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Biosimilars in Focus: Evaluating Their Role Compared to Adalimumab in Clinical Practice

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Abstract:
Introduction and Purpose: Adalimumab, a TNF-α inhibitor, is a cornerstone treatment for autoimmune and inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease. Despite its efficacy, the high cost of adalimumab (Humira®) limits accessibility. The emergence of biosimilars offers cost-effective alternatives with comparable efficacy, safety, and immunogenicity. This article reviews the role of adalimumab biosimilars, their clinical equivalence, and potential to address healthcare challenges.
Materials and Methods: A comprehensive literature review was conducted to evaluate the structural, functional, and clinical parity of adalimumab biosimilars with the reference product. Key studies on pharmacokinetics, efficacy, safety, therapeutic drug monitoring (TDM), and real-world outcomes were analyzed.
Results: Adalimumab biosimilars demonstrate equivalent pharmacokinetic profiles and clinical efficacy across conditions, with comparable remission rates and safety profiles. Innovations, such as citrate-free formulations and advanced delivery devices, enhance patient adherence. Biosimilars significantly reduce treatment costs, increasing accessibility, especially in resource-constrained settings. Challenges remain in patient acceptance and managing therapy transitions.
Conclusion: Biosimilars are transformative in addressing the cost barrier of biologic therapies, maintaining therapeutic equivalence to adalimumab while expanding access globally. Enhanced TDM and patient-centered strategies are essential for optimizing outcomes and maximizing their adoption in clinical practice.

Keywords: adalimumab, biosimilars, Inflammatory Bowel Disease, ankylosing spondylitis, TNF-alpha (TNF-α), Rheumatoid arthritis (RA), hidradenitis suppurativa

1. Introduction

Adalimumab, as the first fully human monoclonal antibody targeting tumor necrosis factor-alpha (TNF-α), plays a pivotal role in the treatment of numerous inflammatory and autoimmune diseases. Its mechanism of action involves the inhibition of TNF-α, a key cytokine involved in the inflammatory process, effectively reducing inflammation and alleviating symptoms in affected patients. Since its approval and market introduction in 2003 in both the United States and Europe, adalimumab (marketed under the trade name Humira®) has become one of the most prescribed biologics worldwide. It is widely used for treating conditions such as rheumatoid arthritis (RA), psoriasis, psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel diseases (IBD) including Crohn's disease and ulcerative colitis. The versatility of adalimumab's therapeutic indications, coupled with its clinical effectiveness, has cemented its status as a cornerstone therapy in managing these chronic and often debilitating conditions. Over the years, Humira® has maintained a dominant presence in the biologics market, achieving record sales exceeding $20 billion in 2021 [1].

However, the high cost of adalimumab has presented a significant barrier to accessibility for many patients globally. Recognizing this challenge, the expiration of its primary patents in Europe in 2018 and later in the United States opened opportunities for the introduction of biosimilars - biological products that are highly similar to the original reference product.

Biosimilars are required to demonstrate no clinically meaningful differences in terms of efficacy, safety, and immunogenicity when compared to the reference biologic. These agents offer the potential for cost savings while maintaining therapeutic equivalence. As of now, the European market has embraced eight adalimumab biosimilars, including Amgevita®, Imraldi®, Yuflyma®, and Hyrimoz®, which have contributed to enhanced accessibility to biologic therapies. In contrast, due to prolonged patent protections in the United States, adalimumab biosimilars became available only in 2023, marking a significant shift in the U.S. biologics landscape [1]. The introduction of adalimumab biosimilars has generated new challenges for healthcare providers and patients. While these products are structurally and functionally comparable to the reference product, minor differences in their formulations, excipients, and delivery devices may influence patient preferences and clinical outcomes. For example, some biosimilars offer citrate-free formulations, which are associated with reduced injection-site pain, or higher-concentration solutions that enable smaller injection volumes. Additionally, variations in the design of delivery devices, such as prefilled pens versus syringes, may affect ease of use and patient satisfaction. These differences necessitate thorough discussions between healthcare providers and patients to ensure optimal treatment adherence and outcomes. Furthermore, the emergence of biosimilars has introduced the potential for cost competition and expanded the availability of biologic therapies to a broader population, addressing an important barrier to care [2].

A critical step in the development of biosimilars is the demonstration of pharmacokinetic (PK) and pharmacodynamic (PD) similarity to the reference product. Population pharmacokinetic (PPK) analyses have played a pivotal role in evaluating biosimilar candidates, such as adalimumab-adbm (Cyltezo®). Studies have confirmed that adalimumab-adbm exhibits highly similar PK profiles compared to Humira®. Key findings from clinical trials include comparable maximum concentrations (Cmax) and area under the curve (AUC) values, both of which fall within standard bioequivalence ranges of 80–125%. Additionally, these studies found no significant differences in the immunogenicity profiles or the presence of anti-drug antibodies (ADAs) between adalimumab-adbm and Humira®. Long-term extension trials have further demonstrated that switching from Humira® to adalimumab-adbm does not negatively impact PK parameters or treatment efficacy. These findings are crucial for fostering confidence in the interchangeability of biosimilars, an important consideration for regulatory approvals and clinical practice [3].

