



Review Article

ISSN : 2277-3657
CODEN(USA) : IJPRPM

Interpreting Biosimilar Switching Across Single, Multiple, Biosimilar-to-Biosimilar, and Reverse Treatment Sequences

Carlos Ramirez^{1*}, Elena Torres², Pablo Ortega¹, Sofia Mendes³

¹Department of Biosimilar Switching and Clinical Outcomes, Faculty of Pharmacy, University of Barcelona, Barcelona, Spain.

²Department of Switching Sequences and Safety, Faculty of Pharmaceutical Sciences, University of Lisbon, Lisbon, Portugal.

³Department of Biosimilar Interchangeability, Faculty of Pharmacy, University of Porto, Porto, Portugal.

***Email:** carlos.ramirez@ub.edu

ABSTRACT

Biosimilar switching is often discussed as a single intervention, although reference-to-biosimilar, repeated reference-biosimilar alternation, biosimilar-to-biosimilar switching, and return to a previous product represent different exposure histories. Combining these sequences can make reassuring evidence appear more transferable than the underlying studies permit. To critically synthesize recent clinical and review-level evidence on biosimilar switching and identify which conclusions are directly supported, context dependent, or still unresolved across products, diseases, outcomes, and switching sequences. A structured critical-review approach was used. Review-level syntheses formed the interpretive foundation, and recent randomized, prospective, registry, and real-world studies were examined where they added direct evidence for sequences or outcomes insufficiently represented in earlier reviews. Evidence was organized by product, switching direction and frequency, therapeutic context, outcome domain, follow-up, and study design. The approach was deliberately interpretive rather than exhaustive or meta-analytic. The evidence is most mature for selected anti-tumour necrosis factor agents and for single reference-to-biosimilar transitions. Randomized and prospective studies now provide direct support for several repeated-switch and biosimilar-to-biosimilar sequences, particularly involving adalimumab and infliximab, without consistent deterioration in pharmacokinetics, efficacy, safety, or measured immunogenicity within the evaluated conditions. Confidence is lower for uncommon outcomes, long-latency harms, reverse switching, some biologic classes, and transfer across products or care settings. Persistence and subjective post-switch symptoms are clinically important but cannot be treated as direct measures of molecular comparability. Biosimilar switching evidence is broadly reassuring but not sequence neutral. The most defensible conclusion is conditional: a studied product and exposure sequence may be supported for the outcomes and observation period evaluated, while broader class-wide or sequence-wide claims require explicit qualification.

Keywords: Biosimilars, Switching, Multiple switching, Biosimilar-to-biosimilar switching, Reverse switching, Interchangeability

Received: 22 May 2026; **Revised:** 05 September 2026; **Accepted:** 09 September 2026

INTRODUCTION

Biosimilar use has moved from an early focus on whether a single transition can be undertaken without loss of disease control toward a more complex set of questions about repeated substitutions, changes among biosimilars, return to a reference product, and implementation across different health systems. Systematic reviews generally report no consistent deterioration in efficacy, safety, or immunogenicity after evaluated switches, but their

conclusions arise from heterogeneous products, diseases, sequence definitions, and study designs [1-3]. The central interpretive problem is therefore no longer a binary determination that switching is either safe or unsafe; it is the calibration of each claim to the exposure history and outcomes that were actually studied.

The density of evidence is also uneven. Adalimumab has a broad international switching literature, yet the number of available biosimilars, device differences, treatment indications, and local substitution policies produce diverse clinical contexts [4]. Infliximab is similarly well represented, especially in inflammatory bowel disease, where systematic synthesis is broadly reassuring but still shaped by observational designs, treatment selection, and variable follow-up [5]. Treating these mature anti-tumour necrosis factor evidence bases as proxies for every biologic would conceal important molecule-, disease-, formulation-, and assay-specific uncertainties.

Switching evidence is embedded in a changing regulatory and economic environment. International analyses describe pressure toward greater regulatory convergence, while also documenting continuing jurisdictional variation in approval, interchangeability, and substitution frameworks [6, 7]. Expanded biosimilar availability may improve affordability and access even when a particular local switching sequence has not been tested in a randomized trial [8]. These system-level benefits are important, but they do not answer the same question as product-specific clinical outcomes.

Terminology is especially consequential in the United States, where statutory interchangeability and pharmacy-level substitution are not synonyms for biosimilarity or for a clinician-directed switch. Policy analyses continue to debate how regulatory change might affect access [9], and surveys show incomplete familiarity with interchangeability rules among clinicians and pharmacists [10]. A clinically stable patient after a switch contributes evidence about that treatment transition; the observation does not independently establish analytical comparability, and it should not be used to erase jurisdiction-specific regulatory distinctions.

This critical review addresses that problem through a sequence-sensitive synthesis. Its purpose is to identify where evidence is direct, where transfer is reasonable but qualified, and where uncertainty remains because the product, switching direction, number of transitions, population, outcome, follow-up, or care context differs from the evidence used to support the claim.

Review approach

Design and scope

This article uses a structured critical-review design rather than an umbrella-review design. Review-level syntheses provide the broad evidence map, while selected recent randomized trials, prospective cohorts, registry analyses, and real-world studies supply direct observations for newer switching sequences and outcome domains. The objective is interpretive rather than exhaustive or meta-analytic, and the article therefore does not present a PRISMA flow diagram. PRISMA 2020 is designed for systematic reviews with auditable identification and selection stages [11]; applying that structure to unavailable database-export counts would create false precision. The clinical scope includes single reference-to-biosimilar switching, repeated alternation between a reference product and one biosimilar, biosimilar-to-biosimilar switching, and reverse switching to a previous product. Outcomes include pharmacokinetics where reported, efficacy or effectiveness, safety, immunogenicity, treatment persistence, discontinuation, subjective symptoms, and patient experience. Regulatory, implementation, and economic evidence is included only to clarify how clinical evidence enters practice; it is not treated as proof of product-level clinical equivalence.

