

Systematic Review

Safety of Switching from a Reference Biologic to Its Biosimilar: A Systematic Review and Meta-Analysis

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Abstract: Background: Biosimilars are designed to closely resemble their reference biologics in terms of quality, safety, and efficacy, with only minor variations in clinically inactive components and manufacturing methods. Evaluating the safety of switching between these products is critical for healthcare providers and patients. Concerns may arise when transitioning patients from a reference biologic to a biosimilar or between different biosimilars.

Objective: This systematic review and meta-analysis aims to evaluate the frequency of adverse events associated with switching from a reference biologic to its biosimilar, using data derived from randomized controlled trials (RCTs). **Methods:** A comprehensive search was conducted in MEDLINE and Cochrane Central databases from their inception to December 2024. Studies included RCTs that reported adverse reactions related to switching between reference-to-reference biologics and reference-to-biosimilar biologics. Record screening, data extraction, and risk of bias assessment were performed independently by two reviewers. Random effects models were applied to pool crude outcome data. **Results:** The search identified 668 abstracts, with an additional 14 studies found through hand-searching review articles. Of these, 12 trials involving 1326 participants in the reference–reference group and 1176 participants in the reference–biosimilar group met the inclusion criteria. The frequency of adverse events, serious adverse events, and treatment-related adverse events did not differ significantly between the reference–reference and reference–biosimilar groups: relative risk (RR) = 0.96 (95% confidence interval [CI], 0.85–1.08), RR = 1.06 (95% CI, 0.68–1.65), and RR = 1.03 (95% CI, 0.66–1.59), respectively. Heterogeneity was generally low to moderate across outcomes, and subgroup analyses based on disease type and reference product showed no differences. **Conclusions:** Switching between reference biologics and biosimilars demonstrates a comparable safety profile, suggesting that both options are viable. However, the findings are limited by the small number of trials and the scope of patient populations and products studied. PROSPERO registration number: CRD42021267205.

Keywords: reference; biosimilar; biologics; interchangeability; switching; safety; adverse events



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1. Introduction

Biosimilars are defined as biological products that are highly similar to a licensed reference product in terms of quality, safety, and efficacy profile, with minor differences in clinically inactive components and manufacturing processes [1,2]. Those products undergo a restricted regulatory standard pathway designed to ensure compliance with stringent standards of similarity to their reference biologics. Taking into consideration that biosimilars will significantly enhance the healthcare challenges of affordability and accessibility as their access to the market not only provides a competitive clinical benefit with lower cost but also works to eliminate the financial burden on the healthcare system [3]. This enhancement in access is expected to address the accessibility challenges faced by patients and reimbursement bodies.

Biosimilars are developed utilizing distinct cell lines and manufacturing processes, which means they may not be identical to their reference products but are highly similar in terms of quality, safety, and efficacy [4]. Acceptable minor differences, such as variations in three-dimensional structures, glycosylation profiles, or acid-base variants, are inherent to their production and are carefully evaluated for their potential impact on immunogenicity and side effects [5,6]. Regulatory authorities have implemented stringent testing requirements and rigorous evaluation processes to address these concerns and ensure biosimilarity [1,2]. These requirements involve inclusive comparative analytical studies, preclinical studies, pharmacokinetic and pharmacodynamic evaluations, and comparative clinical efficacy studies, all designed to confirm that biosimilars maintain comparable efficacy, safety, and immunogenicity profiles to their reference products [7].

Unlike generic drugs, which are chemically identical to their reference products, the principle of switching between reference biologics and biosimilars presents unique considerations due to the inherent complexity of biologics. Biosimilars are large, protein-based molecules that are produced using living cells, and as a result, they exhibit natural variability in their structure, even when produced under stringent manufacturing standards [8,9]. These subtle differences in molecular structure can influence the immunogenic potential of biosimilars, potentially leading to adverse events such as hypersensitivity reactions, diminished therapeutic efficacy, or the development of neutralizing antibodies that counteract the intended biological activity [10]. Consequently, these factors necessitate careful evaluation of switching practices, with attention to both clinical outcomes and patient safety.