2. Overview of Adalimumab

2.1 Mechanism of Action and Clinical Applications

Adalimumab is a fully human monoclonal antibody IgG1 that specifically targets tumor necrosis factor-alpha (TNF-α), a key mediator of inflammation and immune regulation in autoimmune diseases. [4] By binding TNF-α, adalimumab neutralizes its effects, preventing it from activating its receptors (TNFR1 and TNFR2), thereby reducing inflammatory responses [5]. This mechanism underlies its broad application across various immune-mediated diseases. Adalimumab is FDA-approved for numerous indications, including:

- **Rheumatoid Arthritis (RA)**: Used to control symptoms and prevent joint damage in moderate-to-severe cases.

Inflammatory Bowel Diseases: Effective in inducing and maintaining remission in Crohn's disease and ulcerative colitis.

Plaque Psoriasis, Psoriatic Arthritis, and Ankylosing Spondylitis: Targets skin and joint inflammation, reducing disease severity.

Uveitis and Hidradenitis Suppurativa: The only approved biologic for these conditions, offering significant clinical benefits [4].

In addition to neutralizing TNF-α, adalimumab facilitates mechanisms such as complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC), which contribute to its efficacy in inflammatory bowel disease-related actions [4].

2.2 Safety and Efficacy: Reference Adalimumab and Biosimilars

Efficacy Profile

Clinical trials have demonstrated adalimumab's robust efficacy across its approved indications. Key trials, such as ADACCESS and ADMYRA, have also verified equivalent efficacy between reference adalimumab (REF-ADL) and its biosimilars. For example:

ADACCESS: Demonstrated equivalence in efficacy and safety between REF-ADL and GP2017 in treating plaque psoriasis [4].

ADMYRA: Validated biosimilar effectiveness in rheumatoid arthritis with no notable safety or immunogenicity differences after transitioning from REF-ADL [4].

Further, biosimilar adalimumab-aqvh (YUSIMRY™) has undergone extensive testing to confirm its physicochemical, structural, and functional equivalence to REF-ADL. Studies established its similarity in primary structure, disulfide bonding, glycan profiles, and biological activity, such as TNF-α neutralization and ADCC [5]. Any minor differences observed in glycan attributes (e.g., terminal galactosylation) did not translate into functional or clinical disparities [5].

Safety Profile

Adalimumab and its biosimilars have shown comparable safety profiles. Common adverse effects include mild injection-site reactions and increased susceptibility to infections. Biosimilar-specific studies, such as those involving adalimumab-aqvh, have confirmed no meaningful differences in safety outcomes. Moreover, TDM tools like LISA-TRACKER ensure safety by monitoring drug levels and immunogenicity, minimizing risks associated with treatment failure or adverse reactions [5][6].

2.3 Advances in Therapeutic Drug Monitoring (TDM)

The integration of TDM has revolutionized adalimumab therapy by enabling precise measurement of drug concentrations and anti-drug antibodies (ADAs). Tools like LISA-TRACKER assays quantify trough levels of adalimumab and detect ADAs, helping clinicians optimize treatment strategies. [6].

Key benefits of TDM include:

Prevention of Treatment Failure: Early detection of subtherapeutic drug levels or ADAs allows timely dose adjustments.

Enhanced Safety: Prevents complications related to immunogenicity.

Support for Biosimilar Adoption: Ensures comparable efficacy and safety during transitions between reference products and biosimilars.

Studies employing TDM have highlighted its role in reducing unnecessary dose escalations while maintaining clinical outcomes [6]. For example, adalimumab-aqvh demonstrated consistent performance across various TDM parameters, such as stability under stress conditions and immunogenicity detection [5].

2.4 Biosimilars: Expanding Access and Cost-Efficiency

Role of Biosimilars

The expiration of adalimumab's patents has catalyzed the development of biosimilars like ABP501 (Amgevita®) and adalimumab-aqvh (YUSIMRY™). Biosimilars offer cost-effective alternatives without compromising therapeutic efficacy or safety [5][6]. Analytical studies confirm that biosimilars undergo rigorous testing to demonstrate equivalence in structure, function, and clinical outcomes:

Structural Similarity: Adalimumab-aqvh shares identical amino acid sequences, disulfide bonds, and glycan profiles with REF-ADL. Variations in glycan features, such as sialic acid levels, were minimal and clinically irrelevant [5].

Functional Similarity: Both reference and biosimilar products showed comparable results in assays measuring TNF-α binding, neutralization, and Fc-mediated activities like ADCC and CDC [5].

Stability and Degradation Profiles: Forced degradation studies confirmed that biosimilars remain stable under stress conditions, ensuring durability during storage and transport [5].

Clinical Integration

Biosimilars have demonstrated successful integration into clinical practice, as shown in switch studies where patients transitioned from REF-ADL to a biosimilar without significant changes in outcomes [4][6]. For example:

Adalimumab-aqvh exhibited identical pharmacokinetics and immunogenicity to REF-ADL in clinical trials, supporting its FDA approval for indications such as rheumatoid arthritis and Crohn's disease [5].

