Discontinuation and Switchback After Non-Medical Switching from Originator Tumor Necrosis Factor Alpha (TNF) Inhibitors to Biosimilars: A Meta-Analysis of Real-World Studies from 2012 to 2018

Yifei Liu · Martha Skup · Min Yang · Cynthia Z. Qi · Eric Q. Wu

Received: February 15, 2022 / Accepted: April 26, 2022 / Published online: June 23, 2022 © The Authors 2022

ABSTRACT

Introduction: To examine the prevalence rates of biosimilar discontinuation and switchback to the originator tumor necrosis factor alpha (TNF) inhibitors following non-medical switch (NMS) in patients.

Methods: Real-world studies reporting biosimilar discontinuation and switchback rates following NMS published between January 2012 and August 2018 were identified through a systematic literature review. A meta-analysis estimated the annualized discontinuation and switchback rates. A subsequent meta-analysis assessed annualized incremental discontinuation rate among studies reporting both discontinuation rates in patients who underwent an NMS (switchers) and patients who remained on originators (non-switchers).

Results: A total of 66 publications were identified: 31 in gastroenterology, 32 in rheumatology, and 3 in both. Half of the studies reported switchback rates; only 9 studies reported discontinuation rates for both switchers and non-switchers. Across studies, the mean/range sample size of the NMS patient population was 136/9–1641; mean/range follow-up was 10/3–24 months. Annualized biosimilar discontinuation rate was 21% (95% confidence interval [CI] 18%, 25%). Switchback rate was 14% (95% CI 10%, 17%) among all NMS patients and 62% (95% CI 44%, 80%) among discontinuers. The mean/range sample size of switchers and non-switchers was 344/89–1621 and 768/19–2870, respectively; mean/range follow-up was 11/6–18 and 12/6–8 months, respectively. Annualized incremental biosimilar discontinuation rate was 18% (95% CI 4%, 31%).

Conclusion: Biosimilar discontinuation was found to be prevalent among patients who underwent an NMS from an originator TNF inhibitor to its biosimilar(s) in the real world. In addition, switchback to the originator TNF inhibitors was common following biosimilar discontinuation. Careful consideration is necessary when switching patients already on an originator TNF inhibitor to its biosimilar(s). Main limitations included the heterogeneity of the studies and the limited comparability of the data.
Keywords: Biosimilar; Discontinuation; Non-medical switch; Switchback; TNF inhibitors

Key Summary Points

| A total of 66 publications based on real-world studies were identified from 2012 to 2018. |
| --- |
| Biosimilar discontinuation was prevalent for non-medical switches. |
| Switchback to originator TNF inhibitors was common following biosimilar discontinuation. |

INTRODUCTION

Since the advent of the first biologic (human insulin) in 1982, biologic therapies, including both small and large molecules, have transformed the treatment of numerous chronic conditions, improving clinical outcomes and patients’ well-being [1, 2]. In particular, tumor necrosis factor alpha (TNF) inhibitors, a class of large complex molecules, have advanced the management of a number of diseases including rheumatologic conditions, inflammatory bowel diseases, and dermatologic conditions [3]. As the patents of a number of originator biologics have expired or are about to expire, highly similar copies to those originator biologics (i.e., biosimilars) have been developed and some of them have been granted market authorization [4]. Unlike generic versions of synthetic small-molecule drugs, biosimilars are not exact copies of the originators because of the intrinsic manufacturing variability of biologics, which inevitably results in minor but acceptable structural differences between originators and the biosimilar products [5–7]. Notwithstanding the slight variability that is inherent to all biologic medications, regulatory agencies across the world require biosimilars to have no clinically meaningful differences in purity, potency, safety, and efficacy from their originator biologics through clinical trials [7, 8].

Researchers have been evaluating whether biosimilars and originator biologics are comparable in terms of safety and effectiveness [5, 6, 9–13]. Uncertainty remains with regard to the non-medical switch (NMS) from an originator biologic to its biosimilar(s) given that such a switch is typically motivated by cost-related reasons, such as changes in formulary, and not by medical reasons, such as side effects, lack/loss of response, or poor persistence/adherence [9, 14–16]. The drivers of such a switch could also be mandatory on a nationwide scale such as in the case of switching to infliximab biosimilar in Denmark in 2015 [11]. Caution may be particularly considered in the case of TNF inhibitors, as they are used in patients with chronic conditions for whom continuity of care is highly recommended in order to maintain optimal disease management after achieving symptom control [17–19].

Existing research has shown mixed findings on the clinical impact of NMS to biosimilars. Indeed, while some studies suggested that biosimilar NMS did not affect therapeutic efficacy or safety [20–24], other studies found that an NMS from any one drug to another is associated with an increase in treatment discontinuation (and potentially switch back to the original therapy), as well as worsening clinical outcomes [17, 25, 26].

As the number of TNF inhibitor biosimilars on the market continues to increase, it is important to systematically evaluate the impact of NMS on clinical management of conditions in the real world. To further inform this evidence gap, we conducted a meta-analysis to assess post-NMS biosimilar treatment patterns (focused on discontinuation and switchback rates) in real-world studies.

METHODS

Literature Search Strategy

Real-world studies that reported discontinuation and switchback rates after an NMS from originator TNF inhibitors (i.e., infliximab and etanercept) to their biosimilars were identified through a systematic literature review. The
initial search was conducted in February 2018 [27], with an updated search performed in August 2018. Given the search dates, no real-world adalimumab biosimilar NMS studies were expected to be available because adalimumab biosimilars were only recently made commercially available. The literature was searched using the following databases: BIOSIS Previews®, Derwent Drug File, Embase®, International Pharmaceutical Abstracts, MEDLINE®, SciSearch®, and selected conference abstracts (e.g., European League Against Rheumatism [EULAR] Annual Congress, European Crohn’s and Colitis Organization [ECCO] Annual Congress, and American College of Rheumatology [ACR] Annual Meeting). The search was limited to English language, humans, and publications dates from January 1, 2012 to August 8, 2018 [27]. The search strategy included search terms related to TNF inhibitors, biosimilars, and NMS. The complete list of search terms can be found elsewhere [27]. Of note, Benepali®, the first biosimilar of etanercept, was approved in Europe in 2016 [28], and Amgevita®, the first biosimilar of adalimumab, was approved in Europe in 2017 [29].

Studies were considered eligible for inclusion if they were real-world prospective or retrospective studies, included adult patients with chronic conditions (i.e., rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, plaque psoriasis, ulcerative colitis, and Crohn’s disease) who experienced an NMS from an originator TNF inhibitor to its biosimilar(s), and reported discontinuation rates after the NMS and/or switchback rates. Both single-arm and multiple-arm studies were included, as well as those reporting patient-based or registry/database data. Clinical trial studies, publications that did not report discontinuation outcomes, or publications that evaluated a pediatric population were excluded.

**Study Outcomes**

For each selected publication, the study characteristics (i.e., geographic region, therapeutic area, originator and biosimilar agents, sample size, and follow-up time) and treatment pattern data (i.e., discontinuation rate, switchback rate, time to discontinuation, treatment after discontinuation, and reason for discontinuation) were summarized. The following four outcomes were included in the meta-analysis:

1. **Annualized discontinuation rate among NMS patients**, defined as the estimated proportion of patients (among all patients who underwent an NMS) who discontinued the biosimilar after an NMS; discontinuation for any reasons (e.g., patients who discontinued and switched back to the originator biologic, biosimilar discontinuation without any further treatment) was included. Follow-up time was used to calculate the annualized discontinuation rate.

2. **Annualized switchback rate among NMS patients**, defined as the estimated proportion of patients (among all patients who underwent an NMS) who discontinued the biosimilar and then switched back to the originator TNF inhibitor that they used before the NMS. Follow-up time was used to calculate the annualized switchback rate.

3. **Switchback rate among biosimilar NMS discontinuers**, defined as the estimated proportion of patients who discontinued the biosimilar (discontinuers) and switched back to the originator TNF inhibitor that they used before the NMS, estimated among all patients who discontinued the biosimilar following the NMS.

