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Review Article

A Comprehensive Review of Evidence and Challenges in Switching from Originator Drugs to Biosimilars of Monoclonal Antibodies: Focus on Rituximab and Trastuzumab

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Abstract

Objective: The primary objective of the document is to conduct a comprehensive review of the clinical, economic, and regulatory evidence regarding the transition from originator drugs to biosimilars of monoclonal antibodies, focusing specifically on rituximab and trastuzumab. The review aims to analyze data on biosimilar usage, assess barriers to adoption, explore potential strategies to overcome challenges, with the ultimate goal of improving healthcare sustainability and accessibility.

Data source Study selection: The study selection includes clinical trials, economic analyses, and regulatory reviews focusing on biosimilars of rituximab and trastuzumab. It focuses on phase 3 trials, cost-effectiveness studies, and post-marketing surveillance data for assessing safety, efficacy, and adoption barriers. Real-world evidence and regulatory guidelines from agencies such as EMA and FDA are also considered.

Summary: The article reviews the transition from originator monoclonal antibody drugs to biosimilars, focusing on rituximab and trastuzumab. Topics of clinical evidence, economic benefits, regulatory challenges, and adoption barriers include issues related to immunogenicity concerns and perceived physician-patient acceptance. While offering potentially cost-effective treatments for cancer, further research, harmonization of regulations, and education will allow this value to be realized across more patients, improved outcomes.

Conclusion: The transition from originator drugs to biosimilars, like rituximab and trastuzumab, enhances treatment accessibility and affordability. Clinical evidence supports their safety and efficacy, but challenges remain, including immunogenicity concerns, regulatory differences, and stakeholder perceptions. Addressing these barriers through global harmonization and education can optimize biosimilar adoption and healthcare sustainability.

Keywords: Rituximab, Trastuzumab, Biosimilars, Switching, Monoclonal Antibodies.

Introduction

Biosimilars are biologic products that are highly similar to reference biologics in safety, efficacy and quality. The use of biosimilars is informed by an aim to decrease the overall cost of healthcare and increase the availability of biologic products[1,2]. These biosimilars have incorporated the use in the treatment of hematological malignancies and HER2 positive breast cancer[3] The use of biosimilar versions of monoclonal antibodies, particularly rituximab and trastuzumab, which have already received significant attention in oncology and hematology, has now become widespread due to the existence for saving costs and increasing the availability of treatment[4,5] However, this transition is not without its problems, as areas of issues and controversy can be identified as clinical equivalence issues, immunogenicity, stakeholder perceptions and issues[6,7]. The objective of this review was to analyze data regarding biosimilar use and barriers to accessing them, with regard to rituximab and trastuzumab.

Clinical Evidence Supporting Biosimilar Use:

Rituximab (RTX and trastuzumab (TRA) are monoclonal antibodies (mAbs) used in combination with chemotherapy for treating various cancers.[8] RTX, approved in the USA in 1997 and in the EU in 1998, is used for CD20-positive hematological cancers like B-cell non-Hodgkin lymphomas (NHL), including follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and chronic lymphocytic leukemia (CLL). It is also indicated for autoimmune diseases such as rheumatoid arthritis [8]. To prove clinical similarity between a proposed biosimilar and its reference biologic, studies comparing pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, efficacy, and safety are required, often using an equivalence design. This article discusses

rituximab's role in chronic lymphocytic leukemia (CLL) treatment and explores the potential utility of rituximab biosimilars. The evidence suggests that rituximab biosimilars are comparable in efficacy and safety to the originator drug in treating CLL. Several biosimilars are in clinical development, and phase 3 trials have shown no significant differences in treatment outcomes, including progression-free survival and overall survival, between the biosimilars and the reference rituximab.[9] Rituximab levels are measured using ELISA-based assays that detect the rituximab idiotype in its murine region. It's crucial to distinguish between free and CD20-bound rituximab when analysing pharmacokinetics with anti-idiotype antibodies. Circulating CD20, which can bind to rituximab and affect drug levels and clinical response, may be found in patients with hematological cancers. Additionally, 'CD20 shaving,' where rituximab binding removes CD20 from B cells, may reduce B cell killing. The exact process of rituximab degradation and elimination is unclear, but its pharmacokinetics is typically modeled with a two-compartment system, having distribution and elimination half-lives of about 1.3 and 19 days, respectively. Focuses on rituximab biosimilars, highlighting the clinical evidence regarding their use in autoimmune diseases and oncology. The authors emphasize that rituximab biosimilars have demonstrated similar efficacy and safety profiles to the original drug in clinical trials, including treatment for rheumatoid arthritis and non-Hodgkin lymphoma. The data suggest that these biosimilars are an effective alternative to the reference product, with no major safety concerns.[10]