Source identification and selection

Sources were identified through structured scholarly web discovery conducted on 31 August 2026. Search concepts combined biosimilar and reference-product terminology with switch, interchangeability, substitution, single switching, multiple switching, repeated switching, reverse switching, and biosimilar-to-biosimilar switching. Outcome concepts included efficacy, effectiveness, safety, immunogenicity, anti-drug antibody, persistence, discontinuation, nocebo, and patient perception. Product and therapeutic-area terms were used to locate evidence on infliximab, adalimumab, etanercept, rituximab, natalizumab, eculizumab, inflammatory bowel disease, rheumatology, dermatology, oncology, and related settings.

Candidate sources were verified against DOI-indexed records, PubMed or PubMed Central where available, publisher pages, and bibliographic metadata. Selection was purposive: sources were retained when they contributed a distinct sequence, product, outcome, methodological issue, or implementation boundary. Journal quartile was not used as a surrogate for evidence quality. The final evidence set contained 38 sources: 11 review-level clinical or product-context sources, 17 primary clinical or real-world studies, and 10 methodological,

regulatory, economic, or implementation sources. These counts describe the composition of the curated evidence set; they are not screening-flow counts and should not be interpreted as evidence of exhaustive coverage.

Critical appraisal and evidence organization

Review-level sources were examined qualitatively for search breadth, eligibility clarity, risk-of-bias handling, duplicate-study overlap, synthesis method, and whether conclusions exceeded the directness of the included evidence. These domains were informed by AMSTAR 2 [12], but no formal AMSTAR 2 overall confidence rating was assigned because the evidence set included both systematic and narrative reviews. This distinction is explicit: narrative reviews contribute contextual interpretation but do not carry the same evidentiary weight as systematic reviews with reproducible methods.

Overlap was handled by identifying recurring product–study families and avoiding the treatment of several reviews of the same underlying trials as independent replication. Methodological guidance for overviews emphasizes that primary-study overlap can inflate apparent evidence volume [13], and empirical research shows that overlap and discordance are frequently underreported [14]. Because complete citation matrices were not recoverable for every review, a corrected covered-area statistic was not calculated. The synthesis therefore relies on qualitative overlap control rather than a numerical overlap estimate.

Evidence was organized across six dimensions: product and formulation; sequence and direction of switching; disease and prior treatment exposure; outcome domain; observation period and sampling strategy; and study design. Certainty was not replaced by an author-generated scoring system. Instead, the review separates methodological credibility from clinical directness and transferability, consistent with contemporary emphasis on study limitations, consistency, precision, directness, and applicability [15]. The resulting categories—directly supported, supported with qualification, and unresolved or indirect—are interpretive labels, not validated grades of evidence.

Figure 1 shows how the evidence types, observed exposure sequences, outcome domains, and transferability checks are kept separate before a claim is classified.

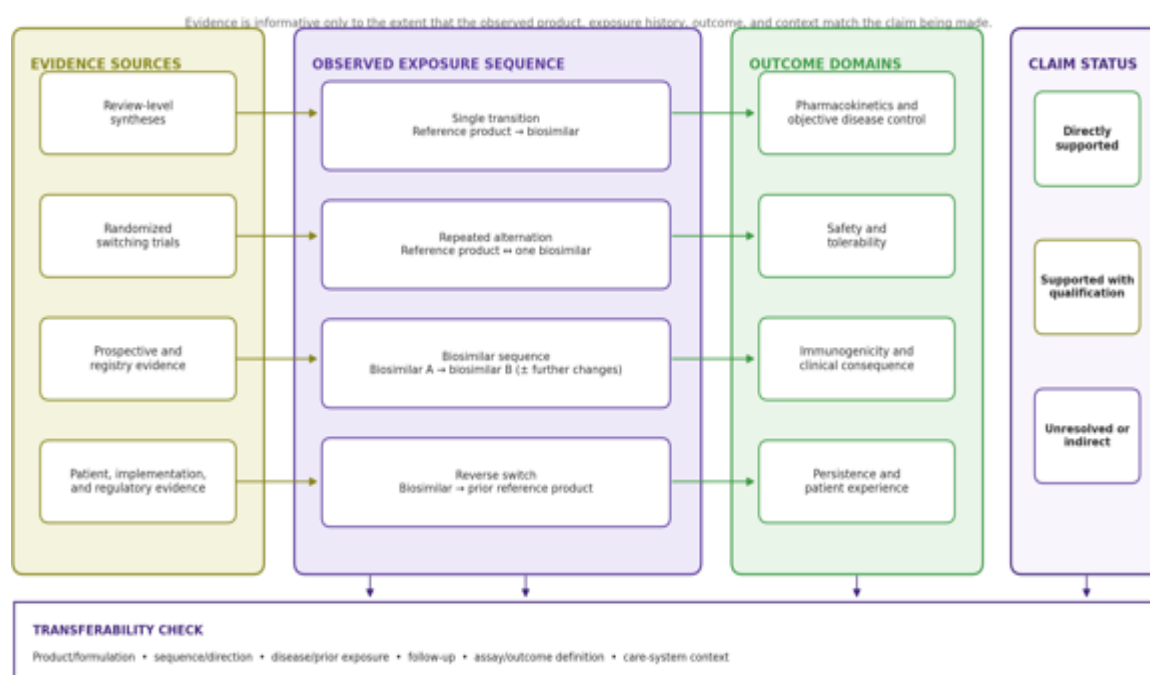


Figure 1. Sequence-sensitive map for interpreting biosimilar switching evidence. The figure separates evidence source, observed exposure history, outcome domain, and transferability before a clinical or regulatory claim is made.