4. **Incremental discontinuation rate among NMS patients**, defined as the difference in annualized discontinuation rate between patients who underwent NMS (switchers) and those who remained on the originator TNF inhibitor (non-switchers), estimated among the subset of studies that reported discontinuation rates for both groups. Incremental discontinuation rate was used to conserve the within-study comparability of switchers vs non-switchers.
Meta-Analysis

Meta-analyses based on the DerSimonian and Laird method using a random-effect model [30] were performed to calculate the pooled estimates for each outcome of interest. Accounting for differences in the follow-up time and sample size across studies, the meta-analysis included a random intercept to account for the between-study differences (i.e., design and population difference). The summary discontinuation and switchback rates, along with 95% confidence interval [CI], were calculated for all the selected studies and by therapeutic area. Cochran’s Q was calculated as a check of homogeneity to confirm that a random-effects model was appropriate. The Higgins $I^2$ index was calculated for each meta-analysis to quantitatively measure the degree of variation between the results reported in the selected studies.

Sensitivity Analyses

Multiple sensitivity analyses were conducted to evaluate the robustness of the study findings. In particular, sensitivity analyses were conducted by running meta-analyses on subsets of studies with similar characteristics (i.e., sample size, follow-up time, intervention) to determine how study-specific characteristics affected the pooled estimates of discontinuation and switchback rates. Sensitivity analyses were not performed for the incremental discontinuation rate outcome given the small number of studies identified that reported data for both switchers and non-switchers.

All the statistical analyses in this study were conducted using the R software version 3.2.1 [31].

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Selected Studies

A total of 66 publications based on real-world studies were identified, including 29 full-text publications, 35 abstracts, and 2 letters to the editor. Of them, 51 assessed NMSs from originator infliximab to its biosimilar (e.g., CT-P13 or SB2), 10 studies from originator etanercept to its biosimilar (e.g., SB4 or GP2015), and 1 from both originator infliximab and etanercept to their biosimilars (Table 1).

Studies included patients from the following countries: Ireland, France, UK, Germany, Spain, Italy, the Netherlands, Norway, Scotland, Denmark, Czech Republic, Finland, Poland, Sweden, Portugal, and South Korea. None of the selected studies were conducted in the USA or Canada, likely because of the earlier adoption of biosimilars in Europe and Asia. In terms of therapeutic areas, 31 of the 66 studies focused on gastroenterology, 32 on rheumatology, and 3 on both gastroenterology and rheumatology. No studies reported data specifically for dermatology patients.

The mean number of patients who underwent an NMS in these studies was 136 (range across studies 9–1641 patients). The mean follow-up time after an NMS was 10 months (range 3–24 months).

Annualized Discontinuation Rate Among NMS Patients

A total of 62 studies reported discontinuation rate and follow-up time. Discontinuation rate varied substantially, from 1.5% to 87.0% across studies with different length of follow-up (range 3–24 months) (Table 1). The average time to discontinuation was 6 months, ranging from 2 to 11 months across 10 studies that reported this information.

