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

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\textbf{ABSTRACT}

\textbf{Introduction}: While prescribing biosimilars to patients naive to a biologic treatment is a well-accepted practice, switching clinically stable patients from an originator to a biosimilar is an issue for clinicians. Well-designed clinical trials and real-world data which study the consequences of switching from an originator biologic treatment to its biosimilar alternative are limited, especially for monoclonal antibodies.

\textbf{Areas covered}: A systematic literature review was conducted on PubMed to identify evidence of the consequences of switching from originator biologics to biosimilars. References of included papers were also scrutinized. After a title-, abstract- and full text screening, out of the 153 original hits and 77 additional ones from screening the references, 58 papers (12 empirical papers, 5 systematic reviews and 41 non-empirical papers) were included.

\textbf{Expert opinion}: Preventing patients on biologic medicines from switching to biosimilars due to anticipated risks seems to be disproportional compared to the expected cost savings and/or improved patient access. Indeed, it is the opinion of the authors that the concern of switching to biosimilars is overhyped.

\section{1. Introduction}

Many innovative treatments in the field of inflammatory rheumatic diseases, inflammatory bowel diseases, and oncology consist of biologic products [1]. The increasing utilization of these high-cost therapies in chronic conditions represents a vast proportion of the total pharmaceutical expenditure [2]. This is especially true for lower income European countries where the growth rate of pharmaceutical spending is greater than in higher income countries [3]. Many originator biologic drugs have already lost their patents, such as erythropoietins, granulocyte-colony-stimulating factors, and recently the monoclonal antibody (MaB) infliximab [2,4,5], but even more biosimilars are awaiting regulatory approval in public health priority areas such as oncology [6].

Despite the complexity of their clinical development and manufacturing process compared to small molecule generics, using biosimilars can result in lower pharmaceutical prices due to price erosion [6–8]. For instance in case of a blind tendering process, both the off-patent originator and the biosimilar manufacturers are competing with their tender price. Therefore, these products may offer a cost-saving opportunity for health-care systems currently facing financial pressure generated by the adoption of innovative treatments [9–11]. High treatment cost currently limits patient access to biologic medical treatments [5,12–14], especially in lower income countries [8,15]. In these countries, biosimilars can increase the number of patients on biologic medicines without the need for additional resources [5,6,16,17].

Immediate cost savings could be realized by starting the treatment with a biosimilar in newly diagnosed (de novo) patients instead of starting with original products. However, since the new generation of biosimilars is complex monoclonal antibodies, their increased utilization in maintenance treatment has become an important question to maximize societal benefit: the option of switching clinically stable patients currently being treated with original biologic products to biosimilars is not an obvious decision for many physicians and payers [18,19]. Macromolecules cannot guarantee the same tertiary and quaternary structure of the molecule due to posttranslational modifications during the manufacturing process. Even for original products, several procedural changes are implemented during production [20] and these changes require notification and approval from the regulatory agency [21].

As stated by some experts based on a few, but often cited cases from the past, switching may have negative consequences [22–26]. For example, the incidence of pure red cell aplasia (PRCA) increased between 1998 and 2001 in patients with chronic kidney disease on original erythropoietin alpha treatment [27–30]. Later studies attributed this temporary increase to changes in the manufacturing process and packaging of the product [31,32]. Although the increased incidence was not related to switching from an original biologic to a...
biosimilar drug, this case was used even to argue against switching. Similarly in 2011, a small group of patients in Thailand developed PRCA while using a recombinant human erythropoietin which was not internationally approved [33]. This study – in some cases has also been misused to underpin concerns against biosimilars in general – provided evidence that immunogenicity is also determined by product quality issues [34]. Another highly cited observation was the development of hemophilia in factor VIII users after being switched between different originator products. In this case, loss of efficacy was attributed to neutralizing antibodies. However, later studies did not replicate this finding and argued that such results should not be generalized [35].

Additionally, other concerns against biosimilar products were linked to their efficacy and safety profile, bioactivity, indication extrapolation, interchangeability, long-term effectiveness, naming issues to ensure traceability, counterfeit copies, manufacturing problems, and constant product quality [36]. These may create a negative perception of biosimilars and thus reduce their market penetration even for patients without a previous history of being treated with biologics [10,14].