Trastuzumab (TRA), approved in 1999, is used for HER2-positive cancers like breast and gastric cancer under the brand name Herceptin. Studies have demonstrated that both drugs and biosimilars show pharmacokinetic (PK) similarity, efficacy, and safety profiles. The article also highlights that biosimilars for trastuzumab have shown comparable PK profiles to the reference product, and clinical trials support their equivalence in efficacy and safety in the treatment of HER2-positive breast cancer. The safety profile and clinical outcomes are consistent with those of the originator drugs.[8] Trastuzumab significantly improves overall survival (OS) and disease-free survival (DFS) in HER2-positive breast cancer. In early-stage HER2+ breast cancer, one year of treatment enhances both DFS and OS. For metastatic breast cancer, adding trastuzumab to chemotherapy increases response rates and OS. The trastuzumab-taxane combination is the standard first-line treatment for metastatic cases. HER2 double blockade with chemotherapy is more effective than trastuzumab alone. Both intravenous trastuzumab and its biosimilars improve OS and response rates, with no significant difference in efficacy between intravenous and subcutaneous forms in early-stage HER2+ breast cancer. The review shows that trastuzumab biosimilars, including SB3, CT-P6, and MYL-1401O, have demonstrated non-inferiority or equivalence in terms of efficacy and safety compared to the reference trastuzumab. The studies support the use of these biosimilars for HER2 positive breast cancer, with no significant differences in outcomes related to progression-free survival or overall survival.[11] An overview of clinical studies related to trastuzumab biosimilars in oncology. It emphasizes that phase 3 trials for trastuzumab biosimilars have shown that they meet the necessary clinical endpoints for equivalence, including progression-free survival and overall survival in HER2-positive breast cancer. The trials also confirm that trastuzumab biosimilars have a similar safety profile to the reference drug, with no new or unexpected adverse events.[12]

Economic Evidence for Biosimilars:

The cost-saving potential of switching from reference biologics to biosimilars, such as rituximab and trastuzumab, is substantial. Studies have examined the cost-saving potential of switching from a reference biologic to a biosimilar, like rituximab, for Non-Hodgkin's lymphoma therapy. It found no significant differences in safety outcomes between patients who switched and those exclusively on the biosimilar. This suggests biosimilars can reduce costs without compromising patient safety.[13] The economic analysis revealed that biosimilars provide significant cost savings compared to their originator counterparts, with rituximab biosimilars offering an economic advantage of 274 € per month, while trastuzumab biosimilars show savings ranging from 3,283 € to 6,310 € per month for time to treatment failure (TTF), which is approximately 40% less than the originator. The study concluded that when combining the pharmacological costs of biosimilars with their efficacy measures, such as TTF and pathological complete response (pCR), both rituximab and trastuzumab biosimilars are considered cost-effective treatment options for advanced follicular lymphoma and breast cancer.[14] The budget impact analysis shows that adopting intravenous biosimilars like rituximab and trastuzumab offers significant cost savings, ranging from €4.05 million to €303.86 million for rituximab and €19 million to €172 million for trastuzumab over five years. These savings could expand patient access, enabling treatment for thousands more patients. Biosimilars may also foster price competition, reducing costs for reference biologics and enhancing affordability. Financial savings could support hiring more healthcare professionals, improving resource utilization and reducing wait times. In conclusion, biosimilars provide a valuable opportunity to improve cost-effectiveness and patient access in healthcare systems.[15] This presents a significant economic opportunity for health authorities worldwide. The projected cumulative budget savings also promise to enhance patient accessibility to treatments.[16] The evaluation of biosimilars in oncology and hematology demonstrated the cost-effectiveness of rituximab and trastuzumab biosimilars.[17] Cedars-Sinai Health System standardized the utilization of biosimilars, conducting a systematic literature review on the economic impact of non-medical switching. The review highlighted significant gaps in understanding costs and healthcare resource utilization. These findings underscore the need for further research to optimize biosimilar adoption and assess their broader economic implication.[18] The study examines the impact of oncology biosimilars on financial risk in value-based payment (VBP) models, filling a gap in research focused on budget

impacts. Using simulation models of Medicare's Oncology Care Model (OCM) with real-world data, biosimilars were shown to reduce costs by approximately $1,200 per episode. Substitution decreased practices exceeding benchmark costs by 33% and increased those below target costs by 42%. Scenario analyses indicated that strategic biosimilar adoption could boost savings to $2,700 per episode. The findings highlight biosimilar's potential to enhance financial sustainability, reduce provider risks, and inform policy for oncology care delivery.[19]