Evidence synthesis

Review-level evidence and its boundaries

The review-level literature is broadly concordant but not interchangeable. A systematic review of adalimumab switching reported generally maintained clinical outcomes across chronic immune-mediated inflammatory diseases while documenting substantial variation in design and switching context [16]. A review of switching

among biosimilars found growing support for biosimilar-to-biosimilar transitions, but also highlighted the limited directness of some product and sequence combinations [17]. In rheumatoid arthritis, a systematic review and network meta-analysis did not identify a clear comparative deterioration across evaluated tumour necrosis factor inhibitor switching strategies, although network assumptions and heterogeneous study designs constrain strong causal conclusions [18].

Patient-perception evidence addresses a different layer. A systematic review found heterogeneous knowledge, expectations, and concerns regarding biosimilars [19]. Those findings justify attention to communication and treatment experience, but they do not establish that every subjective symptom or discontinuation after switching is caused by a placebo mechanism. An updated product-context review identified a larger biosimilar-to-biosimilar evidence base than earlier syntheses had captured [20]. The change is best understood as improved directness for selected product sequences rather than a universal class-wide conclusion.

Table 1. Review-level evidence used in the sequence-sensitive synthesis

Source	Design and scope	Principal contribution	Important constraint
Barbier <i>et al.</i> , 2020	Systematic review across reference-to-biosimilar switches	Broad synthesis of efficacy, safety, and immunogenicity	Heterogeneous products, diseases, and switch designs
Cohen <i>et al.</i> , 2022	Systematic review of biosimilar-to-biosimilar studies	Directly addresses a sequence often inferred from single-switch evidence	Evidence concentrated in selected molecules and observational settings
Schmalzing <i>et al.</i> , 2026	Narrative review of etanercept switching	Recent product-specific clinical and real-world context	Narrative methods limit reproducibility and formal certainty assessment
Tesser <i>et al.</i> , 2025	Clinical review of adalimumab switching outside the USA	Links international practice to US clinical interpretation	Policy and practice translation; not a systematic comparative synthesis
Lichtenstein <i>et al.</i> , 2024	Systematic review of infliximab switching in inflammatory bowel disease	Focused assessment of effectiveness and safety	Findings remain disease- and molecule-specific
García-Beloso <i>et al.</i> , 2022	Systematic review of adalimumab switching	Product-specific evidence across immune-mediated diseases	Variable designs, follow-up, and switching contexts
Allocati <i>et al.</i> , 2022	Review of switching among biosimilars	Maps biosimilar-to-biosimilar clinical evidence	Uneven direct evidence across sequences and products
Ascef <i>et al.</i> , 2023	Systematic review and network meta-analysis in rheumatoid arthritis	Comparative synthesis of tumour necrosis factor inhibitor strategies	Dependent on network assumptions and cross-study comparability
Wu <i>et al.</i> , 2023	Systematic review of patient perceptions	Defines communication and expectation as separate evidence domains	Perceptions do not establish pharmacological causation
Cohen and Bodenmueller, 2024	Structured update on biosimilar-to-biosimilar experience	Captures newer products, populations, and indications	Update is informative but not a replacement for a formal systematic review

Direct evidence for multiple and biosimilar-to-biosimilar switching

Multiple switching now has direct randomized evidence rather than support derived solely from single-switch studies. Trials involving adalimumab-fkjp, PF-06410293, and AVT02 evaluated repeated alternation with the reference product and reported pharmacokinetic, efficacy, safety, and immunogenicity findings that supported the predefined product-specific sequences [21-23]. The VOLTAIRE-X trial supplied corresponding evidence for BI 695501 [24]. These studies are methodologically important because the exposure history was created by design. Their conclusions should nevertheless remain tied to the tested product pair, schedule, population, endpoints, and observation period.

Prospective infliximab cohorts provide complementary routine-care evidence. In inflammatory bowel disease, patients undergoing multiple transitions from originator infliximab to biosimilars generally maintained disease control without a consistent new safety or immunogenicity signal [25]. A separate real-world cohort including single, double, and triple infliximab biosimilar switches reported a similarly reassuring pattern [26]. These studies improve external validity and directly address sequences that randomized interchangeability trials may not reproduce, but they remain susceptible to selection, attrition, treatment-policy, and time-varying clinical confounding.

The combined inference is therefore stronger than it was when repeated switching was discussed mainly by extrapolation: several multiple-switch sequences are supported directly. What remains unjustified is the conversion of those observations into a product-independent rule that every future biosimilar sequence will yield the same result.

Single switching and routine-care effectiveness

Single reference-to-biosimilar switching remains the most mature clinical evidence domain. A matched registry analysis of 1,024 patients with rheumatoid arthritis found broadly comparable outcomes after transition from originator etanercept to a biosimilar, while appropriately retaining the limitations of nonrandomized allocation [27]. European real-world experience with adalimumab biosimilar ABP 501 likewise supports maintained effectiveness and treatment persistence among initiators and switchers in inflammatory bowel disease [28]. These studies strengthen practical confidence, although residual confounding prevents observational concordance from becoming proof of formal equivalence.

Routine-care switching also exposes outcome discordance that is hidden by a binary success–failure label. In a prospective inflammatory bowel disease study, a minority of patients reported nocebo-associated symptoms after nonmedical switching even though group-level objective disease-control, biomarker, or therapeutic-monitoring measures were relatively stable [29]. A single-centre adalimumab switching programme similarly showed that communication, treatment history, clinical support, and implementation design coexist with pharmacological determinants of continuation [30]. A symptom after switching deserves assessment; timing alone does not establish the cause.