There are multiple approaches on how to handle the uncertainty related to switching to biosimilars. One possible approach is to analyze pivotal phase 3 clinical trials of follow-on biologics. However, due to the fact that some MAbs have only recently lost their patents, these studies are not adequately powered in many cases to detect the consequences of switching. Nevertheless, there are ongoing clinical trials evaluating the consequences of switching to biosimilars [37]. Patient registries or payers’ databases may generate robust real-world evidence only after switching is generally applied, yet for now, a sufficient number of cases cannot be identified in many of these databases. Until these data can be obtained, a systematic review of currently available information can be the strongest evidence to support policy decisions.

The aim of this study was to synthesize evidence on negative clinical outcomes of switching from original biologics to biosimilars through a systematic literature review and assess whether the raised concerns of some experts justify limiting the switch from an originator biologic to a biosimilar drug.

2. Literature review strategy

To gather evidence from published medical literature, a search query was designed to reflect the aim of the study that could identify all relevant papers available through PubMed. The query consisted of three linked baskets of key words of which the first was restricted to title or abstract (see Appendix 1 for search query). The first basket was formed to include 14 expressions for follow-on biologics and biosimilars, the second basket focused on 18 synonyms and other frequently used expressions for the intervention of switching from one biologic drug to another, while the third basket focused on 41 phrases describing the potential health outcomes of switching. No time restriction was applied in the search syntax, and only English language papers were considered eligible. The search query was finalized and records from PubMed were downloaded on 13 May 2016.

The hits were processed by EndNote X7 and were checked for duplicates (1.0). A title and abstract screening was conducted by two independent researchers. Based on the predefined study eligibility criteria (Table 1) defined by Participants, Interventions, Comparisons, Outcome(s) and Study design as recommended by the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) Statement [38], the following exclusion categories were applied during the title and abstract screening: (2.1) no English abstract with unspecific title, (2.2) English abstract of non-English language paper (marked if abstract contains relevant evidence), (2.3) animal or in vitro studies of biologics/biosimilars, and (2.4) abstract or text not related to research objective. Since switching between international nonproprietary names (INNs) could not be explicitly identified based on the abstract alone, these papers were only excluded during the full text review (2.5), leaving only articles on biosimilar switch for examination (see Figure 1). Disagreements between the two independent researchers regarding the inclusion and/or exclusion were resolved by a principal researcher not involved in the screening process. Two independent researchers conducted the full text review of all included papers. The full text review applied similar exclusion categories (2.1–2.5).

All included papers were categorized into the following six categories based on a full text review: (3.1) guidelines men-

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Table 1. Study eligibility criteria specified according to PICOS.

| Inclusion criteria | Exclusion criteria |
|--------------------|--------------------|
| **Patients** | Population treated with biologic therapy |
| **Intervention** | Switching to biosimilar therapy with the same INN |
| **Comparator** | Switching to a biologic therapy with different INN; No switching |
| **Outcomes** | Negative outcomes associated with switching between biologic therapies |
| **Study design** | No negative outcomes associated with switching between biologic therapies; No outcomes reported |
| **Conclusion** | Animal or in vitro studies of biologics/biosimilars |
The included articles were subjected to duplicated data extraction onto excel spreadsheets completed by two experts independently. Disagreements were resolved by a principal researcher. The following qualitative and quantitative data were extracted: clinical data including patient numbers, observed negative outcomes, INNs, indications, follow-ups, expert/guideline statements on negative outcomes, conclusions/recommendations on switching/substitution.

3. Evidence on switching to biosimilars

The search resulted in 153 hits, of which, after title-, abstract-, and full-text screening, 34 papers were included and allocated to the predefined categories, as described in Table 2. The snowball search method provided 77 additional articles of which 24 papers were also included; therefore, the current review contains a total of 58 papers. The complete flowchart of literature review based on principles of the PRISMA statement [38] is described in Figure 1.