Despite rigorous regulatory processes, switching from a reference biologic to its biosimilar may remain a concern among healthcare providers, not only due to knowledge gaps but also because of economic interests and market dynamics. These concerns are often driven by a limited understanding of biosimilars as a technology [11,12]. For example, a clinician may be concerned that switching from the reference biologic to the biosimilar may invoke immune response, resulting in adverse events or loss of efficacy [13]. This stems from the claim that even minor variations between a biosimilar and its reference product could hypothetically lead to unwanted immune responses against the biosimilar molecule. Although most regulators do not accept this claim, it could still be adopted by healthcare providers. As a result, it may become a common practice to prescribe biosimilars primarily for treatment-naïve patients to avoid switching.

Evidence suggests that switching from reference biologics to biosimilars is generally safe, as various studies across diverse therapeutic areas, including rheumatoid arthritis, inflammatory bowel disease, and oncology, have demonstrated comparable safety and efficacy profiles for biosimilars and their reference counterparts [14–16]. A meta-analysis conducted by Cohen et al. [17] further supports this, finding no significant differences in the rates of adverse events or immunogenicity between patients who switched to biosimilars and those who remained on reference biologics. However, despite the growing body of

evidence, there remains a gap in research specifically addressing the safety and efficacy of switching through meta-analyses that focus on randomized controlled trials (RCTs) explicitly designed to evaluate switching.

We propose that healthcare providers' hesitance toward the widespread adoption of biosimilar switching may be influenced by the limited availability of systematic reviews and meta-analyses specifically addressing the outcomes of switching between biologics and biosimilars. The absence of such comprehensive analyses underscores the need for a rigorous assessment of current evidence using high-quality data from randomized RCTs. Addressing these gaps in synthesized evidence is essential to building confidence and promoting broader acceptance of biosimilars in clinical practice. Therefore, in this systematic review and meta-analysis, we aim to evaluate whether switching from a reference product to its biosimilar impacts adverse event rates, using data derived from RCTs.

2. Method

2.1. Search Strategy and Study Selection

This systematic review and meta-analysis adhered to the PRISMA guidelines [18] and was registered in PROSPERO 2021 CRD42021267205. We conducted a comprehensive search of MEDLINE and Cochrane CENTRAL from their inception to December 2024. The search strategy included terms for biosimilars, their known synonyms, and reference biologics. Additional keywords targeted switching-related concepts such as substitution, interchangeability, and their variations. Finally, we included terms related to adverse events, such as side effects and adverse reactions. A detailed list of the keywords used in the search strategy is available in Supplementary Table S1.

Recognizing that the terminology surrounding switching is not standardized across studies, we also reviewed and summarized commonly used terms such as “switch”, “interchangeability”, “substitution”, and “automatic substitution”, which are frequently encountered in biologics research. These variations in terminology reflect the diverse ways in which switching is defined and studied in clinical and regulatory contexts, highlighting the importance of a precise and inclusive search strategy to ensure no relevant studies were missed. The summary of these terms and their nuanced definitions can be found in Table 1, providing clarity and context for their application in the reviewed literature. By adopting this comprehensive and systematic approach, we ensured the inclusion of a broad and representative sample of studies relevant to our research question.

Eligible studies included randomized trials with a switching design comparing biosimilars to their reference biologic, Table S2. The trials must have two arms to be included. One is where patients received the reference biologic and, after randomization, continued to receive the reference biologic (reference-to-reference group). In contrast, the other arm included patients switched to a biosimilar after randomization (reference-to-biosimilar group). The methodology used in each included trial can be found in Supplementary Figure S1. Trials must at least report on one safety outcome to be included in the review. A detailed list of the outcomes and their definitions is available in Supplementary Table S3.