Reverse switching

Reverse switching is a distinct exposure history and a clinically meaningful outcome, but it is not self-interpreting. A prospective long-term inflammatory bowel disease cohort examined patients who returned from infliximab biosimilar SB2 to the originator after an earlier switch [31]. A return to the previous product may follow objective deterioration, perceived loss of effect, tolerability concerns, patient preference, administration or device experience, supply or reimbursement changes, or several interacting causes. Unless the reason is documented and supported by objective disease activity, exposure, or immunogenicity data, a switch-back cannot be used as a direct test of biosimilar quality.

Table 2. Directness of evidence across switching sequences

Exposure sequence	Representative evidence base	Supported interpretation	Residual limitation
Single reference → biosimilar	Etanercept registry analysis; European adalimumab cohorts	Generally maintained disease control and persistence in studied settings	Residual confounding, local implementation, and limited rare-event power
Repeated reference ↔ one biosimilar	Randomized adalimumab interchangeability studies	Direct support for predefined product pairs and switching schedules	Does not establish every adalimumab product or sequence
Multiple infliximab / biosimilar sequences	Prospective inflammatory bowel disease cohorts	Broadly maintained effectiveness, safety, and measured immunogenicity	Nonrandomized treatment pathways and concentrated disease setting
Biosimilar A → biosimilar B	Review-level synthesis plus product-specific routine-care studies	Growing direct clinical feasibility evidence	Uneven product coverage and heterogeneous sequence definitions

Exposure sequence	Representative evidence base	Supported interpretation	Residual limitation
Biosimilar → prior reference product	Prospective reverse-switch cohort	Documents a real exposure sequence and reasons for return	Switch-back is not a causal marker of pharmacological failure

Outcome-specific interpretation

Efficacy and effectiveness

Across the better-studied products and sequences, clinically important deterioration has not emerged as a consistent switching-associated pattern. Randomized trials offer internal validity for predefined switching schedules, whereas prospective and registry studies test effectiveness under routine care. Concordance between these designs is reassuring, but “no consistent deterioration detected” is more defensible than “switching has no effect.” The latter statement implies universal equivalence across products, patients, outcomes, and time horizons that the available evidence does not establish.

Interpretation should distinguish group-level stability from individual clinical evaluation. A patient with measurable deterioration after a switch requires the same careful assessment applied to loss of response during any biologic treatment: disease fluctuation, adherence, administration, pharmacokinetics, immunogenicity, concomitant therapy, and unrelated illness are competing explanations. Population-level evidence informs prior probability; it does not eliminate individual causation or replace clinical investigation.

Safety

Safety findings are broadly reassuring within the observation periods and sample sizes studied. A retrospective analysis of a single switch from reference rituximab to Riximyo in non-Hodgkin lymphoma did not identify a major new safety pattern, but the cohort size and observational design constrain broader inference [32]. A randomized transition study of another rituximab biosimilar reported comparable safety and immunogenicity within the evaluated rheumatoid arthritis population [33]. These data expand the evidence beyond anti-tumour necrosis factor therapy while reinforcing the need for product- and indication-specific interpretation.

Most switch studies are not powered to exclude very rare or long-latency harms. Safety conclusions should therefore describe what was observed rather than imply that all possible risks were ruled out. Post-marketing pharmacovigilance remains necessary, particularly when products, formulations, devices, populations, or exposure sequences change.

Immunogenicity

Immunogenicity is often invoked as a singular switching hazard, but measured anti-drug antibody results depend on assay sensitivity, drug interference, sampling schedule, prior biologic exposure, concomitant immunosuppression, the persistence or transience of a response, and its functional or clinical consequence. Comparative natalizumab evidence illustrates how analytical, assay, and clinical components can converge on a matching immunogenicity profile [34]. That result is informative for the evaluated product; it does not establish a universal antibody rate after every switch.

An isolated assay-positive finding should not be equated automatically with loss of efficacy or a safety event. The clinically meaningful chain is longer: exposure history and host factors influence a detected response; the response may or may not alter pharmacokinetics or neutralizing activity; and any biological change may or may not produce an observable clinical consequence. **Figure 2** makes these inferential boundaries explicit.