### 3.1. Nonempirical evidence

#### 3.1.1. General information on nonempirical papers

Categories 3.1–3.4 were pulled together as nonempirical or anecdotal evidence [1,2,4,10,11,14,18,19,22–26,39–66] and consisted of a wide range of papers varying from regulatory affairs to expert opinions and nonsystematic reviews. The majority of the nonempirical papers were not disease specific (n = 15), while among the disease-specific papers, the majority focused on inflammatory bowel disease (n = 9), followed by rheumatoid arthritis (n = 5), chronic kidney disease, and anemia (n = 5) and three focused on malignancies. Similarly, out of the 41 papers, 23 were non- INN-specific, while 8 were related to infliximab, 4 to erythropoietins, 2 to insulin and low-molecular weight heparin, 1 to tumor necrosis factor alpha inhibitors in general and rituximab, respectively. Out of the 41 nonempirical papers, 22 implicitly and 10 explicitly implied that there was an increased risk of switching to biosimilars. From this group of 32 articles, 23 suggested that the increased risk is a general characteristic of either switching under the supervision of a physician or substituting to biosimilars at the pharmacy level (if applicable), while 9 papers associated an increased risk only with automatic substitution of biosimilars. However, statements of

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**Table 2.** Category allocation based on full text screening, subdivided per method.

| Category                        | Included papers from original search query | Included papers from snowball search | Total included papers |
|---------------------------------|--------------------------------------------|-------------------------------------|-----------------------|
| 3.1 Guidelines                  | 3                                          | 0                                   | 3                     |
| 3.2 Expert opinion              | 11                                         | 9                                   | 20                    |
| 3.3 Opinion of expert panel     | 2                                          | 3                                   | 5                     |
| 3.4 Non systematic review       | 8                                          | 5                                   | 13                    |
| 3.5 Systematic review           | 3                                          | 2                                   | 5                     |
| 3.6 Original empirical data     | 7                                          | 5                                   | 12                    |
| Total                           | 34                                         | 24                                  | 58                    |
increased risk in nonempirical papers were only substantiated in very few cases by clinical evidence citings.

3.1.2. The use of PRCA case in nonempirical papers
Sixteen papers cited the case of PRCA, 13 of which used this as a warning for risks related to biosimilars in general (see e.g. Refs. [46,55,61]), while 3 papers argued that PRCA should not be generalized to all biosimilars [49,52,58] and immunogenicity should be evaluated on a case-by-case basis [67]. However, as described above, the PRCA case does not constitute evidence in regards to switching from original biologics to biosimilars. It does, however, suggest a potential risk of utilizing biologic medicines in general and highlights that changes in the manufacturing and packaging process may have an influence on biopharmaceuticals, including original products.

3.1.3. Recommendation on switching in nonempirical papers
All 41 papers had a conclusion either on switch, substitution, or both. Of the nonempirical papers, 5 discouraged switching, 11 did not present a negative opinion on switching, while 16 did not express a negative opinion in general but highlighted the necessity of involving patients and physicians in such decisions, as well as the importance of pharmacovigilance. Regarding the automatic substitution at the pharmacy level, 17 papers had a negative recommendation, 1 paper had no negative opinion, while 17 in general did not oppose substitution to biosimilars but underlined the potential risks, the relevance of monitoring the consequences and the need for further data collection. Many of the papers with no objection to switching discouraged automatic substitution at the pharmacy level without medical supervision by physicians. In general, many papers included in categories 3.1–3.4 used a hypothetical risk as an argument for opposing switching to biosimilars [1,39–41].

3.2. Evidence from systematic literature reviews
Systematic literature reviews collected in category 3.5 (Table 3) [5,6,9,68,69] were considered as a separate category since these comprised a higher degree of evidence compared to the papers in 3.1–3.4. As described in Table 3, these papers varied in scope, some of which even had a broader perspective than the objective of the current systematic literature review. Altogether, three comprehensive reviews were conducted on inflammatory diseases which studied infliximab and related biosimilars, while two had a general scope without focusing on a specific INN. None of these systematic reviews had an objection to switching from the original biologics to biosimilars, although two of them highlighted the importance of concomitant pharmacovigilance surveillance. Three reviews explicitly stated that switching from an original biologic to a biosimilar drug was not associated with increased risk, while efficacy was maintained [6,68,69]. The systematic literature review by Ebbers et al. including both clinical trial data and post-marketing surveillance data stated that no significant safety signals have emerged from switching to and from biopharmaceuticals, including biosimilars. That review included analyses of pharmacovigilance databases by the FDA and EMA as well, resulting in a high number of empirical studies compared to our review, but with similar conclusions [68]. However, the review by Ebbers focused on recombinant growth hormones, epoetins, and granulocyte-colony-stimulating agents; therefore, extrapolation of the lessons learned from the use of these molecules to MaBs should be handled with care. The advent of biosimilar MaBs should be considered as a different challenge from the pharmaceutical policy point of view due to their increased complexity compared to first-generation biosimilars. Other systematic literature reviews included in Table 3 [5,6,69] drew similar conclusions, out of which two explicitly stated that no clinical evidence of negative consequence from switching was found. It is important to mention that these reviews investigated infliximab; hence, their conclusion may be more relevant for other monoclonal antibodies about to lose their patents, like trastuzumab, adalimumab, etanercept, or rituximab, until further INN-specific studies or systematic reviews become available. In addition to the conclusions regarding efficacy and safety, a review by Cornes also highlighted the societal benefit in terms of cost savings, by stating that substitution of biosimilars could ensure that health-care costs remain sustainable [9]. Considering that the clinical trial data required for registration of biosimilars only prove biosimilarity to the originator product, automatic substitution of different biosimilar products, especially MaBs, is not yet substantiated by convincing evidence [37].