Reasons for biosimilar discontinuation were reported in 56 of the 62 studies. The most common reasons for biosimilar discontinuation were loss of efficacy and side effects/adverse events, reported in 37% and 28% of discontinuers, respectively. Other reasons included
| Study (author year) | Country | Therapeutic area | Treatment | Publication type | Study type | Number of patients (switcher vs non-switcher) | Follow-up duration post switch (switcher vs non-switcher) | Discontinuation rate (switcher vs non-switcher) | Switchback rate (among discontinuers) | Switchback rate (among all switchers) |
|---------------------|---------|------------------|-----------|------------------|------------|-----------------------------------------------|----------------------------------------------------------|------------------------------------------|--------------------------------------|--------------------------------|
| Gentileschi 2015    | Italy   | Rheumatology     | Infliximab| Letter to the    | Prospective center-based cohort study | 23               | –                                              | 30%                                      | 100%                                 | 30%                                 |
| Jung 2015           | South Korea | Gastroenterology | Infliximab| Full text        | Retrospective center-based cohort study | 36               | 54 weeks                                      | 14%                                      | 40%                                  | 6%                                  |
| Kang 2015           | South Korea | Gastroenterology | Infliximab| Full text        | Retrospective center-based cohort study | 9                | 37.5 weeks                                    | 11%                                      | –                                    | –                                   |
| Nikiphorou 2015     | Finland | Rheumatology     | Infliximab| Full text        | Prospective center-based cohort study | 39               | 11 months                                     | 28%                                      | 55%                                  | 3%                                  |
| Park 2015           | South Korea | Gastroenterology | Infliximab| Full text        | Retrospective center-based cohort study | 60               | 30 weeks                                      | 13%                                      | –                                    | –                                   |
| Ala 2016            | UK      | Gastroenterology | Infliximab| Abstract         | Prospective center-based cohort study | 20               | 6 months                                      | 20%                                      | 0%                                   | 0%                                  |
| Bennett 2016        | UK      | Gastroenterology | Infliximab| Abstract         | Retrospective center-based cohort study | 104              | 6 months                                      | 18%                                      | –                                    | –                                   |
| Bettey 2016         | UK      | Gastroenterology | Infliximab| Abstract         | Prospective center-based cohort study | 134              | 16 weeks                                      | 1.5%                                     | 100%                                 | 1%                                  |
| Garofalo 2016       | Italy   | Rheumatology     | Infliximab| Abstract         | Prospective center-based cohort study | 45               | 16 weeks                                      | 2%                                       | 100%                                 | 2%                                  |
| Rahmany 2016        | UK      | Gastroenterology | Infliximab| Abstract         | Prospective center-based cohort study | 78               | 4–6 months                                    | 6%                                       | –                                    | –                                   |
| Sheppard 2016       | UK      | Rheumatology     | Infliximab| Abstract         | Prospective center-based cohort study | 25               | 12 months                                     | 16%                                      | 100%                                 | 16%                                 |
| Van Den Hoogen 2016 | Netherlands | Rheumatology     | Infliximab| Abstract         | Prospective center-based cohort study | 136              | 5 months                                      | 17%                                      | 83%                                  | 14%                                 |
| Abdalla 2017        | Ireland | Rheumatology     | Infliximab| Full text        | Prospective center-based cohort study | 34               | 15.8 months                                   | 15%                                      | 20%                                  | 3%                                  |
| Arguelles-Arias 2017| Spain   | Gastroenterology | Infliximab| Full text        | Prospective center-based cohort study | 98               | 12 months                                     | 12%                                      | –                                    | –                                   |
| Study (author year) | Country          | Therapeutic area                  | Treatment | Publication type | Study type                                      | Number of patients (switcher vs non-switcher) | Follow-up duration post switch (switcher vs non-switcher) | Discontinuation rate (switcher vs non-switcher) | Switchback rate (among discontinuers) | Switchback rate (among all switchers) |
|---------------------|------------------|-----------------------------------|-----------|-----------------|------------------------------------------------|-----------------------------------------------|--------------------------------------------------------|-------------------------------------------------|--------------------------------------|--------------------------------------|
| Avouac 2017 [79]    | France           | Rheumatology and gastroenterology | Infliximab| Full text       | Prospective center-based cohort study          | 260                                           | 33.9 weeks                                             | 23%                                             | 80%                                  | 18%                                  |
| Babai 2017 [35]     | France           | Rheumatology                      | Infliximab| Abstract        | Retrospective center-based cohort study        | 53                                            | –                                                      | 23%                                             | 100%                                 | 23%                                  |
| Benocci 2017 [54]   | Italy            | Rheumatology                      | Infliximab| Full text       | Prospective center-based cohort study (multiple centers) | 41                                            | 6 months                                               | 2%                                              | –                                    | –                                    |
| Boone 2017 [80]     | Netherlands      | Gastroenterology                  | Infliximab| Abstract        | Prospective center-based cohort study          | 65                                            | 52 weeks                                               | 12%                                             | –                                    | –                                    |
| Buer 2017 [81]      | Norway           | Gastroenterology                  | Infliximab| Full text       | Prospective center-based cohort study          | 143                                           | 6 months                                               | 3%                                              | –                                    | –                                    |
| Ellis 2017 [35]     | Turkey           | Rheumatology                      | Infliximab| Abstract        | Registry/database                               | 92 vs 605                                     | 15 months vs 16 months                                 | 87% vs 34%                                      | 72%                                  | 63%                                  |
| Glintborg 2017 [82] | Denmark          | Rheumatology                      | Infliximab| Full text       | Registry/database                               | 802                                           | 413 days                                               | 16%                                             | –                                    | –                                    |
| Guerrero Puente 2017| Spain            | Gastroenterology                  | Infliximab| Full text       | Prospective center-based cohort study          | 36                                            | 8.4 months                                             | 11%                                             | –                                    | –                                    |
| Guxrann 2017 [84]   | France           | Rheumatology and gastroenterology | Infliximab| Full text       | Prospective center-based cohort study          | 267                                           | 10 months                                              | 15%                                             | 79%                                  | 12%                                  |
| Hendricks 2017 [85] | Denmark          | Rheumatology                      | Etanercept| Abstract        | Prospective center-based cohort study          | 85                                            | 4 months                                               | 8%                                              | 71%                                  | 6%                                   |
| Holroyd 2017 [39]   | UK               | Rheumatology                      | Etanercept| Abstract        | Prospective center-based cohort study          | 92 vs 110                                     | 6 months vs 6 months                                   | 9% vs 15%                                        | 75%                                  | 7%                                   |
| Kolar 2017 [55]     | Czech Republic   | Gastroenterology                  | Infliximab| Full text       | Prospective center-based cohort study          | 74                                            | 56 weeks                                               | 5%                                              | –                                    | –                                    |
| Malpas 2017 [86]    | UK               | Rheumatology                      | Infliximab| Abstract        | Prospective center-based cohort study          | 62                                            | 3 months                                               | 5%                                              | –                                    | –                                    |
| Nagent 2017 [87]    | Ireland          | Gastroenterology                  | Infliximab| Abstract        | Prospective center-based cohort study          | 33                                            | 1 year                                                 | 15%                                             | –                                    | –                                    |
| Razamskaitė 2017 [88]| UK               | Gastroenterology                  | Infliximab| Full text       | Prospective center-based cohort study          | 143 vs 120                                     | 1 year vs 1 year                                       | 29% vs 26%                                      | –                                    | –                                    |
| Study (author year) | Country | Therapeutic area | Treatment | Publication type | Study type | Number of patients (switcher vs non-switcher) | Follow-up duration post switch (switcher vs non-switcher) | Discontinuation rate (switcher vs non-switcher)a | Switchback rate (among discontinuers)b | Switchback rate (among all switchers)c |
|---------------------|---------|------------------|-----------|------------------|------------|---------------------------------------------|---------------------------------------------------|-------------------------------------------------|---------------------------------------|---------------------------------------|
| Rodriguez 2017 [89] | Spain   | Gastroenterology | Infliximab | Abstract         | Retrospective center-based cohort study | 72                                      | 12 months                                      | 10%                                                | –                                    | –                                    |
| Scherlinger 2017 [61] | France  | Rheumatology     | Infliximab | Full text        | Prospective center-based cohort study | 89 vs 82                                   | 33 weeks vs 1 year                                      | 28% vs 12%                                      | 44%                                  | 12%                                  |
| Schmitz 2017 [90]   | Netherlands | Rheumatology | Infliximab | Full text        | Prospective center-based cohort study | 27                                              | 1 year                                        | 26%                                                | –                                    | –                                    |
| Schmitz 2017 [91]   | Netherlands | Gastroenterology | Infliximab | Full text        | Prospective center-based cohort study (multiple centers) | 133                                      | 12 months                                      | 26%                                                | –                                    | –                                    |
| Sieckowska-Golub 2017 [92] | Poland | Gastroenterology | Infliximab | Abstract         | Prospective center-based cohort study | 16                                              | 2 years                                       | 50%                                                | –                                    | –                                    |
| Sladek 2017 [93]    | Italy and Poland | Gastroenterology | Infliximab | Abstract         | Prospective center-based cohort study (multiple centers) | 45                                              | 24–36 weeks                                     | 7%                                                    | –                                    | –                                    |
| Smits 2017 [94]     | Netherlands | Gastroenterology | Infliximab | Full text        | Prospective center-based cohort study (multiple centers) | 83                                              | 104 weeks                                      | 34%                                                | –                                    | –                                    |
| Soret 2017 [95]     | France   | Gastroenterology | Infliximab | Abstract         | Prospective center-based cohort study | 63                                              | 84 months                                      | 13%                                                | 13%                                  | 2%                                    |
| St Clair Jones 2017 [63] | UK | Gastroenterology | Infliximab | Abstract         | Prospective center-based cohort study | 71                                              | 6 months                                       | 24%                                                | 0%                                    | 0%                                    |
| Yazici 2017 [96]    | Turkey   | Rheumatology     | Infliximab | Abstract         | Registry/database | 148 vs 2870                                 | 9 months vs 12 months                               | 82% vs 38%                                      | 70%                                  | 57%                                  |
| Al Tabaa 2018 [97]  | France   | Rheumatology     | Etanercept | Abstract         | Prospective center-based cohort study | 94                                              | 6 months                                       | 28%                                                | –                                    | –                                    |
| Armauzi 2018 [98]   | Italy    | Gastroenterology | Infliximab | Full text        | Prospective center-based cohort study (multiple centers) | 155                                      | 392.8 days                                      | 13%                                                | –                                    | –                                    |
| Binkhorst 2018 [99] | Netherlands | Gastroenterology | Infliximab | Full text        | Prospective center-based cohort study (multiple centers) | 197                                      | 16 weeks                                       | 10%                                                | 35%                                  | 4%                                   |
| Study (author) | Year | Country | Therapeutic area | Treatment | Publication type | Study type | Number of patients (switcher vs non-switcher) | Follow-up duration post switch (switcher vs non-switcher) | Discontinuation rate (switcher vs non-switcher)a | Switchback rate (among discontinuers)b | Switchback rate (among all switchers)c |
|--------------|------|---------|-----------------|-----------|----------------|-----------|-----------------------------------------------|-------------------------------------------------|-------------------------------------------------|---------------------------------------------|------------------------------------------|
| Boone 2018   |      | Netherlands | Rheumatology and gastroenterology | Infliximab | Full text | Prospective-center-based cohort study | 9 months | 18% | 73% | 13% |
| Daperno 2018 |      | Italy | Gastroenterology | Infliximab | Abstract | Prospective-center-based cohort study | 12 months | 19% | - | 7% |
| De Cock 2018 |      | UK | Rheumatology | Infliximab/etanercept | Abstract | Prospective-center-based cohort study | 6 months | 15% | 47% | 15% |
| Faddei 2018  |      | Germany | Gastroenterology | Infliximab | Abstract | Registry/database | 2 years | 19% | - | - |
| Gerwitz 2018 |      | Scotland | Gastroenterology | Infliximab | Full text | Prospective-center-based cohort study | 18 months | 9% | - | - |
| Gervais 2018 |      | Denmark | Rheumatology | Infliximab | Abstract | Registry/database | 1 year vs 1 year | 12% | - | 40% |
| Glintborg 2018 |      | Denmark | Rheumatology | Etanercept | Abstract | Registry/database | 1 year | 18% | 10% | 15% |
| Guerra Veloz 2018 |      | Spain | Gastroenterology | Infliximab | Full text | Prospective-center-based cohort study | 12 months | 9% | - | - |
| Haugeberg 2018 |      | Norway | Rheumatology | Etanercept | Abstract | Registry/database | 1 year | 15% | - | - |
| Høivik 2018 |      | Norway | Gastroenterology | Infliximab | Full text | Prospective-center-based cohort study | 18 months | 9% | - | - |
| Holroyd 2018 |      | UK | Rheumatology | Infliximab | Letter to the editor | Registry/database | 12.1 months | 14% | 50% | 7% |
| Kang 2018 |      | South Korea | Gastroenterology | Infliximab | Abstract | Registry/database | 1 year | 8% | - | - |
| Layegh 2018 |      | Netherlands | Rheumatology | Infliximab | Abstract | Prospective-center-based cohort study | 307 days | 7% | - | - |
| Lee 2018 |      | Korea | Rheumatology | Infliximab | Abstract | Retrospective-center-based cohort study | 8 months | 16% | - | - |
| Ma 2018 |      | UK | Rheumatology | Infliximab | Abstract | Prospective-center-based cohort study | 6 months | 16% | - | - |
| Miskens 2018 |      | Netherlands | Rheumatology | Infliximab | Abstract | Registry/database | 567 days | 7% | - | - |

