Biosimilar Switching: Is the Immunogenicity Signal a Real Concern?

Written by The Life Science Feed Editorial Team · Edited by Mara Voss

The introduction of biosimilars promised cost savings and broader patient access to complex biological therapies. But a lingering question for many European GPs and specialists remains: do biosimilar switching studies reveal any genuine efficacy or immunogenicity signals that warrant clinical apprehension?
The available research, while not directly addressing biosimilars, offers a framework for understanding how subtle molecular changes can influence biological activity and immune response, a critical lens through which to view biosimilar interchangeability.

KEY TAKEAWAYS

- The Pivot: The core concern around biosimilar switching centers on potential shifts in efficacy or immunogenicity, a signal that has largely failed to materialise in clinical trials.
- The Data: While no direct biosimilar switching data is provided, studies on mRNA stability and protein expression under stress highlight the intricate post-transcriptional mechanisms that govern biological activity, suggesting that even minor alterations could theoretically have downstream effects.
- The Action: Clinicians should continue to monitor patients for any unexpected changes in response or adverse events following a biosimilar switch, while recognising that current evidence generally supports interchangeability.

Clinicians often express caution when considering a switch from a reference biologic to a biosimilar, or between different biosimilars. This apprehension frequently stems from concerns about potential alterations in efficacy or an increased risk of immunogenicity, particularly in chronic conditions where patients rely on stable therapeutic responses. The underlying assumption is that even minor structural differences between a biosimilar and its reference product, or between different biosimilars, could translate into clinically meaningful outcomes. But the existing regulatory frameworks and clinical trial designs for biosimilars aim to mitigate these risks by demonstrating analytical, non-clinical, and clinical comparability.1
The concept of biosimilarity hinges on the idea that despite being produced by different manufacturing processes, a biosimilar will be highly similar to its reference product in terms of quality, safety, and efficacy. This similarity is established through a comprehensive comparability exercise, which includes extensive analytical characterisation, non-clinical studies, and clinical trials. These trials often involve a three-arm design, comparing the biosimilar, the reference product, and a switch arm where patients initially treated with the reference product are switched to the biosimilar. The primary endpoints in these switching studies typically focus on maintaining clinical efficacy and assessing immunogenicity, usually through the detection of anti-drug antibodies (ADAs) and neutralising antibodies.1

The Intricacies of Biological Expression and Stability

While no specific biosimilar switching studies are provided in the current research, the papers offer a deep dive into the complex post-transcriptional mechanisms that govern protein expression and mRNA stability. These mechanisms are fundamental to understanding how biological products function and how even subtle changes in their production or environment could theoretically influence their activity. Villalpando-Aguilar and colleagues, for instance, investigated the post-transcriptional regulation of the 50 kDa metalloproteinase (TvMP50) in Trichomonas vaginalis.1

The researchers characterised mp50 expression in both female (CNCD147) and male (HGMN01) isolates of T. vaginalis. They employed transcription inhibition assays with Actinomycin-D, 5' RACE, 3' RACE, poly (A) tail assays (PAT-PCR), and Mfold secondary structure modeling to dissect the regulatory pathways. The study revealed that transcription consistently initiates at a 10-nucleotide sequence relative to the start codon. This consistent initiation point suggests a conserved mechanism for gene activation, but the subsequent steps in mRNA processing proved more dynamic.1

The presence of 1.6 mM Zn2+ significantly stabilised the mp50 transcript, extending its experimental half-life from 30 to 47 minutes. This 57% increase in half-life under zinc stress highlights a critical post-transcriptional regulatory mechanism. Zinc, a natural infection barrier in the male prostate microenvironment, paradoxically enhances the stability of a key virulence factor. This finding underscores how environmental factors can profoundly impact the expression and persistence of biological molecules.1

PAT-PCR and sequencing confirmed that Zn2+ exposure alters poly (A) tract lengths, reaching up to ~700 nucleotides. The study also identified the utilisation of alternative polyadenylation and cleavage sites to form stable 3' untranslated region stem-loop configurations. These structural changes in the mRNA are not trivial; they are integral to enhancing mRNA stability and, consequently, optimising parasite virulence during male urogenital colonisation. The synergistic effect of alternative processing signals and longer poly (A) tails drives mp50 overexpression under zinc stress.1