3.3. Evidence from original clinical studies
Category 3.6 consisted of empirical evidence from original clinical studies published before our search hits were downloaded (Table 4) [70–81]. Out of the 12 identified empirical evidence papers, 4 had an indication of inflammatory bowel disease, 4 chronic kidney disease and anemia, 2 rheumatoid arthritis, and 1-1 of ankylosing spondylitis and indication of growth hormone, respectively. The average duration of the trials was 6–12 months with a maximum of 30 months. The sample size of patients that switched treatments varied largely between 9 and 481. The 12 trials sampled a total of 1096 patients who switched to biosimilar treatments. The review identified four underlying erythropoietin trials and one somatropin trial for smaller molecule weight biosimilars, while the larger molecule weight MaB infliximab was investigated in seven trials. There were six single arm transition studies in terms of switching, five parallel arm transition studies with a prospective or retrospective design, and one single switch crossover study. Table 4 describes negative patient outcomes related to switching as described in the original studies. Two trials explicitly reported no adverse events or loss of efficacy related to switching, whereas 10 trials concluded that, overall, there was no increased risk of immunogenicity or adverse events, while no statistically significant loss of efficacy was observed. Altogether, none of the empirical papers reported significant negative clinical consequences of switching from an originator biologic to a biosimilar treatment. Albeit that the empirical evidence on switching summarized in Table 4 comprises studies with relatively small patient groups that did not always include a comparator treatment in terms of switch, their conclusion
| Paper ID | Indication | Substance | Aim of the paper | Results/conclusion | Discourage switch? (yes, no, no-but) | Discourage substitution? (yes, no, no-but) |
|----------|------------|-----------|------------------|--------------------|---------------------------------------|------------------------------------------|
| Cornes [9] | Not specified | Biosimilars in general | Discover the degree to which financial constraints will drive future health spending and discover if legal or safety issues could have an impact on trends | Biosimilar substitution could help ensure health-care costs remain sustainable and offer the latest way for oncologists to save costs for reinvestment | No-but | No |
| Ebbers et al. [68] | Not specified | Biosimilars in general | Overview of data related to switching between human recombinant growth hormones, erythropoietins, and granulocyte-colony-stimulating agents | No evidence from clinical trial data or post-marketing surveillance data was found that switching to and from different biopharmaceuticals (including biosimilars) leads to safety concerns | No | No-but |
| Isaacs et al. [5] | Inflammatory diseases | Infliximab | Issues regarding the definition of biosimilarity, the validity of indication extrapolation, the 'switchability' and relative immunogenicity of biosimilars, and their reference drugs | It is possible to switch from reference infliximab to the biosimilar, it remains to be seen whether this is the case in 'real life' clinical practice | No | No-but |
| McKeage et al. [69] | Inflammatory diseases | Infliximab and biosimilar | Review the results of the comparability exercise that was required to demonstrate the biosimilarity of CT-P13 to reference infliximab, focusing on the clinical evaluation program | Preliminary data from trial extensions demonstrated that in patients who switched from reference infliximab to CT-P13, efficacy was sustained and similar to those who were maintained on CT-P13 | No | No |
| Papamichael et al. [6] | IBD | Infliximab and biosimilar | Review the literature on anti-TNF biosimilars (pharmacokinetics, pharmacodynamic properties, and comparative effectiveness in IBD) | The risks of safety and reduced efficacy of alternating and switching are no greater than with the use of the reference product without alternating or switching | No | No |

IBD: inflammatory bowel disease; TNF: tumor necrosis factor.
### Table 4. Empirical evidence (original clinical trials) identified by the review.