Regulatory aspects:

The regulatory framework for biosimilars plays a crucial role in ensuring their safety, efficacy, and quality while facilitating their adoption into clinical practice. The approval process for biosimilars involves rigorous comparison studies with the reference biologic, encompassing analytical characterization, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and clinical efficacy. The regulatory aspects of biosimilars discussed in the article highlight the complexities involved in ensuring that biosimilars meet the necessary standards of quality, safety, and efficacy. Biosimilars are biological medicinal products that closely resemble an already authorized original biological product (reference product). Unlike generic drugs, which are chemically synthesized, biosimilars are produced using living cells and are therefore more complex. To gain regulatory approval, biosimilars must undergo rigorous comparability exercises, including analytical, functional, and clinical evaluations. These exercises are necessary to demonstrate that there are no clinically meaningful differences between the biosimilar and the reference product. This process involves extensive characterization studies, non-clinical evaluations, and at least one clinical trial to confirm biosimilarity. Key regulatory agencies such as the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have established specific guidelines for the approval of biosimilars. The EMA was the first to implement a framework for biosimilar approval in 2003, followed by the FDA in 2015. These agencies emphasize the importance of a stepwise approach to biosimilar development, focusing on quality comparability, pharmacokinetic (PK) and pharmacodynamic (PD) studies, and immunogenicity assessments. Post-marketing pharmacovigilance plays a crucial role in monitoring the safety of biosimilars. Despite rigorous pre-approval testing, the potential for rare adverse events necessitates ongoing surveillance to ensure long-term safety and efficacy. Biosimilars are also subject to additional monitoring during the early years of their market presence. Controversies surrounding biosimilars include issues of immunogenicity, extrapolation of indications, interchangeability, and automatic substitution. Immunogenicity refers to the potential for biosimilars to elicit immune responses, which can impact safety and efficacy. Regulatory agencies require comprehensive studies to assess this risk. Extrapolation of indications allows biosimilars to be approved for multiple therapeutic uses based on evidence from one clinical study. However, this practice is often debated, as some healthcare professionals express concerns about the lack of direct evidence for certain indications. Interchangeability and substitution policies vary between regions. In the U.S., interchangeable biosimilars can be substituted at the pharmacy level without prescriber intervention, while in the EU, interchangeability decisions are left to individual member states.[20]

Rituximab:

Patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) are typically treated with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) in addition to the anti-CD20 monoclonal antibody rituximab. One The European Medicines Agency (EMA) approved the rituximab biosimilars (R-biosimilars) CT-P10 and GP2013 in 2017 for the treatment of DLBCL.[21]

Even with better treatment results, non-Hodgkin lymphoma still has a poor prognosis and an unmet demand for new treatments. The mainstay of treatment for B cell NHL is rituximab, and efforts have been made to increase its therapeutic advantages by combining it with cell therapy, such as natural killer cell therapy, or chemotherapy. Rituximab is utilized in antibody-dependent cell-mediated cytotoxicity therapy, which depends on immune cells triggering anticancer cytotoxicity triggered by target cell-associated antibodies. The trial was carried out in compliance with the Good Clinical Practice guidelines of the International Conference on Harmonization as well as any applicable local laws and regulations. The clinical protocol was in accordance with the 1975 Declaration of Helsinki and approved by the Korean Ministry of Food and Drug Safety (protocol MG4101-NHL-P1; October 2, 2018).[22]

Trastuzumab:

The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have approved and adopted biosimilar trastuzumab medicines, such as CT-P6, according to the article's regulatory features. These organizations have worked to improve drug development, allow for modifications to clinical procedures, and make it less difficult for biosimilars to enter the market. The creation and use of biosimilars are highlighted as a way to lower medical expenses and enhance treatment accessibility, especially in underfunded healthcare systems.[23]

EudraCT (Number: 2013-004172-35) and ClinicalTrials.gov (Identifier: NCT02149524) both have clinical trials registered. Review of primary and secondary outcomes for biosimilars based on guidelines. Statistical analysis using equivalency margins for pharmacokinetic and efficacy analysis and carried out in accordance with regulatory-compliant procedures. Adherence to FDA and EMA standards for biosimilar review, which place a strong emphasis on the entirety of the evidence, including clinical, non-clinical, structural, and functional comparisons. Monitoring of long-term safety and effectiveness through prolonged clinical trials in order to meet requirements for biosimilar licensing.[24,25,26]