Future Perspectives

Adalimumab continues to shape the therapeutic landscape for autoimmune diseases, with biosimilars expanding its reach to more patients worldwide. TDM remains pivotal in enhancing patient outcomes by guiding dose adjustments and supporting biosimilar adoption. Biosimilar advancements, such as those demonstrated by adalimumab-aqvh, highlight the potential for high-quality, cost-effective alternatives that maintain therapeutic equivalence [5][6].

As healthcare systems increasingly prioritize affordability without compromising quality, biosimilars like adalimumab-aqvh are set to play a transformative role. By ensuring structural, functional, and clinical parity with REF-ADL, these products address critical challenges in global healthcare access. [5]

3. Biosimilars – Introduction

3.1 Definition and Characteristics of Biosimilar Drugs

Biosimilars are biologic drugs that are highly similar to an already approved reference product (RP) in terms of quality, safety, and efficacy, but are manufactured by different entities. Unlike traditional generic drugs, which are chemically synthesized and identical to their originators, biosimilars are produced in living systems, resulting in minor natural variability between the biosimilar and its RP. This inherent variability necessitates rigorous testing to confirm that these differences are not clinically meaningful. Biosimilars share the same amino acid sequence as their RPs, ensuring they perform the same therapeutic functions [7].

To illustrate, AVT02, a biosimilar to high-concentration adalimumab (Humira®), underwent extensive analytical, structural, and functional evaluations to establish its similarity to the RP. Analytical methods demonstrated identical amino acid sequences and comparable structural attributes, including glycosylation and post-translational modifications. These evaluations confirmed no clinically meaningful differences in key attributes, such as binding affinities or functional activities, despite minor physiochemical variations [7].

The characteristics of biosimilars are particularly relevant in addressing injection-related patient experiences. Factors like formulation, delivery volume, and device features (e.g., needle gauge size) significantly impact patient satisfaction and adherence. For example, subcutaneous administration of biologics, such as adalimumab, can cause injection-site pain (ISP). Citrate-free formulations are generally associated with reduced ISP, enhancing patient comfort and compliance. This improvement in formulation, along with advanced delivery systems like pre-filled syringes (PFS) and pre-filled pens (PFP), has been integral in improving patient outcomes with biosimilars like AVT02 [2].

3.2 The Development Process and Regulations Governing Biosimilars

The development of a biosimilar follows a systematic, stepwise approach rooted in the "totality of evidence" framework. This process involves comparative analyses at multiple levels: analytical, preclinical, and clinical. Regulatory agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require comprehensive similarity exercises to ensure biosimilars meet stringent safety and efficacy standards [7].

Key stages in biosimilar development include:

1. **Analytical Comparisons**

   Detailed analyses of primary and higher-order structures, post-translational modifications, and physiochemical stability are performed. For example, AVT02 underwent extensive orthogonal testing to confirm its alignment with the RP across these parameters [7]. These assessments also include evaluation of pH and buffer composition, as variations can influence the product's stability and tolerability. Citrate and phosphate buffers are commonly used, but newer biosimilars often employ alternatives to minimize ISP [2].

2. **Functional Comparisons**

Functional bioassays and potency studies ensure that the biosimilar's mechanism of action mirrors that of the RP. AVT02, for instance, demonstrated comparable neutralization of soluble TNF-α and consistent interactions with Fc receptors, aligning with the therapeutic mechanisms of Humira® [7]. Such functional evaluations also address potential variabilities in glycosylation and post-translational modifications, critical to maintaining therapeutic efficacy [2].

3. **Clinical Studies**

Comparative clinical trials verify pharmacokinetic (PK) equivalence, safety, and immunogenicity. AVT02 met PK equivalence criteria and exhibited similar efficacy and safety profiles in patients with chronic plaque psoriasis. These clinical outcomes are supported by comprehensive patient-reported assessments, which often include factors like ISP, adherence, and injection device preferences [2].

3.3 Explanation of the Differences Between Biosimilars and Generic Drugs

While both biosimilars and generic drugs aim to provide more affordable treatment options, their production and evaluation differ significantly due to the complexity of biologic therapies. Generic drugs are small-molecule medicines with identical chemical compositions to their reference products. In contrast, biosimilars are large, complex molecules produced in living cells, making them inherently variable. This variability demands sophisticated manufacturing technologies and extensive comparative analyses to ensure biosimilarity [7].

The regulatory pathways for biosimilars also diverge from generics, focusing on comprehensive analytical and functional assessments rather than duplicating clinical trials for every indication. For example, the clinical data for AVT02 in treating chronic plaque psoriasis were extrapolated to all approved indications of Humira®, leveraging shared mechanisms of action and analytical comparability [7]. This streamlined approval process is critical in reducing costs and increasing patient access to biologic therapies [2].