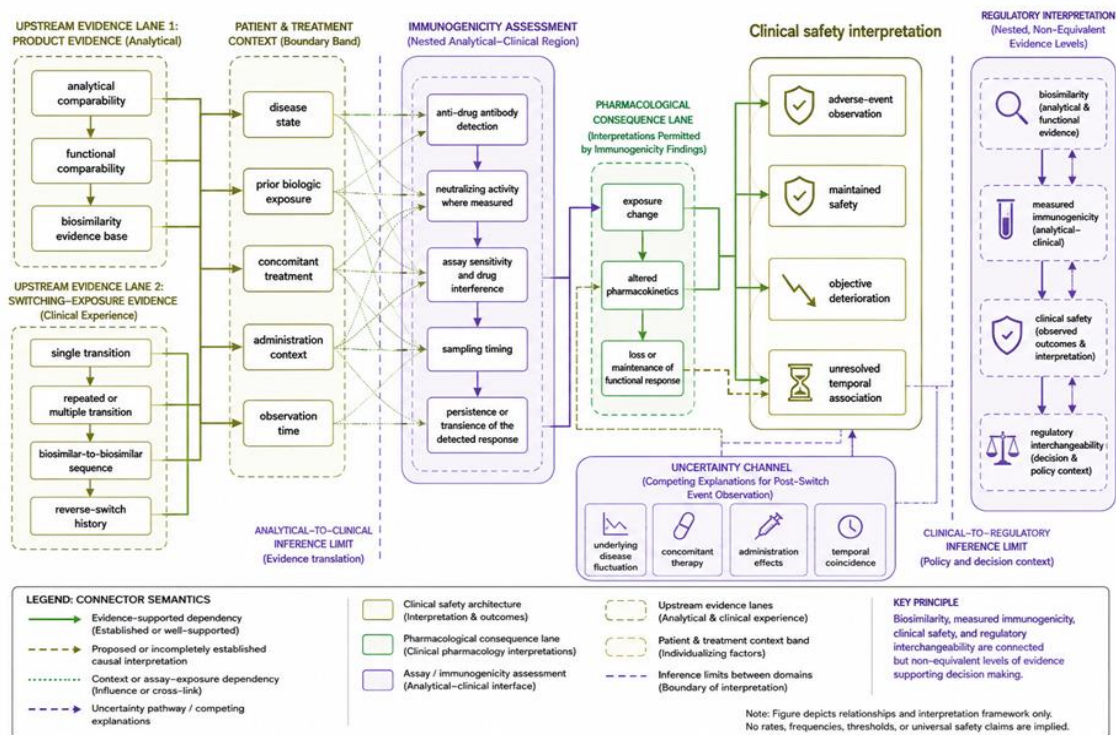


Figure 2. Safety interpretation depends on where immunogenicity evidence enters the switching sequence. Biosimilarity, measured immunogenicity, clinical safety, and regulatory interchangeability are connected but non-equivalent evidence levels.

Persistence, discontinuation, and patient experience

Persistence is a composite outcome rather than a direct assay of molecular comparability. Continued treatment can reflect effectiveness and tolerability, but also convenience, supply, reimbursement, administration device, clinician recommendation, patient preference, and the design of the switching programme. Conversely, discontinuation or reverse switching may arise without objective loss of disease control. Patient experience should be taken seriously without assigning a pharmacological mechanism before competing explanations are assessed. The term nocebo is useful when negative expectations plausibly contribute to post-switch experience, but it can become dismissive if applied to every discordant symptom. A defensible assessment documents the timing and nature of symptoms, objective disease measures, adherence and administration, concomitant treatment, communication conditions, and the response to any subsequent intervention. The evidence supports structured investigation, not automatic attribution in either direction.

Table 3. Outcome domains and the limits of the inferences they support

Outcome domain	Pattern in the assembled evidence	Permitted interpretation	What remains unresolved
Pharmacokinetics	Comparable exposure within predefined randomized switching schedules	Direct for the tested product, schedule, and population	Exposure is not a complete surrogate for every clinical outcome
Efficacy / effectiveness	No consistent group-level deterioration across better-studied contexts	Supports the evaluated transition under stated conditions	Individual deterioration and cross-context transfer require assessment
Safety	No consistent new common safety pattern in evaluated studies	Reassuring within sample size and follow-up	Rare and delayed events remain difficult to exclude
Immunogenicity	Generally comparable measured antibody findings in studied products	Meaningful when assay, timing, persistence, and consequence are specified	Assay-positive results are not automatically clinically harmful

Persistence	Often maintained, with variable discontinuation and switch-back	Useful implementation and treatment-experience outcome	Not a pure measure of biological comparability
Patient-reported symptoms	May diverge from objective disease measures	Clinically important signal requiring investigation	Timing alone cannot distinguish nocebo, disease fluctuation, or product effect

Therapeutic, regulatory, and health-system context

Evidence volume and implementation are not evenly distributed across therapeutic areas. A national rheumatology registry analysis showed that the drivers of new biosimilar initiation differ from the drivers of switching patients already receiving infliximab [35]. This matters because uptake patterns can alter who enters observational cohorts and why. The resulting treatment groups may differ in stability, clinician preference, payer policy, or prior experience before outcomes are measured.

Ecuzumab biosimilars illustrate the limits of transferring conclusions from common anti-tumour necrosis factor programmes to biologics used in rare, high-consequence diseases [36]. Differences in disease natural history, treatment criticality, infusion setting, immunogenicity relevance, outcome frequency, and acceptable uncertainty may change the evidence required for confident implementation. The existence of extensive adalimumab or infliximab experience provides scientific context, not a substitute for direct evidence where the clinical stakes or biological setting differ.

Treatment history further modifies interpretation. European analyses of ABP 501 show that persistence and switching patterns vary across rheumatologic diseases and prior treatment pathways [37]. Broader real-world experience across rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and psoriasis supports practical use while also showing why disease-specific care pathways cannot be collapsed into one generic switching population [38].

Regulatory conclusions require their own boundary. Biosimilarity is established through a totality of analytical, functional, pharmacokinetic, and clinical evidence. Clinical switching studies evaluate defined exposure transitions. Interchangeability and pharmacy-level substitution are jurisdiction-specific legal and regulatory constructs. These layers may inform one another, but none should be used as a substitute for another. In particular, a stable clinical switch does not recreate the analytical biosimilarity assessment, and a regulatory designation should not be presented as proof that every conceivable multi-product sequence has been tested clinically.

Principal interpretation

The most defensible synthesis is both reassuring and bounded. Across systematic reviews, randomized studies, and prospective cohorts, switching has not produced a reproducible pattern of reduced efficacy, new common safety problems, or clinically consequential immunogenicity in the well-studied products and sequences. Direct evidence for multiple switching has materially expanded, especially for selected adalimumab and infliximab programmes. The remaining uncertainty is not evidence of a hidden universal hazard; it reflects incomplete coverage of products, sequences, populations, outcomes, and time horizons.

This conclusion differs from a blanket assertion that all switching is interchangeable. Single switching, repeated alternation with one biosimilar, changes between biosimilars, and reverse switching create different exposure histories. Evidence transfer is most credible when analytical similarity is established, the product and formulation are closely matched to the evidence base, the sequence has been observed directly, the disease and prior exposure are comparable, and outcomes are measured with adequate duration and appropriate assays. As these conditions diverge, claims should become more qualified rather than remaining unchanged.

