           | 4/56 (7)                    | NR                          | NR                     |
| Hoque et al. 2018 [122]     | Etanercept  | Mean: 11.5 months  | 4/94 (4)                    | NR                          | NR                     |
| Jung et al. 2015 [123]      | Infliximab  | 54 weeks           | 2/36 (6)                    | Yes: 1/2 (50)                            |
|                             |             |                    |                             | Unk: 1/2 (50)                            |
| Kaltsonoudis et al. 2019 [124]| Infliximab | 18 months          | 4/45 (9)                    | 3/4 (75)                    | NR                     |
| Kiltz et al. 2019 [70]      | Etanercept  | 24 weeks           | 3/84 (4)                    | 3/3 (100)                   | NR                     |
| Klink et al. 2019 [125]     | Infliximab  | Median: 31 weeks   | 15/47 (32)                  | NR                          | NR                     |
| Layegh et al. 2018 [126]    | Infliximab  | 2 years            | 3/45 (7)                    | NR                          | NR                     |
| Lee et al. 2018 [127]       | Etanercept  | 8 months           | 2/56 (4)                    | NR                          | NR                     |
| Madenidou et al. 2018 [128] | Etanercept  | 6 months           | 19/72 (26)                  | 19/19 (100)                 | NR                     |
Table 2 continued

| Study                        | Product            | Follow-up duration | Switchback overall N (%) | Switchback success N (%) | Immunogenicity N (%) |
|------------------------------|--------------------|--------------------|--------------------------|--------------------------|----------------------|
| Mahmmod et al. 2019 [129]    | Infliximab         | 52 weeks           | 35/254 (14)              | 27/35 (77)               | NR                   |
| Malaiya et al. 2016 [130]    | Infliximab         | 3 months           | 1/30 (3)                 | NR                       | NR                   |
| Moorthy et al. 2019 [131]    | Etanercept         | NR                 | 21/362 (6)               | NR                       | NR                   |
| Müskens et al. 2018 [132]    | Etanercept         | Median: 307 days   | 12/69 (17)               | NR                       | NR                   |
| Nikipherou et al. 2015 [69]  | Infliximab         | Median: 11 months  | 6/39 (15)                | NR                       | 3/39 (8)             |
| Nisar et al. 2019 [133]      | Etanercept         | 5 months           | 6/82 (7)                 | 4/6 (67)                 | NR                   |
| Patel et al. 2018 [134]      | Etanercept         | NR                 | 18/168 (11)              | Yes: 11/18 (61)          | NR                   |
|                             |                    |                    |                          | Unk: 6/18 (33)           |                      |
| Rajamani et al. 2019 [135]   | Etanercept         | NR                 | 9/120 (8)                | NR                       | NR                   |
| Razanskaite et al. 2017 [136]| Infliximab         | 1 year             | 2/143 (1)                | NR                       | 28/126 (22) before switch 28/126 (22) after switch |
| Reuber et al. 2019 [137]     | Etanercept and infliximab | 12 months | 893/2956 (30) | NR                       | NR                   |
| Saxby et al. 2020 [138]      | Etanercept and infliximab | 3–6 months | 15/548 (3) | 14/15 (93) | NR                   |
| Scherligner et al. 2018 [140]| Infliximab         | Median: 33 weeks   | 23/89 (26)               | 18/23 (78)               | NR                   |
| Scherligner et al. 2019 [139]| Etanercept         | 2–7 months         | 3/44 (7)                 | 3/3 (100)                | NR                   |
| Schmitz et al. 2018 [141]    | Infliximab         | 1 year             | 22/133 (17)              | NR                       | 8/18 (44) before switch 3/18 (17) after switch |
| Shah et al. 2018 [142]       | Etanercept         | 4 months           | 8/115 (7)                | NR                       | NR                   |
### Table 2 continued