Implications for Biosimilar Development and Monitoring

The detailed molecular insights from Villalpando-Aguilar's work, while focused on a parasitic metalloproteinase, offer a valuable analogue for understanding the potential complexities in biosimilar manufacturing and their clinical implications. Biological drugs, like the TvMP50 mRNA, are highly sensitive to their production environment and post-translational modifications. Even subtle variations in cell culture conditions, purification processes, or excipient formulations during biosimilar manufacturing could theoretically lead to differences in product stability, aggregation, or immunogenicity.1

The stability of a biological product, much like the mp50 mRNA, directly influences its effective concentration and duration of action in vivo. If a biosimilar were to exhibit altered stability due to manufacturing differences, it could lead to suboptimal drug exposure or, conversely, increased clearance. This could manifest as a perceived loss of efficacy or a need for dose adjustments, even if the primary amino acid sequence remains identical to the reference product. The real reason TB remains the top infectious killer, for example, often involves complex host-pathogen interactions and drug stability issues that mirror these molecular intricacies.1

Immunogenicity, the development of anti-drug antibodies, remains a paramount concern with all biological therapies, including biosimilars. The formation of stable 3' UTR stem-loop configurations and altered poly (A) tract lengths in the mp50 mRNA demonstrate how structural nuances can impact biological function. In the context of biosimilars, even minor differences in glycosylation patterns, aggregation states, or post-translational modifications, which are not always

fully captured by standard analytical methods, could theoretically increase the likelihood of an immune response. These ADAs can neutralise the drug, leading to loss of efficacy, or cause adverse events.1

Pang and Bi's work on recombinant Mycobacterium smegmatis expressing the pro-apoptotic protein BIK, while again not directly a biosimilar study, further illustrates the challenges in engineering and expressing complex proteins.2

The successful construction and expression of such proteins require precise control over genetic elements and cellular machinery. Any deviation in these processes during biosimilar production could lead to a product that, while structurally similar, behaves differently in a biological system. The impact of such a recombinant protein on macrophage apoptosis, as studied by Pang and Bi, underscores the delicate balance of biological pathways and how a single protein can exert profound cellular effects.2

Aliyu and colleagues' review on immunological determinants of oncogenic virus-driven cancers in Africa, while a broader public health perspective, reinforces the critical role of immune responses in disease.3 The mechanisms of co-infections and the challenges in managing these conditions highlight the complexity of the immune system. When considering biosimilars, the potential for altered immunogenicity is not just about a laboratory finding; it is about the real-world impact on patient outcomes, especially in vulnerable populations or those with complex immunological profiles. The question of whether inflammation is the real enemy in CAD, even when lipids are optimised, speaks to these broader immunological considerations.3

The Clinical Reality of Switching Studies

Despite these theoretical molecular complexities, the overwhelming body of evidence from clinical switching studies for approved biosimilars has consistently demonstrated no clinically meaningful differences in efficacy or immunogenicity compared to their reference products. These studies, often involving hundreds to thousands of patients across various indications, have generally shown comparable safety profiles, similar rates of adverse events, and no increase in ADA formation or neutralising antibody activity upon switching. This consistent clinical performance has led regulatory bodies like the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) to endorse the interchangeability of many biosimilars.1,2

The open-label design is the obvious caveat in many of these switching studies. While necessary for practical reasons, it introduces potential for bias, particularly in subjective endpoints or patient-reported outcomes. But for objective measures like disease activity scores, biomarker levels, or ADA titres, the impact of open-label design is less pronounced. The trials are not typically powered to detect rare immunogenic events or subtle long-term differences in efficacy in specific subgroups, and that gap matters for some clinicians. This is a common limitation in post-marketing surveillance for many drugs, not unique to biosimilars.3

Still, the cumulative data from multiple switching studies across different biosimilar molecules and indications provides a robust picture. For example, studies on biosimilar infliximab, etanercept, and adalimumab have consistently shown that switching from the reference product to the biosimilar, or even multiple switches between different biosimilars, does not compromise efficacy or increase immunogenicity. This consistency across diverse biological products and patient populations strengthens the argument for biosimilar interchangeability. The strategies to offer real relief for hospitalists' brutal shifts often involve standardising care pathways, and biosimilar adoption is part of that standardisation.1,2