Why apparently discordant findings can coexist

Several apparent contradictions disappear when outcome levels are separated. Persistence may decline while objective disease control remains stable because continuation also reflects expectations, device experience, access, and programme design. Reverse switching may occur without evidence of pharmacological inferiority because the reason for return can be preference, logistics, or subjective experience. Anti-drug antibodies may be detected without altered exposure or clinical response. Regulatory interchangeability may differ among jurisdictions even when the underlying products meet biosimilarity standards. These findings are not mutually exclusive; they answer different questions.

Differences among reviews can also arise from search dates, eligible study designs, therapeutic-area mix, definitions of switching, treatment-naïve versus previously treated populations, outcome windows, and whether

a review counts every switch event or every patient. A review dominated by single infliximab transitions in stable inflammatory bowel disease should not be expected to produce the same evidentiary scope as a review focused on multiple adalimumab alternations or on patient perceptions. Critical synthesis requires examination of these design features before comparing conclusions.

Implications for clinical practice and evidence generation

For practice, the sequence-sensitive approach supports planned switching when the product and context are represented by reassuring evidence, while preserving individualized evaluation of unexpected deterioration. Baseline disease status, prior biologic exposure, relevant objective measures, and reasons for switching should be documented. Communication should explain the evidentiary basis and practical changes without overstating certainty. When symptoms or discontinuation occur, clinical teams should evaluate disease activity, adherence, administration, pharmacokinetics where relevant, immunogenicity when clinically indicated, and implementation factors before assigning causation.

For research, the priority is not an indiscriminate demand for a randomized trial of every theoretical sequence. Higher-value studies should target genuine transferability gaps: underrepresented biologic classes; biosimilar-to-biosimilar sequences created by procurement changes; reverse switching with documented reasons and objective outcomes; longer follow-up for persistence and uncommon harms; harmonized immunogenicity sampling; and prospective capture of patient experience alongside clinical and pharmacological measures. Transparent sequence notation would also improve future synthesis by making the order, direction, and number of transitions explicit.

Table 4. Transferability boundaries and priority evidence gaps

Boundary	Where evidence is comparatively mature	Residual uncertainty	Priority evidence response
Product and formulation	Strongest for selected adalimumab, infliximab, and etanercept programmes	Transfer to underrepresented molecules, devices, and formulations	Product-specific studies when mechanism, formulation, or clinical stakes differ materially
Sequence and direction	Direct evidence for several single and repeated sequences	Longer biosimilar chains and reverse switching	Report every transition in order and analyze sequence-specific outcomes
Population and prior exposure	Often stable patients with established biologic use	Treatment-naïve, unstable, rare-disease, and highly comorbid populations	Stratified analyses with baseline state and prior exposure documented
Follow-up and event frequency	Adequate for common short-to medium-term outcomes	Rare events, delayed immunogenicity, long-term persistence	Larger linked registries and longer prospective follow-up
Outcome and assay	Common efficacy and safety outcomes; variable immunogenicity methods	Cross-study comparability and clinical meaning of antibody findings	Harmonized outcomes, assay reporting, timing, and consequence mapping
Care-system context	Evidence from diverse but unevenly represented systems	Effects of procurement, communication, substitution policy, and access	Embed implementation measures in comparative clinical studies

Strengths and limitations

The principal strength of this review is conceptual precision. It prevents single, multiple, biosimilar-to-biosimilar, and reverse switching from being treated as equivalent; separates clinical outcomes from regulatory designations; and integrates objective outcomes with persistence and patient experience without reducing one to another. The synthesis also includes recent randomized and real-world studies that postdate several major reviews.

The limitations are substantial and should define how the article is used. Source identification was structured but not exhaustive and did not use duplicate independent screening or a reproducible multi-database systematic-review workflow. The review should therefore not be read as an umbrella review, a complete global census, or a meta-analysis. The evidence set contains overlapping primary-study families, and overlap was controlled qualitatively rather than through a complete citation matrix. Review-level sources differ in methodological rigor, and narrative reviews were used for context rather than treated as equivalent to systematic reviews.

The primary evidence is concentrated in anti-tumour necrosis factor agents and inflammatory diseases. Many studies are observational, follow-up is variable, immunogenicity methods are heterogeneous, and rare outcomes remain difficult to evaluate. The review also does not produce a validated certainty score. Its claim-status labels are intended to discipline interpretation by making directness and transferability visible, not to replace established evidence-certainty methods.

CONCLUSION

Biosimilar switching is generally supported in the products, populations, and exposure sequences that have been studied directly. Evidence for several repeated and biosimilar-to-biosimilar sequences is now substantive enough that these practices should not be described as supported only by extrapolation from single switching. Confidence nevertheless remains conditional on product identity, sequence and direction, disease context, prior exposure, outcome, assay strategy, and observation period.

A sequence-sensitive interpretation preserves the reassuring clinical signal while avoiding a universal claim that the evidence does not support. It also clarifies why persistence, subjective symptoms, immunogenicity, reverse switching, and regulatory interchangeability require connected but distinct analyses. The appropriate endpoint is calibrated confidence: direct support where evidence matches the claim, explicit qualification where transfer is reasonable, and clearly defined uncertainty where it is not.