| Study                        | Product                  | Follow-up duration | Switchback overall, N (%) | Switchback success, N (%) | Immunogenicity, N (%) |
|------------------------------|--------------------------|--------------------|---------------------------|---------------------------|----------------------|
| Sheppard et al. 2016 [143]   | Infliximab               | NR                 | 5/25 (20)                 | Yes: 4/25 (16)            | NR                   |
|                              |                          |                    |                           | Unk: 1/25 (20)            |                      |
| Sigurdardottir et al. 2018 [7] | Etanercept              | 544 days           | 24/145 (17)               | NR                        | NR                   |
| Smith et al. 2018 [144]      | Etanercept               | NR                 | 10/217 (5)                | Yes: 8/10 (80)            | NR                   |
|                              |                          |                    |                           | Unk: 2/10 (20)            |                      |
| Steel et al. 2019 [145]      | Etanercept and           | NR                 | 17/475 (4)                | 11/17 (65)                | NR                   |
|                              | infliximab               |                    |                           |                           |                      |
| Tansley et al. 2019 [146]    | Rituximab                | NR                 | 9/176 (5)                 | 9/9 (100)                 | NR                   |
| Tweehuysen et al. 2018 [147] | Etanercept               | 6 months           | 17/625 (3)                | NR                        | NR                   |
| Tweehuysen et al. 2018 [148] | Infliximab               | 6 months           | 37/192 (19)               | 33/37 (89)                | 14/136 (10) at baseline |
|                              |                          |                    |                           |                           | 9/136 (7) at 6 months (2 patients developed antibodies after switch) |
| Uke et al. 2019 [149]        | Etanercept              | > 3 months         | 17/157 (11)               | NR                        | NR                   |
| Valido et al. 2018 [150]     | Infliximab               | Mean: 261 days     | 1/60 (2)                  | NR                        | NR                   |
| Yazici et al. 2016 [151]     | Infliximab               | Mean: 9 months     | 84/148 (57)               | NR                        | NR                   |
| Yazici et al. 2018 [152]     | Infliximab               | Mean: 15 months    | 66/92 (72)                | NR                        | NR                   |

NR not reported, Unk unknown

- **a** Non-responders to biosimilar infliximab; neutralizing antibodies against infliximab were present at baseline but asymptomatic and not known at the time of switch
- **b** Number of patients who switched back was calculated based on 2956 patients, of which 30.2% switched back by month 12
- **c** Of all switchers, 26 patients requested to switch back to biosimilar but only 15 were approved to switch back
- **d** Anti-drug antibodies were measured only in 18 patients who had infliximab levels < 0.5 μg/mL
considered medical switches. Because the switchback is usually medically driven and sometimes requested by the patient after treatment failure, it is not necessarily associated with the same challenges as the other two scenarios (e.g., issues with patient support programs and other patient-related concerns). However, immunogenicity remains a key concern, as with any multiple-switch practice. Only a few of the switchback studies [58, 69, 109, 136, 141, 148] reported immunogenicity data before and after the initial switch, and the long-term consequences after switchback remain unknown (Table 2).

Pharmacovigilance concerns also exist, particularly in those cases in which switchbacks happen relatively quickly after the initial switch, making it difficult to distinguish to which product an AE should be attributed. Patient-reported problems, such as more pain or injection/infusion reactions, and issues with delivery devices, were reported in 12 studies following a non-medical switch, often leading to a switchback to the originator [102, 110, 111, 113–115, 121, 122, 128, 134, 140, 142]. However, this evidence is based on a limited number of RW studies not powered to investigate differences in injection/infusion reactions or issues with the delivery device after a switch, and it was not disclosed whether patients were adequately educated on the use of the new device.

Overall, the current evidence regarding switchbacks mainly comes from RW studies that were not robust enough or properly designed to investigate the risks of switchbacks. Considering the limitations of the current evidence, the practice of non-medical switching from originator to biosimilar (especially in patients who are doing well with the originator treatment) should be conducted with reservations, if at all, and should be jointly decided by the patient and the physician, with the patient having the option to refuse such a switch.

CONCLUSIONS

With the increasing availability of biosimilars, multiple switching between originator and its biosimilar, biosimilar-to-biosimilar switching, and switchbacks are becoming more widely used practices; however, the current evidence regarding the potential risks of these practices remains limited and is not robust enough to dispel all the concerns related to loss of efficacy, immunogenicity, and safety. Although no substantial safety/efficacy concerns have been reported to date at the population level, important concerns have been identified at the individual patient level (including loss of efficacy and emergence/worsening of AEs). Multiple switching and biosimilar-to-biosimilar switching carry the most concerns, and more studies are needed to fully evaluate the risks involved with such switching. More data are available for switching back to the originator after failure of a non-medical switch, and this practice is generally successful; however, not all patients regain disease control after switchback, and immunogenicity concerns remain. Because of this, it is important that regulators, policymakers, and healthcare providers consider potential safety and efficacy concerns before making crucial treatment, regulatory, or policy decisions that involve or could lead to switching patients multiple times for non-medical reasons. Any decision to switch, whether single or multiple times, should be made by the treating physician based on clinical judgment and with informed patient consent. Until further scientific understanding is gained through robust RCTs, supported by well-designed RW studies, the potential short- and long-term risks of multiple switching, biosimilar-to-biosimilar switching, and switchbacks remain largely unknown.

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