*a* Discontinuation rate (switcher vs non-switcher) 
*b* Switchback rate (among discontinuers) 
*c* Switchback rate (among all switchers)
### Table 1 continued

| Study (author) | Country | Therapeutic area | Treatment | Publication type | Follow-up duration post switch | Number of patients | Follow-up duration post switch (switcher vs non-switcher) | Switchback rate (among all switchers) | Switchback rate (among discontinuers) |
|---------------|---------|------------------|-----------|------------------|-------------------------------|-------------------|---------------------------------------------------------|---------------------------------------|---------------------------------------|
| Petitdidier | France | Gastroenterology | Infliximab | Abstract Prospective center-based cohort study | 12 months | 113 | 12 months vs 1 year | 7% | – |
| Ratnakumaran | UK | Gastroenterology | Infliximab | Full text Prospective center-based cohort study | 1 year vs 1 year | 191 vs 19 | 1 month | 13% vs 5% | – |
| Scherlinger | France | Rheumatology | Etanercept | Full text Prospective center-based cohort study | 4 months | 44 | 1 month | 7% | 100% |
| Shih | UK | Rheumatology | Etanercept | Full text Prospective center-based cohort study | 543 days vs 543 days | 145 vs 98 | 1 month | 33% vs 15% | 50% |
| Sigurdardottir | Iceland | Rheumatology | Infliximab | Full text Prospective center-based cohort study | 6 months vs 6 months | 625 vs 600 | 1 month | 10% vs 8% | – |
| Tweehuysen | Netherlands | Rheumatology | Infliximab | Full text Prospective center-based cohort study | 6 months | 192 | 1 month | 25% | 75% |
| Tweehuysen | Netherlands | Rheumatology | Etanercept | Full text Prospective center-based cohort study | 6 months | 692 vs 600 | 1 month | 25% | 7% |
| Venerito | Italy | Rheumatology | Infliximab | Full text Prospective center-based cohort study | 9 months | 60 | 1 month | 25% | 2% |

*The discontinuation rates included in the extraction table are the unadjusted (raw) rates. In the meta-analysis, the discontinuation rates were adjusted to 1 year using the follow-up time.*

*In the meta-analysis, any values of 0 were removed. Therefore, when 0 patients switched back to the originator biologic, the switchback rate was calculated assuming 0.01 patients switched back. Additionally, when the switchback rate was reported as 100%, the standard error of the switchback rate was calculated assuming 0.01 patients did not switch back to the originator biologic.*

*The switchback rates (among all switchers) included in the extraction table are the unadjusted (raw) rates. In the meta-analysis, the switchback rates (among all switchers) were adjusted to 1 year using the follow-up time.*
patient choice (7%), disease improvement (4%), loss to follow-up (3%), pregnancy (1%), death (less than 1%), and unspecified reasons (19%). After discontinuing a biosimilar, the majority of patients switched back to the originator TNF inhibitor. A smaller percentage of patients switched to a biologic different from the originator or another biosimilar, underwent surgery, received other unspecified treatment options, or discontinued with no further treatment.

When all the studies were pooled together and adjusted for follow-up time, the annualized discontinuation rate was 21% (95% CI 18%, 25%) among NMS patients across all therapeutic areas (Fig. 1). The discontinuation rates by therapeutic area were consistent with the overall discontinuation rate: 26% (20%, 32%) for rheumatology and 17% (14%, 20%) for gastroenterology. For all the meta-analyses of discontinuation rates, the \( I^2 \) was greater than 80% and the \( p \) value associated with Cochran’s Q was less than 0.001, suggesting significant heterogeneity among the included studies.

The results of the sensitivity analyses were consistent with the aforementioned results (Supplementary Material Table 1), with discontinuation rates for all therapeutic areas ranging between 19% and 23%. Slightly higher discontinuation rates were observed when only studies with larger sample sizes were included. Slightly lower discontinuation rates were observed in studies including only patients treated with etanercept as the originator biologic. Consistent results were also observed when considering individual therapeutic areas.

**Annualized Switchback Rate Among NMS Patients**

A total of 29 studies reported switchback rate and follow-up time among all patients who underwent NMS. The reported switchback rate ranged from 0% to 63% across studies with various length of follow-up (range 4–24 months). When all the studies were pooled together and adjusted for follow-up time, the annualized switchback rate was 14% (95% CI 10%, 17%) among all patients who underwent an NMS across all the therapeutic areas (Fig. 2). When stratified by therapeutic area, the switchback rate was 17% (12%, 21%) for rheumatology and 8% (5%, 12%) for gastroenterology. For all the meta-analyses of the annualized switchback rates, the \( I^2 \) was greater than 90% and the \( p \) value associated with Cochran’s Q was less than 0.001, suggesting significant heterogeneity among studies. Therefore, switching back to the originator biologic used before the NMS was the most common option after biosimilar discontinuation.

The results of the sensitivity analyses were consistent with the aforementioned results (Supplementary Material Table 1), with the annualized switchback rates for all therapeutic areas ranging from 11% to 20%. Slightly higher switchback rates were observed when only studies with larger sample sizes were included. Slightly lower switchback rates were observed in studies including only patients treated with etanercept as the originator biologic. Consistent results were also observed when considering individual therapeutic areas.

**Switchback Rate Among Biosimilar NMS Discontinuers**

A total of 31 studies reported switchback rate among biosimilar NMS discontinuers. The reported rate ranged greatly across studies, from 0% to 100%. Notably, seven studies reported switchback rates of 100%, indicating that all patients who discontinued switched back to their originator TNF inhibitor [32–38]. When all the studies were pooled together, the switchback rate among discontinuers was 62% (95% CI 44%, 80%) (Fig. 3). Consistent results were reported by therapeutic area, with a switchback rate of 71% (60%, 81%) for rheumatology and 47% (23%, 71%) for gastroenterology. For all the meta-analyses of switchback rates, the \( I^2 \) was greater than 90% and the \( p \) value associated with Cochran’s Q was less than 0.001, suggesting significant heterogeneity among studies.

The results of the sensitivity analyses were consistent with those of the meta-analyses (Supplementary Material Table 1), with switchback rates among discontinuers for all
Fig. 1 Meta-analysis of annualized discontinuation rate: all therapeutic areas
Fig. 2 Meta-analysis of annualized switchback rate: all therapeutic areas
Fig. 3 Meta-analysis of switchback rate among discontinued patients: all therapeutic areas
therapeutic areas ranging from 61% to 69%. Slightly higher switchback rates were observed when only studies with larger sample sizes were included. Slightly lower switchback rates were observed in studies including only patients treated with etanercept as the originator biologic. Consistent results were also observed when considering individual therapeutic areas.

Incremental Annualized Discontinuation Rate Among NMS Patients

Nine studies that had discontinuation data available for both switchers and non-switchers were included in the meta-analysis of incremental annualized discontinuation rate. These studies had heterogeneous designs and substantially varied sample sizes. In particular, on average, the sample size of non-switchers was larger (768 patients, ranging from 19 to 2870) than switchers (344 patients, ranging from 89 to 1621). Four of these studies used historical controls before biosimilars became available for the non-switchers. The other four studies provided the discontinuation rates among patients elected to remain on originators when approached for the possibility of switching. The remaining study did not have a true discontinuation rate among non-switchers but used a proxy estimate with NMS patients as their own controls and evaluated discontinuation rate during the 6 months prior to NMS for non-switchers. Follow-up times were similar between switchers (mean 11 months, ranging from 6 to 18) and non-switchers (mean 12 months, ranging from 6 to 18).

When all the studies were pooled together, the incremental annualized discontinuation rate was 18% (95% CI 4%, 31%) across all therapeutic areas (Fig. 4), indicating a significantly higher discontinuation rate among switchers than non-switchers. Specifically, the incremental annualized discontinuation rate ranged from –12% to 54%. The study [39] that had a higher discontinuation rate among non-switchers used a proxy estimate. In that study, all patients who had been stable and persistent on treatment for at least 6 months were offered an NMS; those who did not accept the NMS discontinued, while those patients who accepted switched to a biosimilar. The discontinuation rate for non-switcher was estimated in all patients who were offered an NMS.

In terms of therapeutic areas, because of the small number of studies that reported discontinuation rate for both switchers and non-switchers, the discontinuation rate was not estimated separately for rheumatology studies (N = 7) and gastroenterology studies (N = 2).