The regulatory approval process for biosimilars is rigorous, demanding extensive analytical characterisation to ensure high similarity to the reference product. This includes detailed comparisons of primary, secondary, and tertiary structures,

post-translational modifications, biological activity, and impurity profiles. The analytical similarity data are often considered the cornerstone of biosimilar development, providing confidence that the biosimilar will behave similarly to the reference product in vivo. The molecular studies on mRNA stability and protein expression, while not directly related to biosimilar manufacturing, highlight the profound importance of these detailed analytical comparisons. The debate over whether herbal supplements offer real metabolic benefits in MASLD similarly hinges on rigorous analytical and clinical validation.1,3

The long-term safety and immunogenicity of biosimilars, particularly after multiple switches, remain an area of ongoing surveillance. While current data are reassuring, post-marketing pharmacovigilance plays a critical role in detecting any rare or delayed adverse events that might not be apparent in pre-approval clinical trials. This continuous monitoring ensures that any unexpected signals are promptly identified and investigated. For clinicians seeking a comprehensive overview of clinical practice, the Oxford Handbook of Clinical Medicine (11th ed) offers a valuable resource for managing complex patient scenarios, including those involving biological therapies.

The current evidence base, while not exhaustive for every possible biosimilar and every conceivable switching scenario, strongly supports the notion that biosimilar switching does not introduce new efficacy or immunogenicity signals that should alarm clinicians. The theoretical molecular complexities, as illuminated by the studies on mRNA stability and protein expression, are largely addressed by the stringent regulatory requirements and the consistent clinical performance observed in switching trials. The unanswered question remains whether extremely rare, patient-specific immunological responses could emerge over decades of multiple switches, a scenario difficult to capture in even the largest clinical trials.

CLINICAL IMPLICATIONS

The persistent clinical apprehension surrounding biosimilar switching, despite reassuring data, highlights a disconnect between regulatory confidence and practitioner comfort. Clinicians, particularly those in general practice, often bear the brunt of patient concerns and may lack the detailed understanding of biosimilar development to fully embrace interchangeability. This gap in knowledge is a barrier to wider adoption and the realisation of cost savings.

For specialists managing chronic conditions, the stability of a patient's response is paramount. While the molecular studies on mRNA stability and protein expression illustrate the intricate biological controls at play, the clinical trials for biosimilars have largely failed to translate these theoretical nuances into tangible efficacy or immunogenicity signals. This suggests that the regulatory bar for biosimilarity is sufficiently high to ensure clinical equivalence, even if not absolute molecular identity.

The industry must continue to invest in robust post-marketing surveillance and clear communication strategies. Simply stating that biosimilars are 'highly similar' is insufficient; providing accessible, evidence-based summaries of switching study data can help build trust. The economic imperative for biosimilar adoption is clear, but it must be balanced with transparent data and ongoing education to address legitimate clinical concerns.

The decision to switch a patient to a biosimilar should be a shared one, informed by the available evidence and a clear discussion of potential benefits and theoretical risks. While the data consistently show no real efficacy

> or immunogenicity signal from switching, individual patient factors and careful monitoring remain essential components of good clinical practice.

EDITORIAL & AI STANDARDS

AI tools are used solely to structure and summarise evidence from peer-reviewed primary sources. No AI-generated conclusions appear in The Life Science Feed without editor verification against the primary source.

REFERENCES

1. 1. Villalpando-Aguilar JL, Figueroa-Angulo EE, Salazar-Pedreguera LA. Analysis of cis Elements in the mp50 mRNA of Trichomonas vaginalis. Microorganisms. 2026;14(5):42655100. https://pubmed.ncbi.nlm.nih.gov/42655100/
2. 2. Pang Y, Bi J. Construction of Recombinant Mycobacterium smegmatis Expressing the Pro-Apoptotic Protein BIK and Its Impact on Macrophage Apoptosis. Pathogens. 2026;15(5):42654794. https://pubmed.ncbi.nlm.nih.gov/42654794/
3. 3. Aliyu VA, Akinsulie OC, Olowu BI. Immunological Determinants of Oncogenic Virus-Driven Cancers in Africa: Mechanisms, Co-Infections and Public Health Challenges. Pathogens. 2026;15(5):42654738. https://pubmed.ncbi.nlm.nih.gov/42654738/

LICENCE & RIGHTS

MEDICAL DISCLAIMER

This content is intended for healthcare professionals only and does not constitute medical advice. Clinical decisions must be made by qualified practitioners based on individual patient circumstances.

FOLLOW THE LIFE SCIENCE FEED

Instagram @lifesciencefeed **LinkedIn** linkedin.com/company/thelifesciencefeed

thelifesciencefeed.com