sA Study on the Success of Biosimilars and Biologics for the Treatment of Ankylosing Spondylitis and the factors behind Market Share Shift from leading products

Dissertation Submitted to

The IIHMR University, Jaipur

for the partial fulfillment for the award of the degree of

Master of Business Administration (MBA)

in

Pharmaceutical Management

by

AMITABH RAMAN SINHA

Under the Supervision and Guidance of

Dr. Ashok Peepliwal

Associate Professor
IIHMR University, Jaipur

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DECLARATION BY STUDENT

I hereby declare that this dissertation titled 'A Study on the Success of Biosimilars and Biologics for the Treatment of Ankylosing Spondylitis and the factors behind Market Share Shift from leading products' is the bonafide record of my original research work. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished work of others has been duly acknowledged in the text.

Amitabh Raman Sinha

Date: 01/06/2023

PharmaACE

Date: 02/06/2023

TO WHOMSOEVER IT MAY CONCERN

This is to certify that, **Amitabh Sinha,** student of IIHMR University, Jaipur has completed his internship with **PharmaACE Analytics LLP** during the period of **March 01, 2023 to May 31, 2023.** During his internship he worked with the Tech – Product Development department and has successfully worked on the project; **A Study on the Success of Biosimilars and Biologics for the Treatment of Ankylosing Spondylitis and the factors behind Market Share Shift from leading products.**

We wish him every success in life.

Ashima Kumar

Ashima Kumar

Head – Training & Development and Corporate Communications

PharmaACE

Certificate from Faculty Guide and School Dean

CERTIFICATE

This is to certify that dissertation titled 'A Study on the Success of Biosimilars and Biologics for the Treatment of Ankylosing Spondylitis and the factors behind Market Share Shift from leading products' is a record of the research work undertaken by Amitabh Raman Sinha in partial fulfillment of the requirements for the awardof the degree of MBA (PharmaceuticalManagement) from the IIHMR University, Jaipur under my guidance and supervision and his/her approach to the research study has been sincere, scientific, and analytical.

Faculty Guide
IIHMR University, Jaipur
Date

School Dean
IIHMR University, Jaipur
Date

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LIST OF ACRONYMS

ACR	American College of Rheumatology
AS	Ankylosing Spondylitis
AxSpA	Axial SpondyloArthritis
DMARDs	Disease-modifying antirheumatic drugs
FDA	Food And Drug Administration
IL-17	Intra Leukin 17
INNs	International Nonproprietry Name
NSAID	Nonsteroidal anti-inflammatory drug
RBPs	Reference Biological Products
SAA	Spondylitis Association of America
SAA	Spondylitis Association of America
SPARTAN	SpondyloArthritis Research and Treatment Network
TNFi	Tumor necrosis factor inhibitor
U.S.	United States

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1. ABSTRACT

This dissertation explores the success of biosimilars and biologics in managing Ankylosing Spondylitis (AS). The chronic autoimmune disease affects patients through spinal and joint inflammation. Although effective, biologics are often inaccessible due to their high cost. Biosimilars, as more affordable options have been created to address the issue of accessibility but understanding what influences market share shift is critical for policymakers, payers, and manufacturers alike. The objective exploration hopes to promote proper usage of biosimilars for AS treatment while ensuring affordability and patient efficacy.

2. AIM

The aim of the study is to:

(i) Investigate the success of biosimilars and biologics in the treatment of Ankylosing Spondylitis (AS).

(ii) Investigate the factors behind the market share shift from leading products.

(iii) Identify the drivers of success and barriers to the uptake of biosimilars, and provide insights for policymakers, payers, and manufacturers to promote the appropriate use of biosimilars and improve patient access to effective and affordable treatments for AS.