We excluded non-English, non-human, and observational studies. We also excluded editorial notes, short surveys, and studies providing real-world evidence (RWE). Additionally, we excluded studies presenting data on switching only between different classes of originator biologics without a biosimilar arm. Furthermore, we excluded pharmacokinetics and pharmacodynamics crossover studies in healthy volunteers. When safety outcomes were unreported, study authors were contacted for clarification; studies were excluded if no response was received. Two investigators (S.A. and S.S.) independently screened all citations by title and abstract using EndNote X9, with disagreements resolved by a third investigator (A.T.). Full texts of potential eligible studies were retrieved and screened

independently by two investigators (S.A. and S.S.). A third investigator (A.T.) resolved any disagreements. The disagreements mainly stemmed from study objectives or the absence of a reference biologic comparator. Finally, bibliographies of included studies were manually reviewed by S.A. and S.S. to identify additional eligible articles.

Table 1. Definitions and distinctions between key terms in biosimilar utilization.

Term	Definition	Explanation	References
Switching	Changing a patient’s treatment from one product to another (e.g., reference biologic to biosimilar) during clinical care	Switching decisions are typically made by the prescribing healthcare provider with patient consultation	European Medicines Agency (EMA) [19]
Interchangeability	The property of a biosimilar allowing it to be substituted for the reference product without the intervention of the prescriber	In the US, interchangeability requires additional evidence demonstrating that switching produces no negative effects	U.S. Food and Drug Administration (FDA) [20]
Substitution	Replacing a prescribed product with an equivalent or interchangeable product at the pharmacy level	This practice depends on national or regional regulations and typically requires interchangeability status	American Pharmacists Association [21]
Automatic Substitution	A substitution carried out at the pharmacy level without requiring approval from the prescribing healthcare provider	Common in systems where interchangeable biosimilars are authorized; regulations vary across countries	World Health Organization (WHO) [22]

2.2. Data Extraction and Quality Assessment

Two independent reviewers (S.A. and S.S.) evaluated the quality of the included randomized studies using The Cochrane Risk of Bias Tool. Quality assessment considered several domains: random sequence generation (selection bias), allocation concealment (selection bias), participant blinding (performance bias), blinding of outcome assessors (detection bias), completeness of outcome data (attrition bias), and selective outcome reporting (reporting bias). Trials were categorized as high quality if the domains of randomization, allocation concealment, and blinding were all rated as low risk of bias. Studies with unclear risk in any of these domains were classified as intermediate quality, while those with high risk in any domain were categorized as low quality.

2.3. Data Synthesis

In this systematic review and meta-analysis, the primary outcomes evaluated were the number of patients with at least one adverse event, serious adverse events, and treatment-related adverse events associated with switching between reference biologics and their biosimilars. Total adverse events encompassed all reported adverse reactions irrespective of severity, while serious adverse events were defined as those leading to significant clinical consequences such as hospitalization or disability. Emergent adverse events were considered equivalent to total adverse events if the latter were reported solely under this category.

Studies that reported on at least one of the study outcomes were included in the meta-analysis. Study outcomes were analyzed using DerSimonian and Laird random-effects models [23] by using RStudio Version 2022.12.0. Data were pooled using relative risks

(RRs), and heterogeneity was assessed with the chi-square test and I^2 statistic. Substantial heterogeneity ($I^2 > 50\%$) was planned to be explored through subgroup analysis by disease state and reference product type. Sensitivity analysis was conducted for all outcomes using the leave-one-out analysis. Also, sensitivity analyses were performed by excluding low-quality studies.

3. Results

3.1. Study Characteristics and Quality Assessment

A comprehensive search of the databases identified a total of 668 abstracts, with an additional 14 studies found through hand-searching relevant review articles. After the initial screening process, 29 studies were deemed eligible for full-text screening, of which 12 studies met the inclusion criteria [15,16,24–33] (Figure 1). These studies encompassed a combined total of 2502 participants, including 1326 in the reference–reference group and 1176 in the reference–biosimilar group. All the included studies provided data on adverse drug reactions arising from switching or interchanging between reference-to-reference biologics and reference-to-biosimilar biologics. The PRISMA checklist for this study can be found in Supplementary Material Table S4.