Moreover, advancements in biosimilar delivery devices have enhanced patient convenience and satisfaction. High-concentration solutions, such as those offered by some adalimumab biosimilars, allow smaller injection volumes, reducing ISP. Devices like PFPs, with features such as smaller needle gauges and intuitive designs, further contribute to improved patient experiences. Varying needle gauges also have significant impact on patient experiences while taking medication, as smaller outer diameter is directly correlated with less pain on injection. It is important to take into consideration both inner and outer diameters - for example, 29-G thin-walled needle has significantly smaller outer diameter compared to 27-G regular-walled needle, but both have similar inner diameters. (Figure 1). That allows using the same force to the injection device to administer medicine as it passes through the same cylinder size [2].

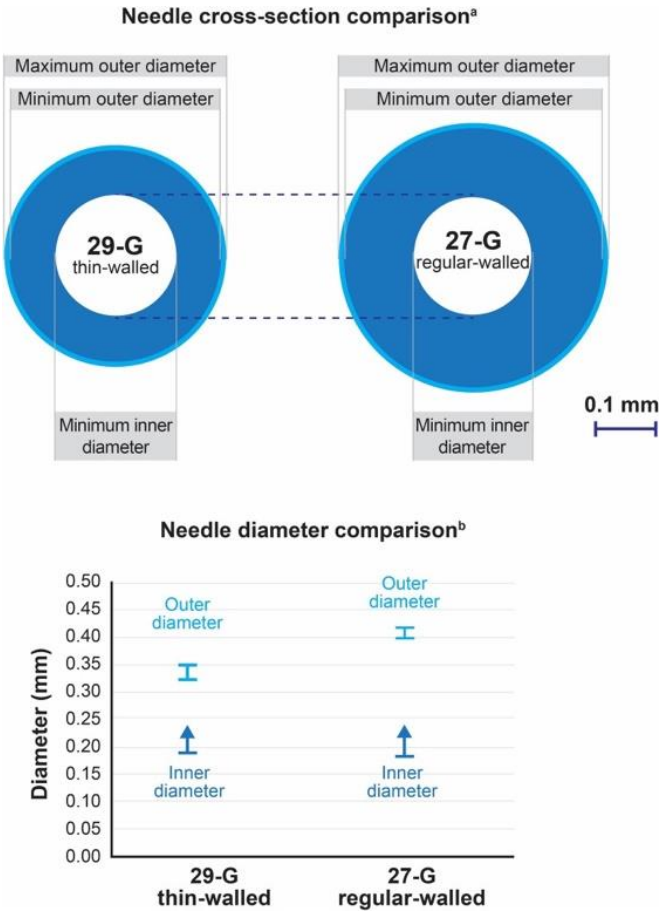

Figure 1. Comparison of 29-G thin-walled and 27-G regular-walled needle diameters. [a]The 29-G thin-walled and 27-G regular-walled needles have different outer diameters, but a comparable inner diameter. Therefore, patients can apply the same force to the injection device to administer medicine at the same speed because it passes through the same size area. [b]The 29-G thin-walled needle measurements are based on the needle used in AbriladaTM (adalimumab-afzb). The outer diameter measurements relate to all 29-G and 27-G needles; however, the inner diameter measurement may not be representative of needles used with other ADL products. ADL adalimumab; G gauge [2]

4. Comparison of Adalimumab with Biosimilars

4.1 Clinical Efficacy

Results of Clinical Trials

Clinical trials and real-world studies consistently demonstrate the equivalence of adalimumab biosimilars to the originator drug (Humira®) in managing inflammatory diseases such as ankylosing spondylitis (AS) and inflammatory bowel disease (IBD). Notably, a phase 3 trial with Chinese AS patients treated with HS016 showed rapid symptom improvement and similar HAQ-S score reductions to adalimumab [8]. In IBD, both HS016 and GP2017 demonstrated remission maintenance rates comparable to the originator, with GP2017 achieving 78.8% remission maintenance at 12 months among patients switching from Humira® [9].

The PROPER study confirmed these outcomes, showing high persistence rates with SB5 at 48 weeks across RA (86.0%), axial spondyloarthritis (axSpA, 80.0%), psoriatic arthritis (PsA, 81.0%), and Crohn's disease (CD, 70.7%) cohorts [10].

Further evidence from the **SURPASS study** highlighted that SDZ-ADL (an adalimumab biosimilar) offers significant benefits in managing AS, particularly in reducing radiographic spinal progression over 104 weeks. SDZ-ADL demonstrated low progression in the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), confirming its efficacy in minimizing structural damage and maintaining clinical remission [11].

Impact on Disease Remission Rates

Biosimilars maintain high remission rates across diseases. In AS, 85% of HS016-treated patients achieved an ASAS20 response at week 24 [8], while in IBD, 68.1% of GP2017-treated patients achieved steroid-free remission at 12 months [9]. Data from the PROPER study emphasize the effectiveness of SB5 in sustaining remission across multiple indications, with no significant disease activity score changes over time [10]. Additionally, the SURPASS study underscores the equivalence of SDZ-ADL in achieving remission and reducing new syndesmophyte development in AS, achieving comparable rates to IL-17A inhibitors [11].