3. METHODOLOGY-

i. **Type of Research** - This study will employ a qualitative research design. Qualitative research allows for an in-depth exploration of the success of biosimilars and biologics in treating Ankylosing Spondylitis (AS) and the factors behind the market share shift from leading products. It provides an opportunity to gather rich, contextual insights from various stakeholders involved in AS treatment.

ii. **Study Design** - The study will follow an observational descriptive type of study design. This design allows for the systematic observation and description of the phenomena related to the success of biosimilars and biologics in AS treatment. It enables the collection of data that can answer research questions and fulfill the objectives of the study.

iii. **Data Collection Method** - Secondary research will be conducted to gather data for this study. The researcher will review existing literature, research articles, reports, and

relevant documents related to the success of biosimilars and biologics in AS treatment and the factors influencing the market share shift. This comprehensive review of secondary sources will provide a foundation for analyzing and synthesizing the available information.

iv. **Data Analysis Plan** - Several methods will be used in the data analysis for this study.

- **Descriptive Analysis**
- **Content Analysis**

4. LITERATURE REVIEW

Ankylosing spondylitis (AS) also known as 'Axial SpondyloArthritis (AxSpa)' is a degenerative, inflammatory condition that affects the axial spine. Chronic back pain and progressive spinal stiffness are the most common signs. Involvement of digits, entheses, sacroiliac joints, peripheral joints, and the spine are common. AS patients often face reduced spinal mobility, postural abnormalities, hip and buttock pain, peripheral arthritis, enthesitis, and dactylitis.

Currently there is no cure for AS, but many drugs are present to manage the symptoms and complications. The most common treatments for AS are:

- **Nonsteroidal anti-inflammatory drugs (NSAIDs)**: NSAIDs work by preventing an enzyme (a protein that triggers changes in the body) from doing its job. The enzyme is called cyclooxygenase, or COX.
- **Biologics:** Biologics block specific parts of the immune system, such as proteins that promote inflammation.
- **Physical therapy:** It helps to improve range of motion and strength in the spine and other joints.
- **Surgery:** Surgery may be recommended if you have severe pain or if a hip joint is so damaged that it needs to be replaced.

Biologics and biosimilars:

Biologics and biosimilars are two important classes of therapeutic drugs that have transformed the medical field.

Biologics:

These medications are created through complex processes and are considered quite sophisticated. They are frequently large, protein-based molecules that are designed to target specific cellular mechanisms or pathways that are involved in disease progression. Monoclonal antibodies, cytokines, growth factors, hormones, and therapeutic enzymes are examples of biologics. Biologics used in the treatment of Ankylosing Spondylitis fall into two categories:

i. **TNF (Tumor necrosis factor alpha) inhibitors**: This drug was approved in 2003. It not only reduces joint pain, but also affects swelling in the stomach and eyes.
ii. **IL-17 inhibitors**: Two FDA-approved drugs for ankylosing spondylitis: They target different cytokines than TNF inhibitors. They are generally used in people whose ankylosing spondylitis does not respond to various TNF drugs.

Biologic Name	Generic Name	Company
Adalimumab	Adalimumab	AbbVie
Certolizumab	Certolizumab pegol	UCB
Entanercept	Entanercept	Pfizer
Golimumab	Golimumab	Janssen Biotech
Infliximab	Infliximab	Janssen Biotech
Ixekizumab	Ixekizumab	Eli Lilly and Company
Secukinumab	Secukinumab	Novartis

Table 1

Biosimilars:

Biosimilars are biological drugs that are highly like an already approved reference biologic, also

known as the originator or innovator product. They are developed to have comparable efficacy, safety, and quality to the reference product. Biosimilars offer a more affordable alternative to the original biologic, as they enter the market after the patent expiration of the reference product.

There are many biosimilars that are approved for the treatment of AS. These include:

Biosimilar Name	Generic Name	Company
MabThera Biosimilar	Abatacept biosimilar	Roche
Amjevita	Adalimumab biosimilar	Amgen
Erelzi	Etanercept biosimilar	Sandoz
Juvisync	Golimumab biosimilar	Merck
Renflexis	Infliximab biosimilar	Merck
Skyrizi	Secukinumab biosimilar	AbbVie