ACKNOWLEDGMENTS: None

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

ETHICS STATEMENT: None

REFERENCES

1. Barbier L, Ebbers HC, Declerck P, Simoens S, Vulto AG, Huys I. The efficacy, safety, and immunogenicity of switching between reference biopharmaceuticals and biosimilars: A systematic review. *Clin Pharmacol Ther.* 2020;108(4):734-55. doi:10.1002/cpt.1836
2. Cohen HP, Hachaichi S, Bodenmueller W, Kvien TK, Danese S, Blauvelt A. Switching from one biosimilar to another biosimilar of the same reference biologic: A systematic review of studies. *BioDrugs.* 2022;36(5):625-37. doi:10.1007/s40259-022-00546-6
3. Schmalzing M, Askari A, Girolomoni G, Perez-Coleman JCV, Salvati C, Bachinskaya E. Clinical and real-world evidence on etanercept biosimilar switching: A narrative literature review of efficacy and safety. *Adv Ther.* 2026;43(1):49-75. doi:10.1007/s12325-025-03367-5
4. Tesser JRP, Charabaty A, Hebert AA. Switching from adalimumab reference product to and among adalimumab biosimilars outside the USA: Insights for US clinicians. *BioDrugs.* 2025;39(4):591-606. doi:10.1007/s40259-025-00719-z
5. Lichtenstein GR, Soonasra A, Latymer M, Singh S, Feagan BG. Systematic review: Effectiveness and safety of switching between originator infliximab and biosimilar infliximab in patients with inflammatory bowel disease. *Expert Opin Biol Ther.* 2024;24(7):691-708. doi:10.1080/14712598.2024.2378090
6. Car E, Barbier L, Schwarzenberger I, Huys I, Simoens S, Vulto AG. Toward regulatory convergence and streamlined biosimilar development: Recommendations from an international qualitative study. *BioDrugs.* 2025;39(6):943-55. doi:10.1007/s40259-025-00746-w
7. Car E, Barbier L, Huys I, Simoens S, Vulto AG. Evolving global regulatory landscape for approval of biosimilars: Current challenges and opportunities for convergence. *Expert Opin Biol Ther.* 2025;25(6):649-68. doi:10.1080/14712598.2025.2507832
8. Woo H, Shin G, Lee D, Kwon HY, Bae S. Is the availability of biosimilar adalimumab associated with budget savings? A difference-in-difference analysis of 14 countries. *BioDrugs.* 2024;38(1):133-44. doi:10.1007/s40259-023-00636-z
9. Jiang TE, Ramachandran R, Skydel JJ. Regulatory change could improve biosimilar access in the US. *BMJ.* 2025;390. doi:10.1136/bmj-2025-084860

10. Ling YL, Gentile D, Kotomale A, Sharpe JA, Geli D, Gruben D, et al. Real-world familiarity with US biosimilar regulatory guidelines and interchangeability state laws among pharmacists and physicians treating immunological disorders. *J Manag Care Spec Pharm*. 2025;31(6):552-64. doi:10.18553/jmcp.2025.31.6.552
11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*. 2021;372. doi:10.1136/bmj.n71
12. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358. doi:10.1136/bmj.j4008
13. Lunny C, Pieper D, Thabet P, Kanji S. Managing overlap of primary study results across systematic reviews: Practical considerations for authors of overviews of reviews. *BMC Med Res Methodol*. 2021;21(1):140. doi:10.1186/s12874-021-01269-y
14. Lunny C, Brennan SE, Reid J, McDonald S, McKenzie JE. Overviews of reviews incompletely report methods for handling overlapping, discordant, and problematic data. *J Clin Epidemiol*. 2020;118:69-85. doi:10.1016/j.jclinepi.2019.09.025
15. Brignardello-Petersen R, Guyatt GH. Assessing the certainty of the evidence in systematic reviews: Importance, process, and use. *Am J Epidemiol*. 2025;194(6):1681-6. doi:10.1093/aje/kwae332
16. García-Beloso N, Altabás-González I, Samartín-Ucha M, Gayoso-Rey M, De Castro-Parga ML, Salgado-Barreira Á, et al. Switching between reference adalimumab and biosimilars in chronic immune-mediated inflammatory diseases: A systematic literature review. *Br J Clin Pharmacol*. 2022;88(4):1529-50. doi:10.1111/bcp.15101
17. Allocati E, Godman B, Gobbi M, Garattini S, Banzi R. Switching among biosimilars: A review of clinical evidence. *Front Pharmacol*. 2022;13:917814. doi:10.3389/fphar.2022.917814
18. Ascef BO, Almeida MO, Medeiros-Ribeiro AC, Andrade DCO, Oliveira Junior HA, Soárez PC. Impact of switching between reference biologics and biosimilars of tumour necrosis factor inhibitors for rheumatoid arthritis: A systematic review and network meta-analysis. *Sci Rep*. 2023;13(1):13699. doi:10.1038/s41598-023-40222-5
19. Wu Q, Wang Z, Wang X, Yu H, Sun J. Patients' perceptions of biosimilars: A systematic review. *BioDrugs*. 2023;37(6):829-41. doi:10.1007/s40259-023-00620-7
20. Cohen HP, Bodenmueller W. Additional data in expanded patient populations and new indications support the practice of biosimilar-to-biosimilar switching. *BioDrugs*. 2024;38(3):331-9. doi:10.1007/s40259-024-00655-4
21. Deodhar S, Loganathan S, Subbarama Reddy RK, Ranganna GM, Liu S, Hummel MA, et al. Multiple switches between adalimumab-fkjp and reference adalimumab in moderate-to-severe chronic plaque psoriasis: A multicenter, double-blind, parallel group, randomized clinical trial for interchangeability. *Adv Ther*. 2025;42(8):3795-809. doi:10.1007/s12325-025-03240-5
22. Fleischmann RM, Saikali W, Lakhanpal S, Alvarez DF, Cox DS, Ianos CA, et al. Multiple switching between the biosimilar adalimumab PF-06410293 and reference adalimumab in patients with active rheumatoid arthritis: A phase 3, open-label, randomised, parallel-group study. *Lancet Rheumatol*. 2023;5(9). doi:10.1016/S2665-9913(23)00161-3
23. Feldman SR, Kay R, Reznichenko N, Sobierska J, Dias R, Otto H, et al. Assessing the interchangeability of AVT02 and Humira in participants with moderate-to-severe chronic plaque psoriasis: Pharmacokinetics, efficacy, safety, and immunogenicity results from a multicenter, double-blind, randomized, parallel-group study. *BioDrugs*. 2023;37(4):551-67. doi:10.1007/s40259-023-00600-x
24. Menter A, Cohen S, Kay J, Strand V, Gottlieb A, Hanauer S, et al. Switching between adalimumab reference product and BI 695501 in patients with chronic plaque psoriasis (VOLTAIRE-X): A randomized controlled trial. *Am J Clin Dermatol*. 2022;23(5):719-28. doi:10.1007/s40257-022-00708-w
25. Hanzel J, Jansen JM, Ter Steege RWF, Gecse KB, D'Haens GR. Multiple switches from the originator infliximab to biosimilars is effective and safe in inflammatory bowel disease: A prospective multicenter cohort study. *Inflamm Bowel Dis*. 2022;28(4):495-501. doi:10.1093/ibd/izab099
26. Gros B, Plevris N, Constantine-Cooke N, Lyons M, O'Hare C, Noble C, et al. Multiple infliximab biosimilar switches appear to be safe and effective in a real-world inflammatory bowel disease cohort. *United European Gastroenterol J*. 2023;11(2):179-88. doi:10.1002/ueg.2.12357
27. Kearsley-Fleet L, Rokad A, Tsoi MF, Zhao SS, Lunt M, Watson KD, et al. Outcomes following switching from etanercept originator to etanercept biosimilar in 1024 patients with rheumatoid arthritis: A matched-