However, disease-specific challenges persist. For example, 20.2% of hidradenitis suppurativa (HS) patients switching to ABP 501 experienced a loss of response (LoR) [12]. Similarly, female sex was identified in the PROPER study as a predictor of biosimilar discontinuation, emphasizing the need for tailored therapeutic strategies [10].

4.2. Safety

Analysis of Reported Adverse Effects

The safety profiles of adalimumab biosimilars align closely with the originator, with mild injection-site reactions, fatigue, and nasopharyngitis being the most common adverse events (AEs) [8][13][9]. The PROPER study further confirmed these findings, with 24.3% of patients experiencing at least one ADR, predominantly mild injection-site reactions (16.4%) [10]. Similarly, the SURPASS study reported a favorable safety profile for SDZ-ADL, with no new safety signals observed over two years [11].

Immunogenicity of Adalimumab vs. Biosimilars

Biosimilars like SB5 exhibit low immunogenicity. The PROPER study found no significant changes in anti-drug antibody (ADA) formation post-transition, reinforcing their reliability [10]. Data from the SURPASS study suggest that SDZ-ADL maintains low immunogenicity over extended treatment periods, critical for long-term disease management [11].

4.3 Economics

Cost of Therapy with Adalimumab vs. Biosimilars

Biosimilars like HS016 and SB5 significantly reduce treatment costs, enhancing affordability and access [8][13][10]. In PROPER, 30.8% of participants cited economic considerations as a primary driver for transitioning to SB5. However, psychological factors like the nocebo effect, where patients perceive reduced efficacy due to lower costs, remain a challenge [10].

Impact of Biosimilars on Therapy Accessibility in Different Countries

Biosimilars have transformed access to biologics globally. The availability of SB5 in Europe and HS016 in China has reduced healthcare disparities, ensuring broader access to advanced therapies [8][13][10]. Insights from PROPER and SURPASS emphasize the need for robust health policies integrating biosimilars to address unmet needs in resource-constrained settings [11].

4.4. Practical Issues

Transition from the Reference Drug to a Biosimilar

Transitions to biosimilars are generally effective. The PROPER study reported a 75.6% persistence rate with SB5 at 48 weeks, with the highest rates in RA (86.0%) and lowest in CD (70.7%) [10]. Furthermore, the SURPASS study provided evidence that SDZ-ADL effectively sustains remission in AS while minimizing radiographic progression, affirming its use in long-term disease management [11].

Acceptance of Biosimilars by Patients and Healthcare Providers

Patient and provider acceptance is increasing due to clinical equivalence and cost benefits. The PROPER study showed that over 92% of patients received adequate training on SB5 administration, resulting in high satisfaction with injection simplicity and duration [10]. The SURPASS study echoed these sentiments, demonstrating high adherence and patient satisfaction with SDZ-ADL in a controlled setting [11].

5. Discussion

5.1 Summary of the Comparison: Do Biosimilars Match Adalimumab in Terms of Efficacy and Safety?

The comparative evaluation of biosimilars, including MSB11022 (Idacio®), HS016, ABP 501, BI 695501, and SB5, with the originator adalimumab (Humira®), consistently demonstrates equivalency in efficacy and safety across a variety of conditions. SB5, also known as Hadlima™ or Imraldi™, has been validated in clinical trials for rheumatoid arthritis (RA), psoriasis, Crohn's disease (CD), and ulcerative colitis (UC), achieving comparable outcomes to the originator [14]. Pharmacokinetic (PK) studies and real-world data further support the sustainability of these findings.

For inflammatory bowel disease (IBD), MSB11022 showed no significant differences in fecal calprotectin (P=0.445) and C-reactive protein (P=0.661), maintaining remission rates measured by Harvey-Bradshaw Index (HBI) and Mayo scores [15]. Similarly, HS016 achieved clinical response rates of 75.4%, 73.8%, and 50.8% at 12, 26, and 52 weeks, respectively, with corresponding remission rates of 55.7%, 65.6%, and 45.9% [10]. SB5 exhibited ACR20 response rates of 72.4% at week 24 and 77.8% at week 52 in RA, comparable to the originator [14].

Safety profiles of biosimilars align closely with those of the originator. For example, MSB11022 reported only mild adverse events (AEs) in 2 out of 9 patients [16], while HS016 noted minor AEs, such as rash and fungal otitis externa, in 5.5% of cases [14].

In RA, SB5 reported treatment-emergent adverse events (TEAEs) in 35.8% of patients versus 40.7% in the originator group, with serious adverse events (SAEs) occurring in 1.1% and 2.9% of patients, respectively [14]. Immunogenicity studies confirm no significant differences in anti-drug antibody (ADA) or neutralizing antibody (nAb) rates [14, 16].

In specific conditions such as hidradenitis suppurativa (HS), challenges emerge. A recent multicenter retrospective study observed a fourfold increase in treatment ineffectiveness (HR=3.8; 95% CI: 2.3–6.2, P<0.001) among patients switched from originator to biosimilars [17]. In ankylosing spondylitis (AS), short-term biosimilar adalimumab therapy demonstrated early improvements, with 82% achieving ASAS 20 at week 12. However, this response waned over time, with 56% maintaining improvement at week 24 and 36% at week 36 [18]. These findings suggest disease-specific variations in therapeutic durability, necessitating tailored strategies.