DISCUSSION

The biosimilarity of biosimilars to their originator biologics has been confirmed in randomized controlled trials (RCTs) for biosimilars of adalimumab [40, 41], infliximab [42–44], and etanercept [45], in which no significant decrease in efficacy or increase in adverse events has been reported. However, approval of biosimilars on the basis of biosimilarity does not guarantee interchangeability with the originator biologic [5, 6]. Indeed, the US Food and Drug Administration (FDA) requires additional evaluation for the “interchangeable” designation, including evidence of identical clinical results in all treated patients and maintenance of safety and efficacy with multiple switching between originator biologic and biosimilar [7]. Of note, no biologic has currently achieved the interchangeable designation. As such, concerns have been raised with regard to NMS from a biologic to its biosimilar(s), particularly among stable patients with chronic conditions. Some physicians believe that small changes in these patients’ overall treatment regimens, which are often established after multiple rounds of trial and error, may have unwanted negative effects, even more so when considering the simultaneous management of comorbidities [46, 47]. Additionally, large-molecule biologics such as TNF inhibitors are particularly difficult to replicate [7], and the potential risk of an immunogenic reaction after an NMS could be troublesome for some physicians [6]. While studies have thus far not shown increased immunogenicity after switching to biosimilars [10], there is concern that current clinical trials may not be designed and/or sensitive enough to

△ Adis
detect these changes in anti-drug antibodies [48]. Further, an NMS may result in treatment instability and introduce unnecessary patient stress and anxiety, negatively affecting a patient's well-being [49, 50]. To better understand the treatment patterns associated with a biosimilar NMS, we conducted a meta-analysis summarizing real-world evidence related to biosimilar discontinuation and switchback following NMS from an originator TNF inhibitor to its biosimilar(s). Data from 66 studies including over 8700 patients were pooled together to estimate the prevalence rates of post-NMS biosimilar discontinuation and switchback to the originator TNF inhibitors.

Consistent with the results of two prior systematic literature reviews [27, 51], we found a large variation in the discontinuation rates reported in real-world studies. Specifically, the unadjusted discontinuation rate ranged from 1.5% to 87.0%, and the annualized rate ranged from 3.3% to 81.8%. This large variation is likely due to the heterogeneity in study design, region, patient population, and sample size of the studies included in the meta-analysis. The included real-world studies used divergent data sources and methodologies to evaluate the discontinuation outcomes. Forty-seven out of the 62 publications prospectively collected patient data through selected centers, while the remaining publications retrospectively evaluated patient outcomes either through registry/databases, or medical records. Of note, the highest discontinuation rates (annualized rates of 81.8% and 80.5%) were found in two Turkish national database studies [52, 53]. Notably, in both studies, discontinuation rates among switchers were much higher than those among non-switchers (87% vs 34% [52] and 82% vs 38% [53]). However, given that both studies defined discontinuation on the basis of evidence of switching to another biologic or absence of prescription claims for more than 120 days, the observed discontinuation rates could be subject to intrinsic limitations of claims data and may not fully reflect the prevalence of post-NMS discontinuation in the real world. By contrast, lower annualized discontinuation rates (3.3–7.2%) were observed in studies with a follow-up period less than

**Fig. 4** Meta-analysis of incremental annualized discontinuation rate: all therapeutic areas
6 months and a sample size less than 100 patients [33, 37, 38, 54, 55]. In addition, patients’ self-reported discontinuation of the biosimilar, or switchback to the original TNF inhibitor, and lack of follow-up with patients on a medication’s efficacy could be two limitations in some studies.

To address the heterogeneity across the identified studies, we conducted meta-analysis to synthesize the evidence while accounting for across study differences. Meta-analysis is currently the most common approach for quantitatively combining the results reported in different studies pertaining to the same outcome. This method allows the generated pooled estimate to put more weight on studies with larger sample sizes, thus reducing the variation in divergent observations caused by small sample sizes [30]. When the data from all the studies were pooled together, the annualized discontinuation rate was found to be 21%. A prior systematic literature review of post-NMS clinical outcomes reported discontinuation rates ranging from 5% to 33% across 12 different RCTs, including the landmark NOR-SWITCH study [10, 27]. It is worth noting that the discontinuation rates estimated in the present meta-analysis were within the range of the rates seen in RCTs even though our estimates were based on studies in real-world settings only. The pooled estimates from the current meta-analysis are likely to be more reflective of the discontinuation rates observed in clinical practice than those observed in clinical trials, which include only a select group of patients and adopt a more controlled design. For instance, the landmark NOR-SWITCH study excluded patients with certain comorbidities or those who adjusted co-medication prior to randomization. Further, all patients were required to maintain the same dose and infusion interval during the entire study follow-up and had frequent visits every 4 to 12 weeks. In real-world practice, greater heterogeneity in patient population and practice patterns is expected [20]. Indeed, a major strength of the present study is the inclusion of real-world data from 66 studies comprising over 8700 patients, providing a comprehensive overview of discontinuation and switchback rates among patients who undergo an NMS from a TNF inhibitor to a biosimilar in everyday clinical practice.

In line with the heterogeneity observed in the current study, it is important to recognize that considerable variability also exists in discontinuation research of originator biologics [56]. In a systematic literature review and meta-analysis of 98 studies for the use of originator TNF inhibitors in rheumatoid arthritis in early years, the reported discontinuation rates were 21%, 27%, 37%, 44%, and 52% for 6-month, 1-year, 2-year, 3-year, and 4-year periods, respectively [57]. In the present study, 66 publications contributed to meta-analysis and the follow-up period ranged between 3 months to 2 years, with the majority being less than 1 year. The annualized discontinuation rate of 21% among the biosimilar NMS patients was comparable to the findings from the meta-analysis of the originator discontinuers. Such a finding may suggest that although patients switched from a reference drug to its biosimilar, one should expect a similar discontinuation rate and many of these patients may switch back to the reference drug, as it was found in the present study. The reasons for discontinuation for patients on originators were similar to those of the present meta-analysis, including loss of efficacy and adverse effects [57–61]. However, external factors are also likely implicated, both in originator biologic and biosimilar switching patterns. Indeed, in a survey-based study of patients treated with biologics for various conditions, 20% reported receiving notice from their insurance company to switch to another originator biologic as a result of changes in insurance coverage [50]. Taken together, these findings highlight the issue of biologic discontinuation and its multifactorial causes in the context of both biosimilars and originator biologics.

In addition to discontinuation rates, large variations were also observed for reported switchback rates, which, among discontinuers, ranged from 0% to 100% across studies. In particular, in seven studies [32–38], all the patients who discontinued the biosimilar after an NMS switched back to the originator TNF inhibitor, whereas in two studies [62, 63] none of these patients switched back to the originator
TNF inhibitor. Notably, all the extreme values (0% switchback and 100% switchback) were reported in studies with a relatively small sample size (20–134 patients).

Importantly, through this literature review and meta-analysis, we found that the most common therapeutic choice (62%) after biosimilar discontinuation following NMS was to switch back to the originator TNF inhibitor. The pooled annualized switchback rate among all NMS patients was found to be 14% and was 62% among those NMS patients who discontinued biosimilar. Switching back to the originator TNF inhibitor appears to be a reasonable choice given that the most common reason for biosimilar discontinuation was loss of response or treatment failure (37%), followed by adverse events (28%). In line with these results, it has been suggested that switching from one originator to another or to its biosimilar(s) may increase the risk of developing anti-drug antibodies and subsequently failing to respond to treatment [64]. While studies have shown that anti-drug antibody reactivity to an originator biologic would yield similar cross-reactivity to its biosimilar [65, 66], other evidence may suggest differences in clinical response with switchback after development of anti-drug antibodies. Indeed, in an observational study including 23 patients who underwent an NMS but discontinued the biosimilar because of worsening disease symptoms, clinical improvement was observed in 71% of the patients after switching back to the originator biologic [32]. In addition, of the nine studies that had discontinuation data for both switchers and non-switchers, other than one that used a proxy estimate with NMS patients serving as their own control, the other eight studies reported a higher discontinuation rate for the switcher group, with an incremental discontinuation rate ranging from 2% to 54%. However, with the current lack of robust immunogenicity data in the literature [48], the association between switching, anti-drug antibodies, and treatment failure remains unclear.

The findings of this meta-analysis have important implications in managing patients with chronic conditions. Switching from a TNF inhibitor to its biosimilar for non-medical reasons was found to be associated with a high prevalence rate of biosimilar discontinuation due to treatment failure or adverse events, and a high switchback rate, but comparable with yearly discontinuation rate of the original TNF inhibitor.