Table 2

5. ANALYSIS AND INTERPRETATIONS

Success of biologics and biosimilars in as treatment

By introducing targeted medicines that were previously unavailable, biologic therapeutics revolutionised the way that Ankylosing Spondylitis (AS) was treated. Prior to the introduction of biologics, nonsteroidal anti-inflammatory medicines (NSAIDs) were the preferred treatment for AS due to the failure of conventional synthetic disease-modifying antirheumatic drugs (sDMARDs). Clinical investigations have demonstrated that TNF inhibitors (TNFi's) dramatically reduce symptoms, CRP levels, and inflammations detected in MRI in the spine or sacroiliac joints (SIJs). The treatment of AS in patients who had not responded to conventional therapy saw a breakthrough because of these findings.

As more affordable alternatives to biological drugs, biosimilar medicines were created. In terms of quality, safety, and efficacy, they are created to be very similar to the original biologics.

In recent years, biological therapies, such as Interleukin-17 (IL-17) inhibitors, have increased the treatment options available in the market. According to the ASAS/EULAR recommendations,

TnFi's are considered for patients with active AS who have not responded to conventional treatment, which primarily consists of NSAIDs. The use of conventional sDMARDs like methotrexate and sulfa-salazine, has not shown proven efficacy in AS. Typically, a therapeutic trial of at least two different NSAIDs for a minimum of 4 weeks is undertaken.

- Efficacy of TNFis in AS has been demonstrated by significant improvements in clinical, laboratory, and imaging parameters of disease activity in clinical trials. The ASAS20 and ASAS40 response rates with TnFis were respectively 57%–64% and 40%–50%, while the placebo groups had response rates of 19%–37% and 15%–19%, respectively. Patients treated with TNFis were three to four times more likely to have an ASAS40 response at six months, according to a Cochrane analysis of 18 randomized, controlled trials in AS. The examination additionally uncovered enhancements in actual capability and spinal aggravation as surveyed by the X-ray SpondyloAnkylosing Spondylitis Exploration Consortium of Canada (SPARCC) score.
- TNFi treatment has shown a long-term response rate of 82% for ASAS20 responders in Ankylosing Spondylitis (AS) patients after five years.
- TNFi treatment effectively manages symptoms and reduces inflammation in the spine and sacroiliac joints (SIJs) over time.
- Radiographic progression, characterized by the formation of spinal syndesmophytes, can be slowed down with TNFi treatment.
- Studies indicate a link between spinal inflammation and the development of syndesmophytes, suggesting a connection between inflammation and ankylosis.
- Patients with a shorter disease duration may experience enhanced response to TNFi treatment.
- Interleukin-17 inhibitors like Secukinumab and Ixekizumab have demonstrated effectiveness in AS patients, showing positive ASAS40 response rates.
- Secukinumab has shown sustained response and reduced MRI spinal inflammation in long-term follow-up studies.
- Initial findings suggest that IL-17 inhibition, including Secukinumab, may slow down radiographic progression in AS.

- Bimekizumab, an antibody targeting both IL-17A and IL-17F, has exhibited promising results in a Phase IIb trial and is currently undergoing Phase III trials for AS.