5.2 Importance of the Results for Clinical Practice and the Healthcare System

Biosimilars are pivotal for expanding access to biologic therapies and alleviating financial burdens in healthcare systems. Biosimilars such as MSB11022, HS016, and SB5 provide cost-effective alternatives for managing chronic conditions like RA, IBD, and AS, enabling equitable resource allocation [15, 16].

Real-world evidence, particularly for SB5, underscores its global applicability in conditions like psoriasis and UC, demonstrating comparable remission rates to the originator [14].

Innovations such as citrate-free, high-concentration formulations of biosimilars enhance patient comfort, reduce injection site pain, and improve adherence. For example, SB5's user-friendly autoinjector has been preferred by patients and healthcare professionals, promoting better usability and adherence [14].

The study by Chopra et al. ([18]) offers a compelling perspective on biosimilar utilization in resource-constrained settings. A 10-week regimen of biosimilar adalimumab (Exemptia™) in AS patients yielded significant early improvements in pain and function, as measured by ASAS 20 and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). While responses declined over time, the short-term therapy demonstrated economic feasibility and acceptable safety, emphasizing its utility in low-resource contexts.

In HS, retrospective studies reveal significant efficacy challenges with biosimilar switches, highlighting the need for consistent therapy planning [17]. Moreover, switching back to the originator following biosimilar inefficacy rarely restores therapeutic effectiveness. These findings emphasize minimizing treatment interruptions or switches in diseases with high durability demands.

5.3 Challenges Associated with the Implementation of Biosimilars

Despite their clinical and economic advantages, the uptake of biosimilars faces barriers related to perception, logistics, and regulatory inconsistencies. Patient and clinician concerns about interchangeability and immunogenicity persist, particularly in conditions like HS, where biosimilar switches have shown greater risks of ineffectiveness [15, 17]. Education campaigns and standardized regulatory frameworks are crucial to building trust and ensuring informed adoption.

Logistical challenges, such as regional regulatory disparities and limited long-term real-world data, further complicate biosimilar integration. In AS, proactive therapeutic drug monitoring (TDM) could address efficacy loss observed in short-term regimens, as evidenced by the study on biosimilar adalimumab in AS [18]. Long-term surveillance and post-marketing assessments are necessary to strengthen confidence in biosimilars.

Economic dynamics also play a role. Aggressive pricing strategies by originator manufacturers and insufficient biosimilar adoption incentives hinder their market potential. Policies that balance cost savings with clinical considerations, such as promoting cyclic short-term therapies in AS ([18]), could facilitate broader access to biosimilars.

6. Future Perspectives

6.1 Directions for the Development of Biosimilars

The evolution of biosimilars is accelerating through advances in biotechnology and precision medicine. Innovations such as nanobody technologies exemplify how smaller, more targeted biologics like ozoralizumab can improve patient adherence by reducing dosage frequency while maintaining efficacy [19]. Computational biology and artificial intelligence are also transforming biosimilar development by optimizing molecular stability and mitigating adverse effects [19]. The clinical equivalence demonstrated by AVT02, a biosimilar to adalimumab, in treating chronic plaque psoriasis, underscores the potential of newer biosimilars to match or exceed reference biologics in efficacy and safety [20].

Evidence supporting biosimilar-to-biosimilar switches, such as ABP 501 to SB5 in Crohn's disease, highlights their adaptability and expanding role in diverse therapeutic areas [21].

Despite these advancements, switching between biosimilars or from originators to biosimilars can pose challenges in specific conditions like hidradenitis suppurativa (HS). For instance, a study reported that 58.8% of HS patients switching from originator adalimumab to biosimilars experienced issues such as pain at the injection site or loss of efficacy. Switching back to the originator resolved most problems but sometimes eroded patient confidence in treatment [22]. These findings emphasize the importance of personalized assessments when switching biosimilar therapies.

6.2 Opportunities for Further Reducing the Costs of Biological Therapies

Biosimilars have substantially reduced healthcare costs by offering affordable alternatives to high-cost biologics like adalimumab. Agents such as ABP 501 and SB5 have improved the economic accessibility of treatments without compromising efficacy [19, 21]. Future cost reductions may arise from continuous bioprocessing, single-use bioreactors, and enhanced manufacturing techniques that streamline production [19]. Regulatory harmonization across international markets could expedite biosimilar approvals and broaden patient access [19].

The introduction of high-concentration biosimilars, such as AVT02, has further enhanced cost efficiency by reducing administration times and healthcare resource use, potentially boosting patient compliance [20]. Moreover, evidence from real-world studies, such as those analyzing cost-effectiveness in multiple biosimilar switches, highlights the economic and clinical viability of biosimilars [20, 22].

However, non-medical switching to biosimilars in well-controlled HS patients underscores the need to evaluate potential trade-offs in adherence and efficacy on a case-by-case basis [22].