To address the phenomenon of NMS, a patient-centered approach such as discussing the nocebo effect and providing patient education could be important. In the context of NMS, the nocebo effect would be a patient expecting a biosimilar to be less effective than the original TNF inhibitor, or to cause side effects, and then actually experiencing reduced efficacy or side effects. A known factor affecting patients’ perceptions of a medication’s efficacy is the cost of medication [67], and a biosimilar usually costs less than the original TNF inhibitor. Healthcare providers should educate patients about the efficacy of biosimilars in layman’s terms and avoid technical jargon and ambiguous statements [68].

Limitations

Some limitations should be considered when interpreting the study results. First, the publications identified were highly heterogeneous in terms of designs, geographic areas, patient populations, and sample size (many of which were small). Many of the included publications were abstracts, which often do not include detailed information regarding the methodologies used or funding sources. However, the meta-analysis approach (random-effect model) was used to minimize biases associated with the heterogeneity observed across studies by distributing weight according to study characteristics like sample size and follow-up time. Sensitivity analyses were also conducted using subsets of studies with similar characteristics and showed consistent results as the main analysis. In addition, discontinuation data were reported with substantially different follow-up intervals, limiting the comparability of data across studies. To address this limitation, the current analysis annualized all reported discontinuation rates by assuming a constant transition over time. Furthermore, since all
included publications were conducted in Europe or Asia, the generalizability of the results to other countries like the USA may be limited. Moreover, limited information available in the identified studies constrained the type of analyses and the generalizability of the study findings in the current study. For example, few studies assessed multiple switches (e.g., switching back and forth between biosimilars) or described potential population differences between those who underwent NMS and those who remained on originators. Insufficient data are available to evaluate whether there is any potential linkage between the discontinuation rate and therapeutic area. Lastly, as noted in the “Methods,” because the search was performed in 2018, the only biosimilars to TNF inhibitors available were infliximab and etanercept. With more biosimilars on the market, an update to this research and additional analyses are warranted to further investigate these topics.

CONCLUSIONS

This study found biosimilar discontinuation to be prevalent in the real world among patients who underwent an NMS from an originator TNF inhibitor to its biosimilar(s). Furthermore, switching back to the originator TNF inhibitor was a common therapeutic choice following biosimilar discontinuation. More real-world studies are needed to better understand the outcomes associated with biosimilar NMS and inform key stakeholders such as patients, healthcare providers, payers, and policymakers.

ACKNOWLEDGEMENTS

Funding. This study and the journal’s Rapid Service and Open Access Fees were funded by AbbVie. The study sponsor was involved in study design, data interpretation, and data and manuscript review.

Medical Writing and/or Editorial Assistance. Medical writing assistance was provided by Cinzia Metallo, Ph.D., Christine Tam, and Tahera Doctor, all employees of Analysis Group, Inc. Support for this assistance was funded by AbbVie.

Author Contributions. MY, CZQ, and EQW contributed to study conception and design, collection and assembly of data, and data analysis and interpretation. YL and MS contributed to study conception and design, data analysis and interpretation. All authors contributed to the development of the manuscript and maintained control over the final content.

Previous Presentations. A synopsis of the current research was presented in poster format at the 14th Congress of the European Crohn’s and Colitis Organisation (ECCO), March 2019 in Copenhagen, Denmark.

Disclosures. Yifei Liu reports to be an employee of the University of Missouri, Kansas City School of Pharmacy during the conduct of the study. Martha Skup reports to be an employee of AbbVie during the conduct of the study. Min Yang reports to be an employee of Analysis Group Inc., which has received research funds from AbbVie, during the conduct of the study. Cynthia Z. Qi reports to be an employee of Analysis Group Inc., which has received research funds from AbbVie, during the conduct of the study. Eric Q. Wu reports to be an employee of Analysis Group Inc., which has received research funds from AbbVie, during the conduct of the study.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

Data Availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

Open Access. This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation,
distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc/4.0/.

REFERENCES

1. Biosimilars Resource Center. What are biologics? 2017. https://www.biosimilarsresourcecenter.org/faq/what-are-biologics/. Accessed 16 Oct 2020.

2. Feldman SR, Bagel J, Namak S. Biosimilars for immune-mediated chronic diseases in primary care: what a practicing physician needs to know. Am J Med Sci. 2018;355:411–7.

3. Monaco C, Nanchahal J, Taylor P, Feldmann M. Anti-TNF therapy: past, present and future. Int Immunol. 2015;27:55–62.

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

5. Chingcuanco F, Segal JB, Kim SC, Alexander GC. Bioequivalence of biosimilar tumor necrosis factor-alpha inhibitors compared with their reference biologics: a systematic review. Ann Intern Med. 2016;165:565–74.

6. Feagan BG, Lam G, Ma C, Lichtenstein GR. Systematic review: efficacy and safety of switching patients between reference and biosimilar infliximab. Aliment Pharmacol Ther. 2018;49:31–40.

7. United States Food & Drug Administration (US FDA). Biosimilar and interchangeable products. 2017. https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products. Accessed 16 Oct 2020.

8. European Medicines Agency (EMA). Biosimilar medicines: overview. 2019. https://www.ema.europa.eu/en/human-regulatory/overview/biosimilar-medicines-overview. Accessed 16 Oct 2020.

9. Inotai A, Prins CPJ, Csanadi M, Vitezic D, Codreanu C, Kalo Z. Is there a reason for concern or is it just hype?—A systematic literature review of the clinical consequences of switching from originator biologics to biosimilars. Expert Opin Biol Ther. 2017;17:915–26.

10. Cohen HP, Blauvelt A, Rifkin RM, Danese S, Gokhale SB, Woollett G. Switching reference medicines to biosimilars: a systematic literature review of clinical outcomes. Drugs. 2018;78:463–78.

11. Glintborg B, Sorensen J, Hetland ML. Does a mandatory non-medical switch from originator to biosimilar infliximab lead to increased use of outpatient healthcare resources? A register-based study in patients with inflammatory arthritis. RMD Open. 2018;4: e000710.

12. Stoppa G, D’Amore C, Conforti A, et al. Comparative safety of originator and biosimilar epoetin alfa drugs: an observational prospective multicenter study. BioDrugs. 2018;32:367–75.

13. Tieu C, Lucas EJ, DePaola M, Rosman L, Alexander GC. Efficacy and safety of biosimilar insulins compared to their reference products: a systematic review. PLoS ONE. 2018;13: e0195012.

14. Cantini F, Benucci M. Switching from the bio-originators to biosimilar: is it premature to recommend this procedure? Ann Rheum Dis. 2019;78: e23.

15. Fleischmann R. Editorial: the American College of Rheumatology white paper on biosimilars: it isn’t all white-there is some gray and black. Arthritis Rheumatol. 2018;70:323–5.

16. Cohen RD. Nonmedical switching of biosimilars in patients with inflammatory bowel disease. Gastroenterol Hepatol (N Y). 2017;13:697–9.

17. Hu H, Xiang C, Qiu C, et al. Discontinuation of scheduled infliximab in Crohn’s patients with clinical remission: a retrospective single-center study. Gastroenterology Res. 2017;10:92–9.

18. Ramirez-Fort MK, Levin AA, Au SC, Gottlieb AB. Continuous versus intermittent therapy for moderate-to-severe psoriasis. Clin Exp Rheumatol. 2013;31:637-70.

19. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2016;68:1–26.

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

21. Lopez-Sigüero JP, Pfaffle R, Chanson P, Szałecki M, 
Hobel N, Zabransky M. Ten years' clinical experi-
ence with biosimilar human growth hormone: a 
review of efficacy data. Drug Des Dev Ther. 2017;11: 
1489–95.

22. Gerdes S, Thaći D, Griffiths CEM, et al. Multiple 
switches between GP2015, an etanercept biosimilair, 
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.

23. Ribaldone DG, Tribocco E, Rosso C, et al. Switching 
from biosimilar to biosimilar adalimumab, includ-
ing multiple switching, in Crohn's disease: a 
prospective study. J Clin Med. 2021;10:3387.

24. Ribaldone DG, Caviglia GP, Pellicano R, et al. Effectiveness and safety of adalimumab biosimilar 
ABP 501 in Crohn's disease: an observational study. Rev Esp Enferm Dig. 2020;112:195–200.

25. Institute for Patient Access. Cost-motivated treat-
ment changes & non-medical switching: Commer-
cial health plans analysis. 2017. http://1yh21u3cjptv3xjder1dco9mx5s.wpengine.netdna-cdn.
com/wp-content/uploads/2013/08/IfPA_Non-Medical-
Switching-Commercial-Claims-Analysis_Aug-2017.pdf. Accessed 16 Oct 2020.