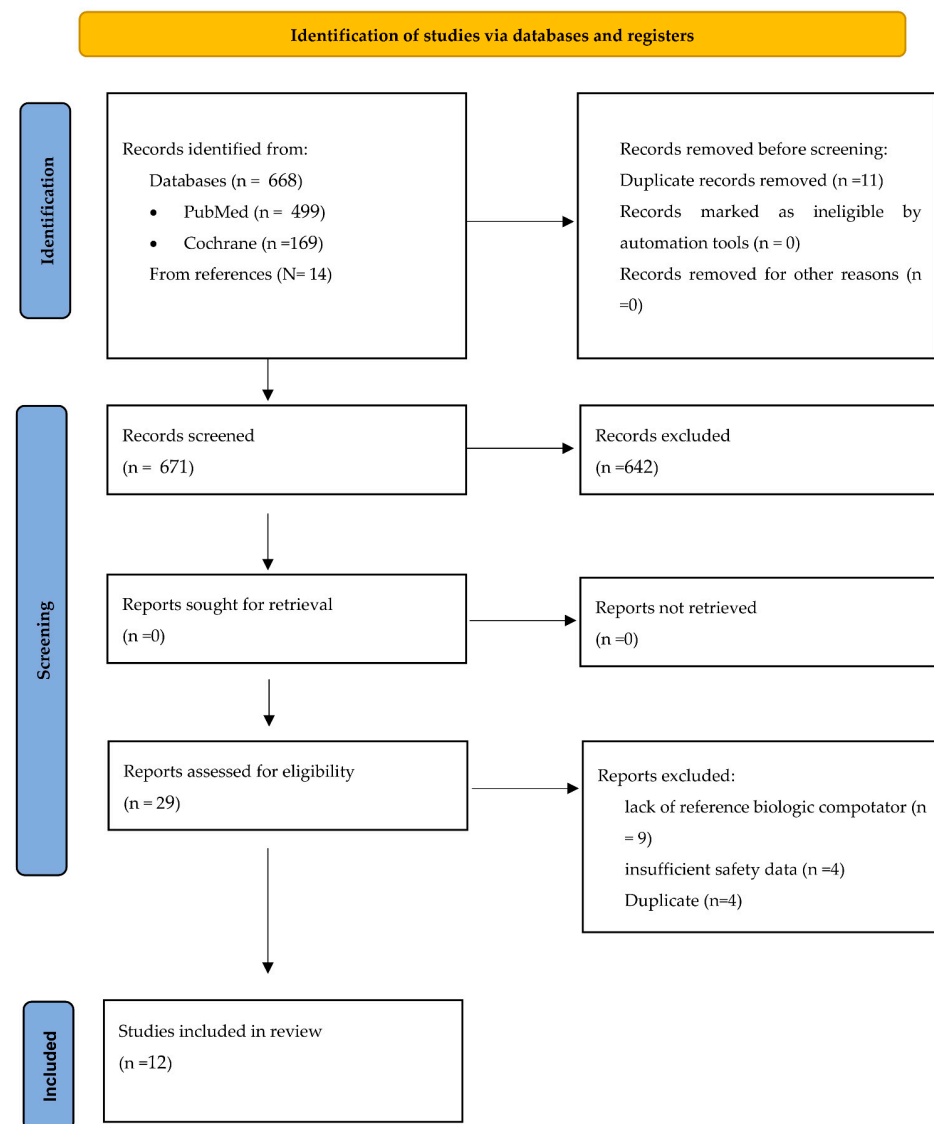


Figure 1. Study selection.

Of the 12 studies, 3 investigated adalimumab biosimilars, 3 focused on rituximab biosimilars, and 3 evaluated infliximab biosimilars, and one study each assessing natalizumab, ustekinumab and trastuzumab biosimilars. The sample sizes varied significantly, with some studies including 171 participants in each group, while others had fewer than 60 participants in one or both arms. Despite these differences, all studies consistently reported on adverse drug reactions related to switching between reference and biosimilar biologics (Table 2).