| Paper ID         | Indication          | Substance                        | No. of switcher subjects | Intervention                                      | Follow-up | Negative clinical outcomes on patient-level (reduced efficacy or loss of effect, discontinuation, adverse events, immunogenicity, etc.) | Conclusion (no increased immunogenicity, no increased adverse events, no lack of efficacy) | Discourage switch? | Discourage substitution? |
|------------------|---------------------|----------------------------------|--------------------------|---------------------------------------------------|-----------|---------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|---------------------|-------------------------|
| Flodmark et al.  | Human growth hormone treatment | Somatropin | 98 | Switch from original rhGHs to biosimilar | 12 months | Nineteen patients experienced adverse events. Eighteen patients experienced pain at injection site (6 switched back, 12 continued biosimilar). One patient experienced pitting edema | No increased risk of immunogenicity and/or adverse events. Equal efficacy | No | Not mentioned |
| Harzallah et al. | CKD, anemia         | Epoetin alpha                    | 53 | Switch from original human recombinant erythropoietin to a biosimilar | 7 months | Five patients discontinued (2 for abdominal pain, 3 withdrew consent) | Overall, no increased risk of immunogenicity and/or adverse events. Equal efficacy | No | Not mentioned |
| Jung et al.      | IBD                 | Infliximab                       | UC: 9, CD: 27            | Switch from original infliximab to biosimilar    | 54 weeks | CD: 2 discontinuations due to lack of efficacy. No adverse events. UC: 3 discontinuations (1 lack of efficacy, 1 switch back for personal reasons, 1 adverse event). Six patients experienced an adverse event (skin rash, infusion reaction, leukopenia, and B-viral hepatitis reactivation), and 1 patient who switched from infliximab to CT-P13 discontinued CT-P13 because of both skin rash and arthralgia. One anti-TNF-naïve UC patient experienced scaling of the palm but could maintain CT-P13 therapy because scaling of the palm cleared up of its own accord | One adverse event took place after switching. Equal efficacy | No | No (CT-P13 seems to be interchangeable with originator) |
| Kang et al.      | IBD                 | Infliximab                       | UC: 5, CD: 4             | Switch from original infliximab to biosimilar   | 42.5 weeks | CD: 1 patient had loss of efficacy. UC: 1 patient experienced arthralgia and discontinued the treatment | Overall, no increased risk of immunogenicity or adverse events. Equal efficacy | No | Not mentioned |
| Lonneman and Wrenger | CKD, anemia         | Epoetin alpha and epoetin zeta  | 18 | Switch from darbepoetin alpha to epoetin zeta  | 6 months | No adverse events or loss of efficacy | Overall, no increased risk of immunogenicity or adverse events. Equal efficacy | No | Not mentioned |
| Lonneman and Wrenger | CKD, anemia         | Epoetin alpha and epoetin zeta  | 33 | Switch from darbepoetin alpha to epoetin zeta  | Up to 30 months | No adverse events or loss of efficacy | Overall, no increased risk of immunogenicity or adverse events. Equal efficacy | Not mentioned | Not mentioned |
| Nikizhoorou et al. | RA                  | Infliximab                       | 39 | Switch from original infliximab to biosimilar | 11 months | Eleven patients discontinued (6 for personal reasons, 1 reactivation of tuberculosis) | Overall, no increased risk of immunogenicity or adverse events. Equal efficacy | No | Not mentioned |
| Park et al.      | IBD                 | Infliximab                       | 60 | Switch from original infliximab to biosimilar | 30 weeks | Six treatment-related adverse events occurred in the switch group (1 anaphylactic reaction, 1 lung abscess, 3 infused related reactions), vs. 16 treatment-related adverse events in the normal group | Overall, no increased risk of immunogenicity or adverse events. Equal efficacy | No | Not mentioned |
| Paper ID | Indication | Substance | No. of switcher subjects | Intervention | Follow-up | Negative clinical outcomes on patient-level (reduced efficacy or loss of effect, discontinuation, adverse events, immunogenicity, etc.) | Conclusion (no increased immunogenicity, no increased adverse events, no lack of efficacy) | Discourage switch? | Discourage substitution? (yes, no, no-but) |
|----------|------------|-----------|------------------------|-------------|----------|--------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-----------------|-----------------------------------------|
| Park et al. [78] | Ankylosing spondylitis | Infliximab | 86 | Switch from original infliximab to biosimilar | 54 weeks | Nine switchers discontinued (4 adverse events, 1 withdrew consent, 1 lost to follow-up, 1 investigator’s decision). 7 maintenance patients discontinued (3 adverse events, 2 withdrew consent, 2 lost to follow-up). No difference in antidrug-antibodies. The proportion of patients who experienced at least one TEAE was 48.9% (n = 44 of 90) in the maintenance group and 71.4% (n = 60 of 84) in the switch group during the extension study. | Overall, no increased risk of immunogenicity or adverse events. Equal efficacy | No | Not mentioned |
| Sieczkowska et al. [79] | IBD | Infliximab | CD: 32, UC: 7 | Switch from original infliximab to biosimilar | 8 months | One patient experienced adverse events (abdominal ache and depression). Two patients required shortened infusion intervals. 12 patients discontinued after follow-up (3 patients in remission were referred to an adult center, 2 lost therapeutic response, 1 had an allergic reaction during infliximab infusion, 1 was switched to adalimumab due to dermatitis, and 5 finished therapy in remission due to financial constraints. | Overall, no increased risk of immunogenicity and/or adverse events. Equal efficacy | No | Not mentioned |
| Wiecek et al. [80] | CKD, anemia | Epoetin alfa and epoetin zeta | 481 (in 4 switch groups) | Switch from eptokin alfa to epoetin zeta, or vice versa | 24 and 56 weeks | Incidence and nature of serious AEs were similar among all subgroups and appeared to be unaffected by the switch in study medication. | Overall, no increased risk of immunogenicity or adverse events. Equal efficacy | No | No data suggest interchangeability between epoetin alfa and zeta |
| Yoo et al. [81] | RA | Infliximab | 144 | Switch from original infliximab to biosimilar | 50 weeks | Sixteen switchers discontinued (8 adverse events, 5 withdrew consent, 2 lost to follow-up, 1 lack of efficacy), 25 maintenance patients discontinued (16 adverse events, 4 withdrew consent, 2 lost to follow-up, 1 lack of efficacy, 1 death, 1 investigator’s decision). No difference in antidrug-antibodies. The proportion of patients who experienced at least one TEAE was 53.5% (n = 85 of 159) in the maintenance group and 53.8% (n = 77 of 143) in the switch group during the extension study. | Overall, no increased risk of immunogenicity or adverse events. Equal efficacy | No | Not mentioned |