6.3 Advancement of Comparative Methods in Clinical Studies of Biosimilars

The future of biosimilar research lies in adopting advanced comparative methodologies to ensure robust evaluation of safety, efficacy, and patient-centered outcomes. Omics technologies, including proteomics and transcriptomics, are enabling deeper molecular insights into biosimilar performance [19]. Techniques such as high-resolution mass spectrometry provide precise comparisons, ensuring biosimilar quality and similarity to reference biologics [19].

Real-world evidence (RWE) is crucial in understanding long-term outcomes and addressing clinical uncertainties around biosimilar use in diverse populations. For instance, AVT02 demonstrated equivalent immunogenicity and tolerability compared to its reference product in clinical trials, providing critical data to support its broader adoption [20]. Additionally, adaptive trial designs that allow interim adjustments can optimize resource utilization and expedite biosimilar development [19, 20].

Emerging data on biosimilar-to-biosimilar switches, such as the successful transition between ABP 501 and SB5 in Crohn's disease, reinforce their potential in clinical practice [21]. However, challenges in conditions like HS, where switching can lead to injection-site pain and loss of efficacy, highlight the importance of tailoring decisions to patient-specific factors [22]. Building patient trust and maintaining therapeutic continuity are essential for maximizing the benefits of biosimilar therapies.

7. Conclusions

Adalimumab, a pioneering fully human monoclonal antibody, has set the benchmark in managing autoimmune and inflammatory diseases due to its ability to neutralize TNF-α, offering extensive therapeutic benefits across conditions such as rheumatoid arthritis, inflammatory bowel diseases, psoriasis, and ankylosing spondylitis. However, the high cost of adalimumab has posed significant barriers to accessibility. The introduction of biosimilars following patent expirations has provided clinically equivalent and cost-effective alternatives. Extensive analytical, preclinical, and clinical studies have established the equivalence of biosimilars to adalimumab in terms of safety, efficacy, and immunogenicity, with comparable PK/PD profiles and sustained remission rates. The adoption of biosimilars has been further bolstered by innovations in citrate-free formulations, high-concentration solutions, and advanced delivery devices, which enhance patient adherence and satisfaction. Therapeutic drug monitoring has emerged as a critical tool in optimizing therapy and ensuring effective transitions between reference products and biosimilars.

Biosimilars play a transformative role in expanding access to biologic therapies by providing cost-effective alternatives to adalimumab without compromising quality. They have demonstrated robust clinical performance, particularly in sustaining disease remission and improving patient outcomes in real-world settings. Challenges such as patient and provider perceptions, logistical barriers, and disease-specific considerations like those observed in hidradenitis suppurativa require tailored solutions to maximize biosimilar integration.

Continued advancements in biosimilar development, including cutting-edge manufacturing and real-world evidence generation, will further solidify their role in global healthcare systems. By addressing both economic and clinical demands, biosimilars are poised to enhance healthcare equity and sustainability while maintaining therapeutic parity with reference adalimumab.

Disclosures

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References:

1. Abitbol V, Benkhalifa S, Habauzit C, Marotte H. Navigating adalimumab biosimilars: an expert opinion [published correction appears in J Comp Eff Res. 2024 Feb;13(2):e240003c1. doi: 10.57264/cer-2024-0003c1]. *J Comp Eff Res*. 2023;12(11):e230117. doi:10.57264/cer-2023-0117
2. Allegretti JR, Brady JH, Wicker A, Latymer M, Wells A. Relevance of Adalimumab Product Attributes to Patient Experience in the Biosimilar Era: A Narrative Review. *Adv Ther*. 2024;41(5):1775-1794. doi:10.1007/s12325-024-02818-9
3. Kang J, Eudy-Byrne RJ, Mondick J, Knebel W, Jayadeva G, Liesenfeld KH. Population pharmacokinetics of adalimumab biosimilar adalimumab-adbm and reference product in healthy subjects and patients with rheumatoid arthritis to assess pharmacokinetic similarity. *Br J Clin Pharmacol*. 2020;86(11):2274-2285. doi:10.1111/bcp.14330
4. Gaylis N, Both C, Lemke L, von Richter O, Yamauchi P. 'Totality of Evidence' Approach in the Development of GP2017, an Approved Adalimumab Biosimilar. *Adv Ther*. 2024;41(5):1795-1814. doi:10.1007/s12325-024-02809-w
5. Jiang Y, Arora T, Klakamp S, et al. Demonstration of Physicochemical and Functional Similarity of Biosimilar Adalimumab-aqvh to Adalimumab. *Drugs R D*. 2023;23(4):377-395. doi:10.1007/s40268-023-00437-3