Table 2. Characteristics of included studies.

Authors	Treated Disease	Sample Size (Reference–Reference)	Sample Size (Reference–Biosimilar)	Reference Product	Biosimilar Product	Risk of Bias
Alten et al. [24]	Rheumatoid arthritis	143	143	Infliximab	GP1111	Intermediate
Blauvelt et al. [15]	Psoriasis	127	63	Adalimumab	GP2017	Low quality
Burmester et al. [16]	Rheumatoid arthritis	104	103	Rituximab EU	ABP 798	Intermediate
Cohen et al. [25]	Rheumatoid arthritis	148	146	Adalimumab	BI 695501	Low quality
Feldman et al. [26]	Psoriasis	122	122	Ustekinumab	SB17	High quality
Fleischmann et al. [27]	Rheumatoid arthritis	135	134	Adalimumab	PF-06410293	Intermediate
Hemmer et al. [28]	Multiple sclerosis	103	30	Natalizumab	PB006	High quality
Minckwitz et al. [29]	HER2-positive early breast cancer	171	171	Trastuzumab	ABP 980	High quality
Shim et al. [30]	Rheumatoid arthritis	64	62	Rituximab US	CT-P10	Intermediate
Smolen et al. [31]	Rheumatoid arthritis	101	94	Infliximab	SB2	Low quality
Tony et al. [32]	Rheumatoid arthritis	54	53	Rituximab	GP2013	Intermediate
Ye et al. [33]	Crohn’s disease	54	55	Infliximab	CT-P13	High quality

Regarding study quality, most studies were rated as either high or intermediate quality based on the Cochrane risk of bias tool, with only three studies classified as low quality. High-quality studies often involved larger sample sizes and robust methodologies, whereas low-quality studies were characterized by smaller sample sizes or potential methodological limitations (Table 2).

The studies demonstrated variability in the diseases treated and biosimilars tested, highlighting a broad spectrum of evidence. This diversity underscores the robustness of the findings while also emphasizing the need for further research to address gaps in specific patient populations and products (Table 2).

3.2. Total Adverse Events

All the included studies reported on the outcome of patients with at least one adverse event. The number of total adverse events was not significantly different between the reference–reference, and reference–biosimilar arms, with a relative risk (RR) = 0.96 (95% confidence interval [CI], 0.85–1.08). Heterogeneity was reported as $I^2 = 19\%$ ($p = 0.248$) (Figure 2). In subgroup analysis, the results did not differ using the disease type or reference product (Figures S2 and S3). Results did not significantly differ using sensitivity analyses.

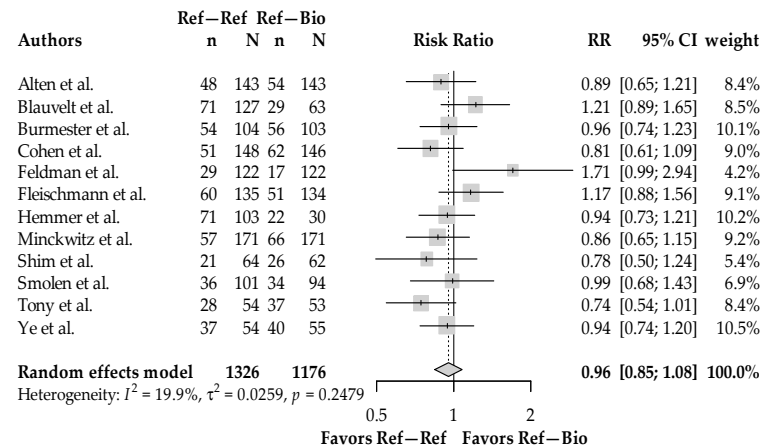


Figure 2. Total adverse events in the reference–reference arm versus the reference–biosimilar arm. Meta-analysis of the total adverse events; CI—confidence interval; RR—relative risk; Ref—reference product; Bio—biosimilar product [15,16,24–33].