rhGHs: recombinant human growth hormones; IBD: inflammatory bowel disease; TNF: tumor necrosis factor; RA: rheumatoid arthritis; CKD: chronic kidney disease; UC: ulcerative colitis; CD: Crohn’s diseases; TEAE: treatment emergent adverse event.
seems to overrule the unsubstantiated risk stated by nonempirical papers.

Studies conducted in a real-life setting included more patients but generally made similar conclusions. For instance, the study by Loiacono et al. which was an Italian drug utilization study on epoetins based on the hospital records of epoetin users [58] or the PASCORI study by Dellanna et al. [82] that was conducted on renal anemia patients both suggested that switching between different original and biosimilar epoetins was already in clinical practice, without reporting any increase in negative consequences.

The overall conclusion of the empirical evidence was in line with the conclusion of other systematic reviews identified by this study. Considering the limitations of currently available empirical studies in terms of the limited number of patients who switched to biosimilars, study design, and short follow-up, additional well-designed clinical studies would be needed to gain more insight into this issue [37], especially for larger molecule weight MaBs.

4. Additional evidence after finalizing the systematic literature review

After finalizing our systematic literature review, some valuable additions have been published to extend current knowledge on switching to biosimilars. The NORSWITCH study aimed to assess the safety and efficacy of switching from original infliximab to its biosimilar treatment in patients with rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, ulcerative colitis, Crohn’s disease, and chronic plaque psoriasis [37,83]. This study included data on 482 patients of both genders, which outnumbered the sample sizes of the 2 most comprehensive single switch transition studies currently available on MaBs (the follow-up of the PLANETRA and PLANETAS, see Table 4) [78,81]. The NORSWITCH study is an important addition to the currently available evidence regarding clinical consequences of switching with a significant health policy impact on estimating the cost-saving potential of biosimilars. However, due to limitations in its study design, even data from this study need to be analyzed with caution seeing that its design is similar to other single transition studies discussed above (where patients are switched from an original to a biosimilar drug but not vice versa). Therefore, future trials designed specifically to evaluate multiple switches (where patients undergo a series of switching, back and forth) even between different biosimilars could provide better evidence to simulate real-world scenarios where multiple biosimilars are present on the market [37].