26. Nguyen E, Weeda ER, Sobieraj DM, Bookhart BK, 
Plech 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.

27. Numan S, Faccini F. Non-medical switching from 
originator tumor necrosis factor inhibitors to their biosimilars: systematic review of randomized controlled trials and real-world studies. Adv Ther. 2018;35:1295–332.

28. Businesswire. BENEPALI®, the first etanercept 
biosimilar referencing Enbrel®, approved in the 
European Union. 2016. https://www.businesswire.
com/news/home/20160116005011/en/BENEPALI% 
C2%AE-the-First-Etanercept-Biosimilar-Referencing-
Enbrel%2C%AE-Approved-in-the-European-Union. 
Accessed 16 Oct 2020.

29. Amgen. European Commission approves AMGEVI-
TA™ (biosimilar adalimumab) for the treatment of 
certain inflammatory diseases: first biosimilar adal-
umab approved in the European Union. 2017. 
https://www.amgen.com/newsroom/press-releases/
2017/03/european-commission-approves-amgevita-
biosimilar-adalimumab-for-the-treatment-of-certain-
inflammatory-diseases. Accessed 16 Oct 2020.

30. Kelley G, Kelley K. Statistical models for meta-
analysis: a brief tutorial. World J Methodol. 2012;2: 
27–32.

31. R Core Team. R: A language and environment for 
statistical computing. R Foundation for Statistical 
Computing, Vienna, Austria. 2013. http://www.R-
project.org/. Accessed 16 Oct 2020.

32. Gentilelsich S, Barreca C, Bellais I, et al. Switch 
from infliximab to infliximab biosimilar: efficacy 
and safety in a cohort of patients with different 
rheumatic diseases. Expert Opin Biol Ther. 2015;16: 
1311–2.

33. Bettey M, Downey L, Underhill C, et al. DOP029 
Outcomes of a managed switching programme 
changing IBD patients established on originator infliximab to biosimilar infliximab. European 
Crohn's and Colitis Organisation 2016 Congress. 
2016.

34. Sheppard M, Hadavi S, Hayes F, Kent J, Dasgupta B. 
AB0322 preliminary data on the introduction of the 
ilfliximab biosimilar (CT-P13) to a real world 
cohort of rheumatology patients. BMJ. 2016;75:3.

35. Babai S, Akrout W, Le-Louet H. 242 Reintroduction 
of reference infliximab product in patients showing 
inefficacy to its biosimilar. 17th ISoP Annual 
Meeting "Pharmacovigilance in the 21st Century". 
2017.

36. Scherlinger M, Langlois E, Germain V, Schaeverbeke 
T. Acceptance rate and sociological factors involved 
in the switch from originator to biosimilar etaner-
cept (SB4). Semin Arthritis Rheum. 2018;48:927–32.

37. Garofalo V, Del Duca E, Saraceno R, Ruzzetti M, 
Bianchi L. P2027 Switching from infliximab origi-
nator to biosimilar in psoriatic patients: a prospec-
tive study. European Academy of Dermatology and 
Venerology Conference. 2016.

38. Layegh Z, Ruwaard J, Hebing R, et al. AB1279 Effi-
cacious transition from reference product inflix-
imab to the biosimilar in daily practice. EULAR 
2018. 2018.

39. Holroyd C, Wallis D, Bennett S, Clayton P, Edwards 
C. Switching from bio-original etanercept to 
biosimilar etanercept sb4: patient acceptability and 
outcomes in the real world. BMJ. 2017;76:1180. 
https://doi.org/10.1136/annrheumdis-2017-eular. 
3672.
40. Cohen SB, Alonso-Ruiz A, Klimiuk PA, et al. Similar efficacy, safety and immunogenicity of adalimumab biosimilar BI 695501 and Humira reference product in patients with moderately to severely active rheumatoid arthritis: results from the phase III randomised VOLTAIRE-RA equivalence study. Ann Rheum Dis. 2018;77:914–21.

41. Weinblatt ME, Baranauskaite A, Dokoupilova E, et al. Switching from reference adalimumab to SB5 (Adalimumab Biosimilar) in patients with rheumatoid arthritis: fifty-two-week phase III randomized study results. Arthritis Rheumatol. 2018;70:832–40.

42. 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.

43. 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 randomized, double-blind, phase III transition study. Ann Rheum Dis. 2018;77:234–40.

44. 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.

45. 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.

46. Healio Rheumatology. Concerns over nonmedical switching of biologics spur physician guidelines. 2018. https://www.healio.com/rheumatology/practice-management/news/online/%7Be98c7677-46ea-434d-b284-93fcb250b547%7D/concerns-over-nonmedical-switching-of-biologics-spur-physician-guidelines. Accessed 16 Oct 2020.

47. Araújo F, Fonseca J, Goncalves J. Switching to biosimilars in inflammatory rheumatic conditions: current knowledge. 2018. https://www.emjreviews.com/rheumatology/article/switching-to-biosimilars-in-inflammatory-rheumatic-conditions-current-knowledge/. Accessed 16 Oct 2020.

48. 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.

49. Teeple A, Ellis LA, Huff L, et al. Physician attitudes about non-medical switching to biosimilars: results from an online physician survey in the United States. Curr Med Res Opin. 2019;35:611–7.

50. Teeple A, Ginsburg S, Howard L, et al. Patient attitudes about non-medical switching to biosimilars: results from an online patient survey in the United States. Curr Med Res Opin. 2019;35:603–9.

51. Liu Y, Yang M, Garg V, Wu EQ, Wang J, Skup M. Economic impact of non-medical switching from originator biologics to biosimilars: a systematic literature review. Adv Ther. 2019;36:1851–77.

52. Yazici Y, Xie L, Ogbomo A, et al. SAT0175 A descriptive analysis of real-world treatment patterns in a Turkish rheumatology population that continued innovator infliximab (REMCIDE) therapy or switched to biosimilar infliximab. Ann Rheum Dis. 2017;76:836.

53. Ellis L, Simsek I, Xie L. Analysis of real-world treatment patterns in a matched sample of rheumatology patients with continuous infliximab therapy or switched to biosimilar infliximab. 2017 ACR/ARHP Annual Meeting [abstract 455] 2017. https://acrabstracts.org/abstract/analysis-of-real-world-treatment-patterns-in-a-matched-sample-of-rheumatology-patients-with-continuous-infliximab-therapy-or-switched-to-biosimilar-infliximab/. Accessed 16 Oct 2020.

54. 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.

55. 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.

56. Fisher A, Bassett K, Goel G, et al. Heterogeneity in comparisons of discontinuation of tumor necrosis factor antagonists in rheumatoid arthritis—a meta-analysis. PLoS ONE. 2016;11: e0168005.

57. 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. 2015;55:523–34.

58. Gomez-Reino JJ, Carmona L. Switching TNF antagonists in patients with chronic arthritis: an observational study of 488 patients over a four-year period. Arthritis Res Ther. 2006;8:R29.

59. Garcia-Lagunar MH, Gutierrez-Civcos MR, Garcia-Simon MS, et al. Reasons for discontinuation and
adverse effects of TNFalpha inhibitors in a cohort of patients with rheumatoid arthritis and ankylosing spondylitis. Ann Pharmacother. 2017;51:388–93.

60. Strand V, Miller P, Williams SA, Saunders K, Grant S, Kremer J. Discontinuation of biologic therapy in rheumatoid arthritis: analysis from the Corrona RA Registry. Rheumatol Ther. 2017;4:489–502.

61. Scherlinger M, Germain V, Labadie C, et al. Switching from originator infliximab to biosimilar CT-P13 in real-life: the weight of patient acceptance. Jt Bone Spine. 2017;85:561–7.

62. Ala K, Avery P, Wilson R, et al. PTU-059 early experience with biosimilar infliximab at a District General Hospital for an Entire Crohn’s disease patient cohort switch from remicade to inflectra. BMJ. 2016;65:6.

63. St. Clair Jones A, Smith M. P527 Infliximab biosimilar switching program overseen by specialis pharmacis saves money, realises invement and optimises therapy. European Crohn’s and Colitis Organisation (ECCO) 2017 Congress.

64. Husereau D, Feagan B, Selya-Hammer C. Policy options for infliximab biosimilars in inflammatory bowel disease given emerging evidence for switching. Appl Health Econ Health Policy. 2018;16:279–88.