- analysis of the BSRBR-RA. Rheumatology (Oxford). 2024;63(8):2082-92. doi:10.1093/rheumatology/kead470
28. Jin R, Nduka C, Courmier D, Knight H, Meadows R, Piercy J, et al. Real-world experience of adalimumab biosimilar (ABP 501) use in patients with inflammatory bowel disease in Europe. *Adv Ther.* 2024;41(1):331-48. doi:10.1007/s12325-023-02712-w
 29. Wetwittayakhleng P, Karkout K, Wongcha-Um A, Tselekouni P, Al-Jabri R, Afif W, et al. Clinical efficacy and placebo effect following non-medical biosimilar switch in patients with inflammatory bowel disease: A prospective observational study. *Dig Liver Dis.* 2024;56(1):35-42. doi:10.1016/j.dld.2023.06.022
 30. Rabbitt L, Keogh Á, Duane L, Ferguson J, Hobbins A, McGuire BE, et al. A single-centre analysis of a biosimilar switching programme for adalimumab in inflammatory bowel disease. *Br J Clin Pharmacol.* 2025;91(9):2628-35. doi:10.1002/bcp.70086
 31. Fischer S, Donhauser M, Cohnen S, Fietkau K, Vetter M, Gröbel-Liehr M, et al. Reverse switching from the biosimilar SB2 to the originator infliximab in previously switched patients with inflammatory bowel diseases: Results of a prospective long-term cohort study. *Therap Adv Gastroenterol.* 2024;17:17562848241301887. doi:10.1177/17562848241301887
 32. Song NK, Musa H, Soriano M, Hibbs DE, Ramzan I, Ong JA. Safety of rituximab biosimilar (Riximyo) following a single switch from the reference product in patients with Non-Hodgkin's lymphoma: A retrospective study. *Ann Hematol.* 2024;103(11):4607-12. doi:10.1007/s00277-024-05981-9
 33. Maharaj N, Uppada DR, Reddy N, Reddy P, Batalov A, Ivanova D, et al. Comparing immunogenicity and safety following transition from reference rituximab to biosimilar rituximab (DRL_RI) in patients with rheumatoid arthritis: A randomized, double-blind, phase 3 study. *Arthritis Res Ther.* 2024;26(1):225. doi:10.1186/s13075-024-03456-w
 34. Chamberlain P, Hemmer B, Höfler J, Wessels H, von Richter O, Hornuss C, et al. Comparative immunogenicity assessment of biosimilar natalizumab to its reference medicine: A matching immunogenicity profile. *Front Immunol.* 2024;15:1414304. doi:10.3389/fimmu.2024.1414304
 35. Roberts ET, Bansback N, Tseng CW, Shiboski S, Li J, Schmajuk G, et al. Drivers of infliximab biosimilar uptake: A comparative analysis of new biosimilar initiations versus switching in a national rheumatology registry. *Health Serv Res.* 2025;60(3). doi:10.1111/1475-6773.14410
 36. Jang JH, Han B, Jung J, Russo P, Kulasekararaj AG. The path to accessible care: Development and impact of eculizumab biosimilars for paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome. *BioDrugs.* 2025;39(2):281-95. doi:10.1007/s40259-025-00707-3
 37. Jin R, Kruppert S, Scholz F, Bardoulat I, Karzazi K, Morand F, et al. Treatment persistence and switching patterns of adalimumab biosimilar ABP 501 in European patients with rheumatologic diseases. *Rheumatol Ther.* 2024;11(3):523-37. doi:10.1007/s40744-024-00647-4
 38. Jin R, Haughton JM, Goddard EJ, Courmier D, Radziszewski W, Meadows RH, et al. Real-world experience with an adalimumab biosimilar (ABP 501) in patients with rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and psoriasis in Europe: Results from the Adelphi Disease Specific Programme. *Rheumatol Ther.* 2025;12(3):469-92. doi:10.1007/s40744-025-00755-9