Additional studies on switching were published after our literature search was conducted which include a systematic review on the clinical efficacy, safety and immunogenicity of infliximab therapy [84], a single-arm open-label clinical trial on safety and efficacy of switching to biosimilar infliximab in Japanese patients with rheumatoid arthritis [85], four prospective cohort transition studies with real-world data collection on switching to biosimilar infliximab [86–89], and a randomized, double-blind study (with multiple switching in one pooled arm) on the efficacy, safety, and immunogenicity of etanercept biosimilar compared to the originator product in patients with chronic plaque-type psoriasis [90]. Neither did these studies find any additional risk in terms of efficacy, safety, and immunogenicity in case of patients who switched from the originator biologics to biosimilar alternatives. Their findings are therefore in line with the results of this systematic review, while the real-world evidence published after finalizing our search strategy can be considered a valuable addition to clinical trials.

5. Review limitations

The conclusions of our systematic literature review cannot be fully generalized for several reasons. Direct links between switching and subsequent negative outcomes could not be reliably established due to the limited availability of information in publications and in some cases owing to the single arm design of the empirical studies. Also, no formal quality assessment of the identified publications was performed in this systematic literature review, because of the significant heterogeneity in the types of studies included, ranging from expert opinions to systematic literature reviews or clinical trials.

6. Conclusion

The expiring patent protection of many originator biologic medicines in the upcoming years is a reason why gathering evidence on the clinical consequences of switching to biosimilars is of utmost importance. The implied risk of negative clinical consequences of switching from an originator biologic to a biosimilar is not substantiated by convincing clinical evidence; we found that the majority of nonempirical papers mentioned a risk of switching to biosimilars without backing up such statements with solid clinical evidence, and therefore, these risks were classified as hypothetical. On the other hand, the magnitude of the identified empirical evidence is modest, but straightforward.

Neither the included empirical evidence from original studies showed an additional risk or negative clinical outcomes in patients switching to biosimilars nor did the systematic literature reviews. Although the empirical evidence only stems from relatively small-scale controlled and real-life studies, mainly containing infliximab as an active compound, the prevention of switching patients on biologic medicine to biosimilars due to a hypothetical risk seems to be disproportional compared to the potential societal benefits, especially in countries with more limited healthcare resources. It may even have a larger negative effect in the long term on the sustainability of affordable health-care in the future, assuming that an even larger share of healthcare resources will be allocated to biologic treatments. Authors of the review suggest a wider utilization of high-quality biosimilars in clinical practice, be it through switching, with appropriate pharmacovigilance and clinical surveillance to improve patient access to modern medicines, especially in lower income countries.
7. Expert opinion

According to the general opinion, switching macromolecules might have negative consequences, such as immunogenic reactions or loss of efficacy. Mandatory phase 3 clinical trials for new biosimilars are not adequately powered in many cases to detect the consequences of switching and also have limitations in their study designs to provide robust evidence on switching. Real-world data on the consequences of switching from original biologics to biosimilars can be generated in patient registries or other databases only after switching is generally applied. Especially, for some MAbs with a recent patent expiry, these data are eagerly expected. This is today’s great challenge for biosimilars: policymakers and clinicians seem to be reluctant to switch patients until convincing evidence on efficacy and safety becomes available. Therefore, until the final data are published from some ongoing post-marketing clinical trials and randomized, controlled, multiple switch studies specifically designed to evaluate the safety and efficacy outcomes of switching original MAbs to biosimilars, a systematic review of relevant publications can provide the most comprehensive evidence.

Based on the results of our review, prevention of switching seems to be disproportional compared to the expected societal benefit. The review of a wide spectrum of nonempirical studies indicates that some cases have been cherry-picked (e.g., see the PRCA and the Hemophilia cases) and misused to generate concern against switching patients on originator products to biosimilars. On the other hand, systematic reviews and empirical studies on switching to biosimilars presented in this review do not confirm these hypothetical risks with solid scientific evidence. Therefore, the opinion of the authors of this review is that the fear against switching to biosimilars is overhyped. Still, the theoretical background for the hypothetical risk is well formulated, and therefore, the concept should not be disregarded immediately. Authors of this paper argue that while hypothetical risk should not restrict switching patients under medical supervision, it can form the theoretical backbone for a well-established pharmacovigilance system for biologic medicines. Therefore, the need for surveillance is still in place, as evidence in terms of large studies investigating the consequences of switching to biosimilars remains limited for now and focuses only on the lessons learned from the use of first generation biosimilars and recently published studies on infliximab as the only MAb available with biosimilar alternatives.