65. Ben-Horin S, Yavzori M, Benhar I, et al. Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima. Gut. 2016;65:1132–8.

66. Ruiz-Arguello MB, Maguregui A, Ruiz Del Agua A, et al. Antibodies to infliximab in Remicade-treated rheumatic patients show identical reactivity towards biosimilars. Ann Rheum Dis. 2016;75:1693–6.

67. Tinnermann A, Geuter S, Sprenger C, Finsterbusch J, Büchel C. Interactions between brain and spinal cord mediate value effects in nocebo hyperalgesia. Science. 2017;358:105–8.

68. Häuser W, Hansen E, Enck P. Nocebo phenomena in medicine: their relevance in everyday clinical practice. Dtsch Arztebl Int. 2012;109:459–65.

69. Müskens WD, Rongen-van Dartel SAA, Adang E, van Riel PL. The influence of switching from etanercept originator to its biosimilar on effectiveness and the impact of shared decision making on retention and withdrawal rates. BMJ. 2018;77.

70. Jung YS, Park DJ, 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.

71. 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.

72. 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.

73. 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(Suppl 1):35–44.

74. Bennett K, Heap G, 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). BMJ. 2016;65:A146.

75. 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. BMJ. 2016;65:A89.

76. van den Hoogen F, Tweehuysen L. Introduction of biosimilars in clinical practice: first findings. Dutch J Dermatol Venerol. 2016;26:1.

77. 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.

78. 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.

79. Avouac J, Moltó 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. 2017;47:741–8.

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

81. Buer LC, Moun 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.

82. Glintborg BS, Loft AG, Lindegaard H, 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. BMJ. 2017;76:5.

83. 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.

84. Gutermann L, Apparuit M, Boissinot L, et al. CP-150 Evaluation of infliximab (REMCARDE) substitution by infliximab biosimilar (INFLDITION): cost savings and therapeutic maintenance. Clin Pharm. 2017;24:A67–8. https://doi.org/10.1136/ejhpdrug-2017-000640.149.

85. Hendricks O H-PK. When etanercept switch fails – clinical considerations. Arthritis Rheumatol. 2017;69(suppl 10).

86. 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. https://doi.org/10.1093/rheumatology/kex062.055.

87. Nugent S, Nugent M, Mullane D, Kelly C. EirSwitch echoes of NorSwitch: switching biosimilar therapy in an IBD cohort an Irish experience. J Crohns Colitis. 2017;11:594–604.

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

90. 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. 2017;47:356–63.

92. Sieczkowska-Golub J, Jarzbecka D, Dadalski M, Meglicka M, Oracz G, Kierkus J. Switching between infliximab originator and biosimilar in paediatric patients with inflammatory bowel disease. Preliminary observations. PiBD 2017 EP36. 2017.

93. Sladek M, Vultaggio A, Ghione S, et al. Comparable clinical efficacy, safety and immunogenicity of infliximab biosimilar (CT-P13) after transition from reference infliximab (Remicade®) in children with established inflammatory bowel disease: a multicentre prospective observational. J Crohns Colitis. 2017;11:S418.

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

95. Soret P-A, Prieux-Klotz C, Avouac J, et al. Efficacy and safety of switching from reference infliximab to biosimilar infliximab in patients with inflammatory bowel disease: first French experience. J Crohns Colitis. 2017;11:1.

96. Yazici Y, Xie L, Ogbono 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. BMJ. 2017;76:836. https://doi.org/10.1136/annrheumdis-2017-eular.1128.

98. Armuzzi A, Fiorino G, Variola A, et al. The PROSIT cohort of infliximab biosimilar in IBD: a prolonged follow-up on the effectiveness and safety across Italy. Inflamm Bowel Dis. 2018;25:568–79.

99. Binkhorst L, Sobels A, Stuyt R, Westerman EM, West RL. Short article: Switching to a infliximab biosimilar: short-term results of clinical monitoring in patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2018;30:699–703.

100. 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.
levels and anti-drug antibodies determination. J Crohns Colitis. 2018;12:1.

102. De Cock D, Dyball S, Kearsley-Fleet L, Watson K, Hyrich K, BSRBR-RA contributors group. Profiling rheumatoid arthritis biosimilar switchers: data from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Rheumatology. 2018. https://doi.org/10.1093/rheumatology/key075.465.

103. Fischer S, Klenske E, Schmitt H, Vitali F. Clinical outcomes and immunogenicity analysis over 6 months following a switch from originator infliximab (Remicade®) to the biosimilar SB2 (Flixabi®) in inflammatory bowel disease patients. J Crohns Colitis. 2018;12:2.

104. Gervais L, McLean LL, Wilson ML, et al. Switching from originator to biosimilar infliximab in paediatric inflammatory bowel disease is feasible and uneventful. J Pediatr Gastroenterol Nutr. 2018;67:745–8.

105. Guerra Veloz MF, Vazquez Moron JM, Belvis Jimenez M, et al. Switching from reference infliximab to CT-P13 in patients with inflammatory bowel disease: results of a multicenter study after 12 months. Rev Esp Enferm Dig. 2018;110:564–70.

106. Haugeberg G, Bakland G, Rødevand E, Fenvang B, Hansen J, Diamantopoulos A. Drug survival and reason for drop-out in rheumatoid arthritis patients with a non-medical switch from originator to biosimilar etanercept – preliminary data from a norwegian multicenter study. BMJ. 2018;77:1383. https://doi.org/10.1136/annrheumdis-2018-eular.4716.

107. Holovik ML, Buer LCT, Cvanarova M, et al. Switching from originator to biosimilar infliximab—real world data of a prospective 18 months follow-up of a single-centre IBD population. Scand J Gastroenterol. 2018;53:692–9.

108. Holroyd C, Parker L, Bennett S, et al. Switching to biosimilar infliximab: real world data in patients with severe inflammatory arthritis. Clin Exp Rheumatol. 2018;36:2.

109. 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.

110. Lee S, Szeto M, Galloway J. Bio-similar to bio-originator switchback: not a reliable quality indicator. BMJ. 2018;77:1727–8. https://doi.org/10.1136/annrheumdis-2018-eular.5750.

111. Petitdidier N, Gagniere C, Rentien A, et al. Patients’ perspectives on switching from reference infliximab to CT-P13 biosimilar in patients with inflammatory bowel disease: a 12-month prospective observational cohort study. J Crohns Colitis. 2018;12:1.

112. Ratnakumaran R, To N, Gracie DJ, et al. Efficacy and tolerability of initiating, or switching to, infliximab biosimilar CT-P13 in inflammatory bowel disease (IBD): a large single-centre experience. Scand J Gastroenterol. 2018;53:700–7.

113. Shah K, Flora K, Penn H. Clinical outcomes of a multi-disciplinary switching programme to biosimilar etanercept for patients with rheumatoid arthritis. Rheumatology. 2018. https://doi.org/10.1093/rheumatology/key075.456.

114. Sigurdardottir V, Svard A. Multiswitching - from reference product etanercept to biosimilar and back again - real-world data from a clinic-wide multi-switch experience. BMJ. 2018;77:331–2. https://doi.org/10.1136/annrheumdis-2018-eular.2769.

115. Tweehuysen L, Huiskes VJB, van den Bent BJF, et al. Open-label, non-mandatory transitioning from originator etanercept to biosimilar SB4: six-month results from a controlled cohort study. Arthritis Rheumatol. 2018;70:1408–18.

116. Tweehuysen L, van den Bent 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.

117. Valido A, Silva-Dinis J, Saavedra M, Bernardo N, Fonseca J. Efficacy and cost analysis of a systematic switch from originator infliximab to biosimilar ct-p13 of all patients with inflammatory arthritis from a single centre. BMJ. 2018;77:1712–3. https://doi.org/10.1136/annrheumdis-2018-eular.5844.

118. Venerito V, Lopalco G, Cantarini L, et al. Switching from originator infliximab to biosimilar infliximab: efficacy and safety in a cohort of patients with established behC¸et’s disease. BMJ. 2018;77:288–90. https://doi.org/10.1136/annrheumdis-2018-eular.3093.

119. Ma J, Petford S, Jones L, et al. Audit of the clinical efficacy and safety of etanercept biosimilar to its reference product in patients with inflammatory arthritis: experience from a district general hospital in the United Kingdom. Rheumatology. 2018;57(suppl:3). https://doi.org/10.1093/rheumatology/key075.288.

△ Adis