3.3. Serious Adverse Events

Eleven out of the included studies reported the number of patients with at least one serious adverse event, and one study reported severe adverse events, which were all combined in the analysis of serious adverse events. The number of patients with at least one serious adverse event did not differ significantly between the reference–reference and reference–biosimilar arms: RR = 1.06 (95% CI, 0.68–1.65). Heterogeneity was reported as $I^2 = 0\%$ ($p = 0.676$), as shown in Figure 3. Results did not differ using subgroup analysis (Figures S4 and S5). Results did not significantly differ using sensitivity analyses.

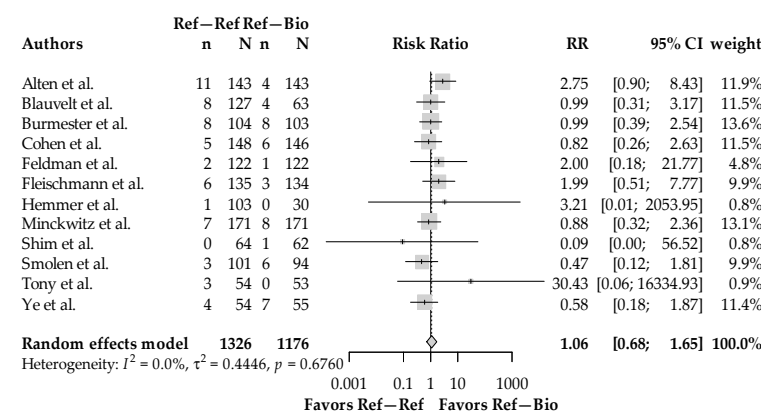


Figure 3. Total number of serious adverse events in the reference–reference arm versus the reference–biosimilar arm. Meta-analysis of the serious adverse events; CI—confidence interval; RR—relative risk; Ref—reference product; Bio—biosimilar product [15,16,24–33].

3.4. Treatment-Related Adverse Events

Only nine studies reported the number of patients with at least one treatment-related adverse event, and the results did not differ significantly between the groups, RR = 1.03

(95% CI, 0.66–1.59), as shown in Figure 4. Heterogeneity was reported as $I^2 = 0\%$ ($p = 0.560$). Results remained consistent using sensitivity analyses.

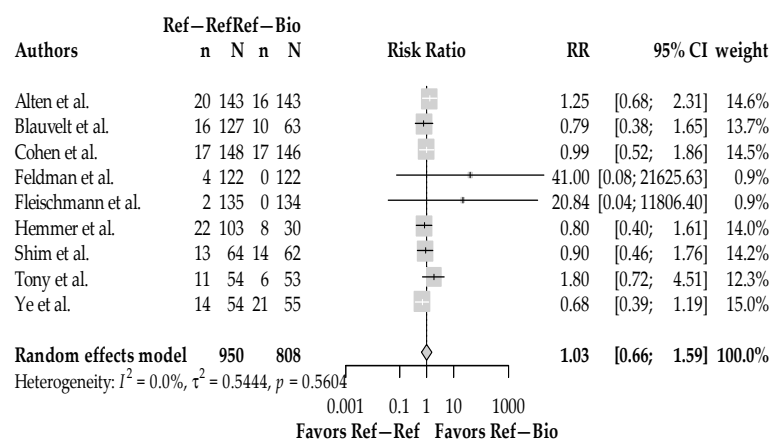


Figure 4. Total number of treatment-related adverse events in the reference–reference arm versus the reference–biosimilar arm. Meta-analysis of the treatment-related adverse events; CI—confidence interval; RR—relative risk; Ref—reference product; Bio—biosimilar product [15,24–28,30,32,33].

4. Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis specifically aimed at assessing the safety of switching from a reference product to its biosimilar across various biological agents and a wide range of medical conditions, relying exclusively on evidence from RCTs. Previous studies have often focused on individual biologics or specific therapeutic areas, leaving a gap in the comprehensive assessment of safety profiles when switching across different biologics and patient populations. This review provides a broad perspective on the potential risks associated with switching, thereby addressing a critical concern for healthcare providers, patients, and regulators.

We conducted this systematic review and meta-analysis to determine whether the safety of treatment differs between patients who continue on their biological reference product and those who transition from the reference biologic to its biosimilar. Our aim was to provide robust, data-driven insights to guide clinical decision-making and improve confidence in the use of biosimilars. The analysis included 12 RCTs, which collectively evaluated the safety of switching in 2502 participants across a variety of diseases and biologics.

The analysis revealed no significant differences in the number of adverse events—whether total, treatment-related, or serious—between patients who continued using their biological reference product and those who switched to a biosimilar. This consistency was maintained across all examined categories, including specific biologics (Infliximab, Adalimumab, Rituximab, and Trastuzumab) and disease conditions, whether rheumatoid arthritis or others. These findings demonstrate that switching from a reference biologic to its biosimilar does not compromise safety, regardless of the product or underlying disease.

Our findings are further supported by prior research, including a systematic review and meta-analysis of observational studies that evaluated switching from Infliximab (a reference biologic) to CT-P13 (a biosimilar) in patients with inflammatory bowel disease (IBD). That study similarly reported no difference in the overall rate of adverse events between groups [30]. However, it is important to note that unlike our study, which analyzed randomized controlled trials across multiple biologics and disease conditions, this prior meta-analysis focused specifically on Infliximab and its biosimilar in the context of IBD [34]. This highlights the scope of our analysis, which provides evidence across a wider range of biologics and medical conditions, further affirming the general safety of switching from reference biologics to biosimilars.

Results from other systematic reviews and meta-analyses align with our findings, further supporting the safety of switching between reference biologics and biosimilars [17,35]. For instance, a review by Cohen et al. demonstrated a conclusion that switching between biologics and biosimilars did not lead to any significant increase in treatment-related adverse events [17]. Correspondingly, another systematic review included data from observational studies, retrospective analyses, and RCTs to evaluate the safety and efficacy of switching between reference infliximab and its biosimilar [35]. This review found that the rates of adverse were similar for patients who remained on the reference infliximab and those who were switched to the biosimilar [35].

However, while these findings are consistent with ours, the majority of the evidence included in these reviews was from observational studies. A significant number of these studies lacked a comparator arm where patients remained on the reference infliximab, which limited the ability to directly assess the impact of switching. Furthermore, many of the larger, controlled studies included in the reviews were not randomized at the switching stage, introducing potential biases in the assessment of safety outcomes [17,35]. Regardless of these limitations, the consistency of findings across systematic reviews, including ours, reinforces the conclusion that switching between reference biologics and biosimilars is not associated with increased safety risks.

Several barriers might contribute to the difficulty in switching from reference biologics to biosimilars. A key factor is the reluctance of healthcare professionals, which may be influenced by regulatory complexities, clinical data interpretation, and economic considerations [11,12]. Furthermore, misconceptions regarding the comparability of biosimilars to reference products may also impact clinicians' decision-making [12]. Concerns about safety, particularly related to immunogenicity and potential adverse effects following switching, remain a key barrier, even though current evidence indicates no major differences in safety or efficacy between biosimilars and their reference biologics [13,36].

Additionally, institutional or policy-related barriers, such as the different guidelines across countries and regions, the lack of automatic substitution policies for biosimilars, limited education programs or initiatives, and reimbursement challenges, can impact biosimilar uptake [37]. Other practical issues, such as differences in administration devices, dosing concentrations, or storage requirements, may also impact the use of biosimilars in clinical practice [38]. To emphasize the utilization of biosimilars, it is essential to establish targeted educational initiatives for healthcare professionals; standardized institutional policies and clear communication of biosimilar safety and efficacy data are essential. These efforts can encourage greater acceptance of utilizing biosimilars.