Due to its expensive cost as a biologic therapy, trastuzumab may prevent some patients from receiving it or discourage some medical professionals from prescribing it. This agent is being scribed. Though the availability and adoption of biosimilars may differ by region, rely on a number of nation-specific factors, and be influenced by the demands of healthcare systems, policymakers, and payers, it is anticipated that the growing availability of biosimilars will significantly lower the costs associated with biologics over the next ten years.[27]

The confirmatory study, a phase III, randomized, double-blind clinical trial comparing the immunogenicity, safety, and effectiveness of Ontruzant SB3 and the reference trastuzumab in patients receiving neoadjuvant therapy for HER2 overexpressed early BC, served as the basis for the regulatory approval.[28]

Biosimilars are pharmaceuticals that, despite slight variations in their inclinically inactive ingredients, are very similar to their reference biologic drugs. Biosimilars, like hematopoietic growth factors (e.g., filgrastim, erythropoie-tin), are currently being employed in clinical practice for the supportive care of patients with cancer. One The monoclonal antibodies (mAbs) trastuzumab, rituximab, cetuximab, and bevacizumab will no longer be the only biologics used to treat cancer patients in the coming years. Biosimilar mAbs can now be approved by regulatory bodies and go into clinical use thanks to this loss of exclusivity. Clinicians, pharmacists, patients, and their caregivers may find it very beneficial to be aware of these impending changes in order to make sure that less expensive alternatives allow healthcare systems to save money.[29]

Global Harmonization:

1. Rituximab:

The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) take distinct tacks. Member states make the decision about interchangeability; the EMA does not make a distinction between biosimilars and interchangeable products. Global alignment is made more difficult by the FDA's explicit definition of biosimilar interchangeability standards.[30]

2. Trastuzumab:

Although organizations such as the FDA and EMA have overseen the approval and use of trastuzumab, regional differences in regulatory standards still exist. To guarantee consistent criteria for biosimilar review, approval, and post-marketing surveillance, it is imperative to harmonize international regulatory regimes.[31]

Interchangeability Designations:

Biosimilars must meet strict comparability standards to be deemed interchangeable with reference biologics.

1. Rituximab:

Product switching is still a problem. Switching between reference rituximab and its biosimilars, or between various biosimilars, was safe and did not increase adverse events, according to observational studies like the one conducted at Trento General Hospital.[30]

2. Trastuzumab:

Without a prescription, pharmacy-level substitution is permitted in the United States due to FDA interchangeability. Although EMA standards do not permit automatic substitution, they do place a strong emphasis on manufacturing uniformity and equivalency in clinical trials. Due to worries regarding safety and efficacy, a lack of interchangeability designation makes adoption more difficult and causes reluctance among patients and prescriber.[31] The WHO has promoted the trastuzumab in the List of Essential Medicines to facilitate worldwide access and consistency in standards.[32]

Post-Marketing Surveillance:

Continuous monitoring of biosimilars is essential to detect any long-term differences in efficacy, safety, or immunogenicity compared to reference products.

1. Rituximab:

The safety profile of rituximab biosimilars has been bolstered by observational studies and real-world evidence, with adverse event rates that are equivalent to those of the original product. With this surveillance, switching issues are addressed and trust in the use of biosimilars is increased.[30]

2. Trastuzumab:

Robust post-marketing surveillance systems are necessary to monitor the long-term safety and efficacy of biosimilars. Both FDA and EMA require pharmacovigilance plans to track real-world performance. Ongoing surveillance data have demonstrated comparable safety, efficacy, and immunogenicity to the reference product, bolstering confidence in biosimilar use.

Challenges in Regulation:

- Trust and Acceptance
- Economic Barriers
- Variability in Guidelines
- Lack of Education and Training
- Regulatory Divergence

Challenges in Switching:

Conversion from originator drugs to biosimilars still has challenges that act as barrier to their use. These challenges arise due to factors as stereoscopy in health, stakeholder attitudes, immunological issues, and cost. These issues must be tackled to optimise outcomes from biosimilars and make them accessible to many patients as well as efficient in the overall system. The challenges can be categorised under: perceived barriers by the physicians, perceived barriers by the patient, immunological safe guard and constraints accruing to cost.