6. Francois F, Naimi L, Roblin X, Berger AE, Paul S. Adalimumab and anti-adalimumab LISA-TRACKER immunoassays performance criteria for therapeutic drug monitoring of adalimumab-amgen biosimilar (ABP501). *BMC Immunol*. 2021;22(1):81. Published 2021 Dec 25. doi:10.1186/s12865-021-00473-1
7. McClellan JE, Ómarsdóttir S, Roy N, Berger V, Michel C, Berti F. The totality of evidence approach in the development of AVT02 (adalimumab), a biosimilar to Humira. *Ther Adv Chronic Dis*. 2024;15:20406223231223286. Published 2024 Jan 19. doi:10.1177/20406223231223286
8. Su J, Li M, He L, et al. Evaluation of adalimumab biosimilar candidate (HS016) in Chinese patients with active ankylosing spondylitis based on a health survey: sub-analysis of a phase 3 study. *Clin Rheumatol*. 2022;41(3):731-739. doi:10.1007/s10067-021-05943-w
9. Vernero M, Bezzio C, Ribaldone DG, et al. Efficacy and Safety of Adalimumab Biosimilar GP2017 in Patients with Inflammatory Bowel Disease. *J Clin Med*. 2023;12(21):6839. Published 2023 Oct 29. doi:10.3390/jcm12216839
10. Müller-Ladner U, Dignass A, Gaffney K, et al. The PROPER Study: A 48-Week, Pan-European, Real-World Study of Biosimilar SB5 Following Transition from Reference Adalimumab in Patients with Immune-Mediated Inflammatory Disease. *BioDrugs*. 2023;37(6):873-889. doi:10.1007/s40259-023-00616-3
11. Baraliakos X, Østergaard M, Gensler LS, et al. Comparison of the Effects of Secukinumab and Adalimumab Biosimilar on Radiographic Progression in Patients with Ankylosing Spondylitis: Design of a Randomized, Phase IIIb Study (SURPASS). *Clin Drug Investig*. 2020;40(3):269-278. doi:10.1007/s40261-020-00886-7
12. Kirsten N, Ohm F, Gehrdau K, et al. Switching from Adalimumab Originator to Biosimilar in Patients with Hidradenitis Suppurativa Results in Losses of Response-Data from the German HS Registry HSBest. *Life (Basel)*. 2022;12(10):1518. Published 2022 Sep 29. doi:10.3390/life12101518
13. Wang F, Li X, Shi Y, et al. Efficacy and safety of adalimumab biosimilar (HS016) in inflammatory bowel disease from the real-world study. *Front Pharmacol*. 2023;14:1259183. Published 2023 Oct 16. doi:10.3389/fphar.2023.1259183
14. Kay J, Cross RK, Feldman SR, Park Y, Hanauer SB. Review of Adalimumab Biosimilar SB5 in Immune-Mediated Inflammatory Diseases. *Adv Ther*. 2024;41(2):509-533. doi:10.1007/s12325-023-02737-1
15. Poquet-Jornet JE, Ibáñez-Sala I, Garrigues-Pelufo T, Munilla-Das A, Valdivia-Pérez A, Carrera-Hueso FJ. Effectiveness and safety of adalimumab biosimilar in patients with inflammatory bowel disease. *Farm Hosp*. Published online April 2, 2024. doi:10.1016/j.farma.2024.01.002
16. Lu X, Hu R, Peng L, Liu M, Sun Z. Efficacy and Safety of Adalimumab Biosimilars: Current Critical Clinical Data in Rheumatoid Arthritis. *Front Immunol*. 2021;12:638444. Published 2021 Apr 6. doi:10.3389/fimmu.2021.638444
17. Burlando M, Fabbrocini G, Marasca C, et al. Adalimumab Originator vs. Biosimilar in Hidradenitis Suppurativa: A Multicentric Retrospective Study. *Biomedicines*. 2022;10(10):2522. Published 2022 Oct 9. doi:10.3390/biomedicines10102522

18. Chopra A, Khadke N, Saluja M, Kianifard T, Venugopalan A, Gharia M. The Long-Term Effects of Short-Period Adalimumab Biosimilar Usage in Ankylosing Spondylitis. *Cureus*. 2023;15(3):e36444. Published 2023 Mar 20. doi:10.7759/cureus.36444
19. Leone GM, Mangano K, Petralia MC, Nicoletti F, Fagone P. Past, Present and (Foreseeable) Future of Biological Anti-TNF Alpha Therapy. *J Clin Med*. 2023;12(4):1630. Published 2023 Feb 17. doi:10.3390/jcm12041630
20. Kang C. AVT02: An Adalimumab Biosimilar [published correction appears in Clin Drug Investig. 2022 Nov;42(11):1017. doi: 10.1007/s40261-022-01211-0]. *Clin Drug Investig*. 2022;42(10):875-878. doi:10.1007/s40261-022-01196-w
21. Ribaldone DG, Tribocco E, Rosso C, et al. Switching from Biosimilar to Biosimilar Adalimumab, Including Multiple Switching, in Crohn's Disease: A Prospective Study. *J Clin Med*. 2021;10(15):3387. Published 2021 Jul 30. doi:10.3390/jcm10153387
22. Montero-Vilchez T, Cuenca-Barrales C, Rodriguez-Tejero A, Martinez-Lopez A, Arias-Santiago S, Molina-Leyva A. Switching from Adalimumab Originator to Biosimilar: Clinical Experience in Patients with Hidradenitis Suppurativa. *J Clin Med*. 2022;11(4):1007. Published 2022 Feb 15. doi:10.3390/jcm11041007