Our meta-analysis has several notable strengths, including a well-defined search strategy that encounters a comprehensive search across multiple electronic databases to ensure the inclusion of all relevant studies. In preparing this manuscript, we adhered rigorously to the PRISMA checklist, which provides a standardized framework for conducting and reporting systematic reviews. All the steps of the review process were conducted in alignment with the Cochrane Handbook of Systematic Reviews for Interventions, ensuring rigorous methodological standards. Importantly, we improved the validity and reliability of our findings by primarily concentrating on RCTs that assessed the safety and efficacy of switching from reference biologics to their biosimilars.

Regarding the limitations, there are several limitations in our meta-analysis that warrant mention. Firstly, a relatively small number of RCTs met our inclusion criteria, which restricted the scope of our analysis to a limited number of product types and patient populations. Additionally, the included studies provided insufficient information regarding hypersensitivity reactions, which are a critical component of safety evaluations for biologics, as most of the included trials assessed only a single switch between the reference biologic

and its biosimilar, leaving the safety of multiple switches largely unexplored. Moreover, there is a chance of introducing bias in the assessment and reporting of safety outcomes as the majority of the studies were open-label during the switching phase and lack blinding in the clinical trial design.

The absence of detailed stratification of safety outcomes by patient-specific characteristics, such as age, gender, or disease severity, was an additional key drawback. This missing information limited our ability to ascertain whether adverse effects differed among subgroups, which could be crucial for tailoring treatment decisions in clinical practice. Furthermore, the discrepancies in the definitions and reporting of safety outcomes across the studies led to difficulties in conducting detailed subgroup or sensitivity analyses, which limited the overall comprehensiveness of our conclusions.

Despite these limitations, the results of this systematic review and meta-analysis provide data-driven evidence supporting the safety of single switching between a reference biologic and its biosimilar. To improve the quality and applicability of future research in this field, we propose several methodological enhancements for clinical trials investigating biological agents. First, future studies should explore the safety and efficacy of multiple switches between reference biologics and biosimilars to address concerns about long-term safety. Second, randomization during the switching phase should be implemented to minimize bias and strengthen the evidence base. Third, efforts should be made to uphold blinding or allocation concealment after switching to minimize potential reporting bias. Finally, standardizing the definitions and reporting of safety outcomes across studies is essential to facilitate better comparisons. These recommendations aim to address the existing gaps in the literature and guide future research toward producing more robust and generalizable evidence.

5. Conclusions

The findings of this systematic review and meta-analysis suggest that switching between reference biologics and biosimilars is generally safe, with no significant differences in the safety profiles observed when compared to switching between two reference biologics. This indicates that both approaches can be considered acceptable in clinical practice, providing reassurance to healthcare providers and patients regarding the use of biosimilars. However, it is important to acknowledge the limitations of the current evidence. The data available are constrained by the relatively small number of trials that met the inclusion criteria and the limited diversity in the types of patients and biological products studied.

Further research is needed to address these gaps, particularly through larger, well-designed trials that evaluate switching in broader patient populations and across a wider range of biosimilar products. Additionally, ongoing post-marketing surveillance will be essential to assess long-term safety and efficacy, thus fostering confidence in the switching of biosimilars and reference biologics.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/biologics5010006/s1>, Figure S1: Method of study inclusion; Figure S2: Total adverse events in reference-reference arm versus reference-biosimilar arm by patients or by disease (studies on rheumatoid arthritis (RA) patients versus non-RA patients; Figure S3: Total adverse events in reference-reference arm versus reference-biosimilar arm by reference product; Figure S4. Total number of serious adverse events in reference-reference arm versus reference-biosimilar arm by disease; Figure S5. Total number of serious adverse events in reference-reference arm versus reference-biosimilar arm by reference product; Table S1: The list of the keywords used in the search strategy; Table S2: Studies Inclusion/exclusion criteria; Table S3: list of the outcomes and their definition; Table S4: PRISMA 2020 Checklist.

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Conflicts of Interest: The authors declare no conflict of interest.

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