1. Physician related:

The use of trastuzumab has barriers across the world due to physician aspects which consists of gaining the treatment and cost. The implementation of HER2-directed therapies has increased according to the survey of physicians compared to that of attainable of reduced cost of biosimilar HER2 monoclonal antibody.[33]

2. Health care system related:

The study in each countries are varied by the healthcare system. In Turkish system, it is mainly based on government and directed by Ministry of Health. Social security system is the one who funds the centralized coverage that depends on the employee, employer and government contributions. Availability of biosimilar in trastuzumab are advantageous to HER2+ breast cancer patients.[33]

3. Patient related:

The patients are also participating in making decisions and treatment options and the physicians also decides the main treatment. The impact of the treatment adherence and treatment outcomes are based on the opinion of biosimilars. The patients to be educated about biosimilars in a clear manner.[34]

4. Immunological related:

Through studies, they had concluded that multiple switching leads to contraindications. The multiple switching can leads to contraindications which has minute structural differences. The patient's immune system detects the drug as an foreign body and that leads to immunological reactions.[31]

5. Cost related:

The cost of anticancer monoclonal antibodies are high which are trouble to both public and private health care systems. 20-30% is estimated as cost of trastuzumab biosimilars which is decreased to the reference product. There is no clinical significance in safety, efficacy and immunogenicity which has been compared with that of reference product.[31] The biological products which are identical to reference product with their safety, potency and efficacy. Health costs are decreased and higher in global access to the cancer treatment. Safety and efficacy profile of rituximab in HER2 positive breast cancer which is higher in cost as a barrier. The CT-P6 biosimilar is efficacious and rituximab has cardiac safety in HER2-positive early breast cancer (EBC) and metastatic breast cancer (MBC). The use of biosimilars are increased such as CT-P6 has the potential to increase the access to life-extending treatment for women with HER-2 positive breast cancer.[36]

Future Prospectives:

1. Regulatory and Policy Reforms:

New biosimilars are probably going to be made available as alternate treatment alternatives as more original biological medications approach the end of their patent protection periods. Wider use of biosimilar medications should result from increased accessibility and knowledge of biosimilar principles. Utilizing biosimilar rituximab could free up funds so that medical systems can offer more costly and cutting-edge new treatments.[37]

2. Expanding Biosimilar Applications:

In an effort to make this medication more affordable, pharmaceutical companies are creating biosimilars of trastuzumab, and the number of registered phase III clinical trials awaiting regulatory agency approval is increasing annually. However, efforts should be directed toward creating biosimilars for other monoclonal antibodies used in Breast Cancer treatment so that patients worldwide can receive the right treatment.[38]

Next-generation mAbs will face additional difficulties in terms of characterisation, manufacturing, comprehending the CQAs, and creating a suitable control plan. Over time, additional isotypes, including IgM, IgE, IgA, and IgG3, have been developed in preclinical and clinical settings, especially for oncology applications, in addition to these products.[39]

3. Innovations in Treatment Strategies:

The effect of rituximab on response rates for other vaccines requires more investigation. Additionally, our study lacked the power to identify variations in adverse events, such as infection rates, engraftment times, and immune reconstitution times. It is necessary to conduct larger prospective trials that evaluate graft and patient survival in addition to long-term clinical outcomes in future aspects.[40]

The development of RIT and rituximab has significantly increased the range of treatment choices available for follicular lymphoma and opened up exciting new avenues for study. We think that more advancements are still possible, even though combination therapies that assess RIT with chemotherapy and extended rituximab treatment are likely to enhance the prognosis for individuals with indolent lymphomas.[41]

Immuno-oncology is a developing therapeutic approach, with drugs being researched for their capacity to offer sustained survival for a variety of tumor types as well as their ability to work in concert with other therapeutic approaches. Now, it's critical to ascertain how Combinations of immuno-oncology to progress this area and learn the best ways to employ these novel immunotherapies to provide the greatest possible results for patients. Now, it's critical to ascertain how Combinations of immuno-oncology to progress this area and learn the best ways to employ these novel immunotherapies to provide the greatest possible results for patients. Now, with the limited data and the rather unexpected appearance of toxicity with certain combos (e.g., ipilimumab and vemurafenib), it is challenging to determine which combination techniques are best to pursue. Data from early clinical trials will be used to guide future research.[42]

Conclusion:

The transition from originator drugs to biosimilars, particularly in the context of monoclonal antibodies such as rituximab and trastuzumab, represents a significant advancement in the accessibility and affordability of

cancer and autoimmune disease treatments. This comprehensive review highlights the robust clinical evidence supporting the safety and efficacy of biosimilars, their economic advantages, and the rigorous regulatory frameworks ensuring their quality. While biosimilars offer a cost-effective alternative, challenges such as immunogenicity concerns, varying regulatory standards, and stakeholder perceptions must be addressed to maximize their impact. Future efforts should focus on global regulatory harmonization, education for healthcare professionals and patients, and the development of next-generation biosimilars. By overcoming these barriers, biosimilars have the potential to enhance healthcare sustainability and broaden treatment access, ultimately improving patient outcomes across diverse healthcare systems.

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