Extrapolation between different biologics and therapeutic areas should be done with caution, therefore, further single switch crossover clinical trials and observational studies are expected in multiple disease areas to estimate the outcomes of single switching. Also, uncertainty related to switching from original biologic therapies to biosimilars is expected to be increasingly managed by risk-sharing agreements between payers and manufacturers, such as money-back guarantees or coverage with evidence development. Such schemes could be fueled by data from real-world data sources, including payers’ databases. Along with this, authors expect that switching under medical supervision will be allowed or even encouraged in some jurisdictions to improve the allocative efficiency of scarce resources spent on pharmaceuticals.

Similarly to generic medicines in selected areas, such as products with narrow therapeutic windows, decisions on single switching should be made on a case-by-case basis.

While in many countries even a single switch under medical supervision is of concern, one of the most debated questions will be alternating (switching back and forth) multiple times between selected biosimilars, even by pharmacy-level substitution. However, this should be preceded by even more experience with single switching under medical supervision beforehand. Seeing that repeated switching may increase the likelihood of antidrug antibodies [37, 91], well-designed multiple switch studies are needed to demonstrate interchangeability and clinical trial design should be more adjusted to real-life scenarios with multiple biosimilars on the market. Study design has an influence on the feasibility of detecting potential negative consequences of switching. In the case of a single-switch randomized controlled study, which is planned to detect a 20% increase of a negative event that occurs in the reference group with 1/100 frequency, the necessary sample size should be more than 80,000 with 5% type I error and 80% power. The limited feasibility of such randomized trials calls for post-authorization safety studies with a case-control design. In this case, if in a certain indication 10% of patients switched to a biosimilar treatment, the necessary sample size to detect a similar effect would be only around 10,000. In the case of multiple switches, the probability of negative events can be higher, hence even less patients may be needed. In real-world databases, such sample sizes seem to be realistic even for rare events. The authors believe that the availability of such data must precede the active promotion of substituting biologics at the pharmacy level. Even if the results of such future studies are encouraging, in similar fashion to small molecule follow-on products, multiple criteria (such as maintaining drug quality, supply reliability, or ensuring safety), not only price erosion, should qualify the off-patent biologic drug policy as successful.

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### Appendix 1: Literature review strategy

| Keywords                                                                 | Hits |
|------------------------------------------------------------------------|------|
| (“biosimilar”[Title/Abstract] OR “biological therapy”[Title/Abstract] OR “biological drug”[Title/Abstract] OR “biological medicine”[Title/Abstract] OR “biologic drug”[Title/Abstract] OR “biologic medicine”[Title/Abstract] OR “biologic product”[Title/Abstract] OR “biologic therapy”[Title/Abstract] OR “follow on biologic”[Title/Abstract] OR “biogenetic”[Title/Abstract] OR “biobetter”[Title/Abstract] OR “biodrug”[Title/Abstract] OR “biopharmaceutical”[Title/Abstract]) | 8347 |
| (therapy switch* OR therapy chang* OR therapy interchange* OR therapy substitute* OR therapy exchange* OR therapy shift* OR drug switch* OR drug chang* OR drug interchange* OR drug substitut* OR drug exchang* OR drug shift* OR medicine switch* OR medicine chang* OR medicine interchange* OR medicine substitute* OR medicine exchange* OR medicine shift*) | 137 642 |
| (efficacy OR effectiveness OR efficiency OR consequence OR “Quality of life” OR QoL OR survival OR safety OR adverse effect OR side effect OR adverse event OR adverse reaction OR health outcome OR “patient reported outcome” OR adverse outcome OR quality loss OR immunogen* OR mortality OR life years OR burden OR “quality adjusted life years” OR disability OR cost OR budget OR financial consequence OR financial OR monetary OR economic OR price OR expenditure OR hospitalisation OR productivity OR resource OR access* OR afford* OR consum* OR equity OR morbidity OR discontinue* OR remiss* OR progress* OR risk) | 7 868 |

#1 AND #2 AND #3

Due date: 13th May 2016