Market penetration and utilization of AS biologic

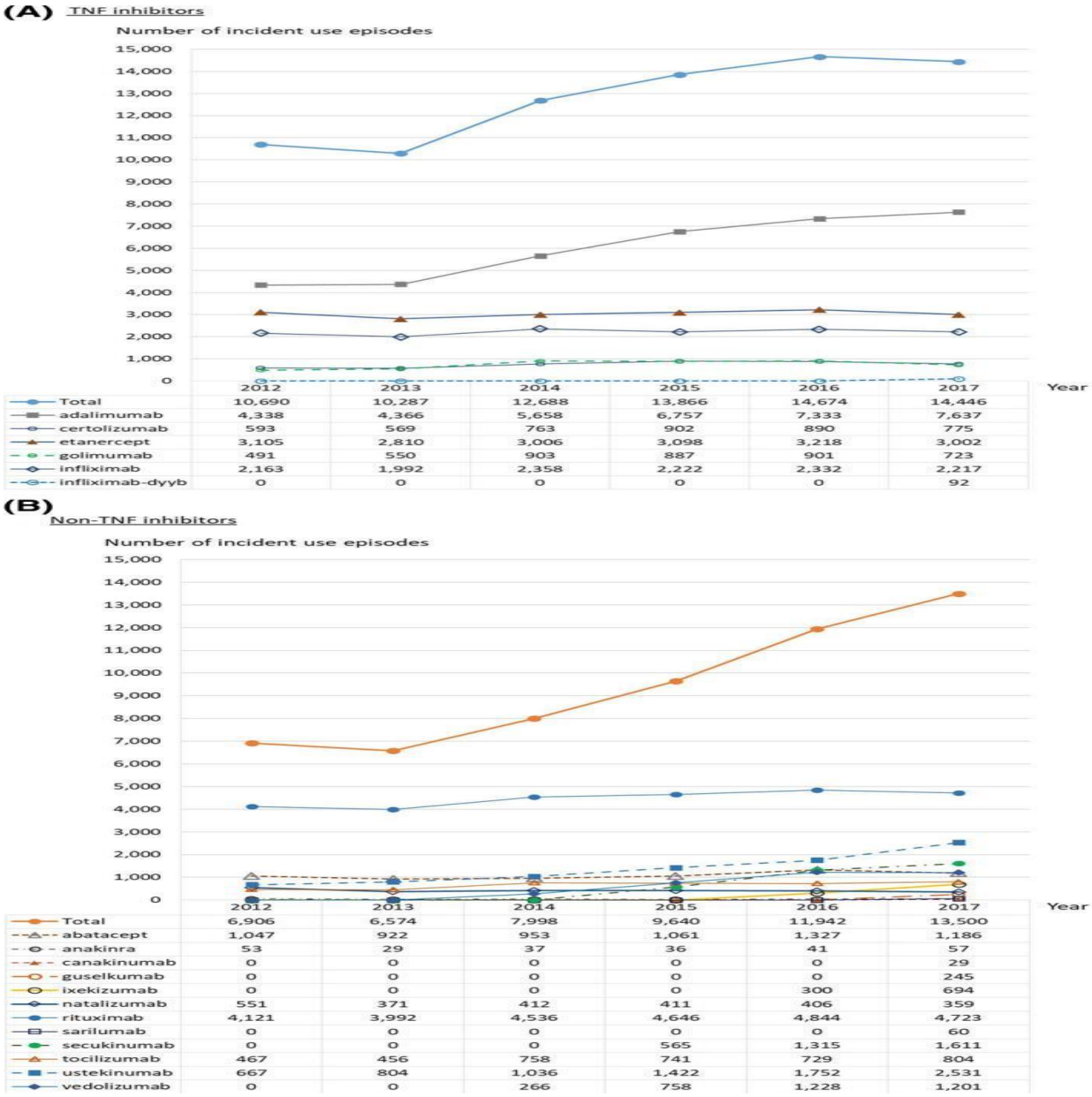

Figure: 1

The most common TNFi was Adalimumab, which was followed by etanercept and Infliximab. Rituximab, Ustekinumab, and abatacept were the three non-TNFi drugs that were most frequently administered. The number of episodes using Infliximab-dyyb increased from 92 in 2017 to 634 in 2018, making it the most popular biosimilar. Starting in 2018, 39 episodes were noticed briefly Infliximab biosimilar, Infliximab-abda.

- **Figure 1** depicts trends in incident drug episodes between 2012 and 2017. Cases of Adalimumab have progressively risen, from 4,338 in 2012 to 7,637 in 2017. Rituximabuse hasn't changed considerably, whereas other TNFi medications have stayed consistent.
- • The effectiveness of newer drugs like Vedolizumab and Secukinumab, as well as non-TNFi drugs like Ustekinumab, has not altered considerably.

Treatment Pattern in AS

According to a study by BMC Rheumatology, In 2016, 14,729 (0.09%) of 16,097,400 elderly patients had AS. Of these 14729 patients, 7842 were male (53.24%), and 6887 were female (46.76%).

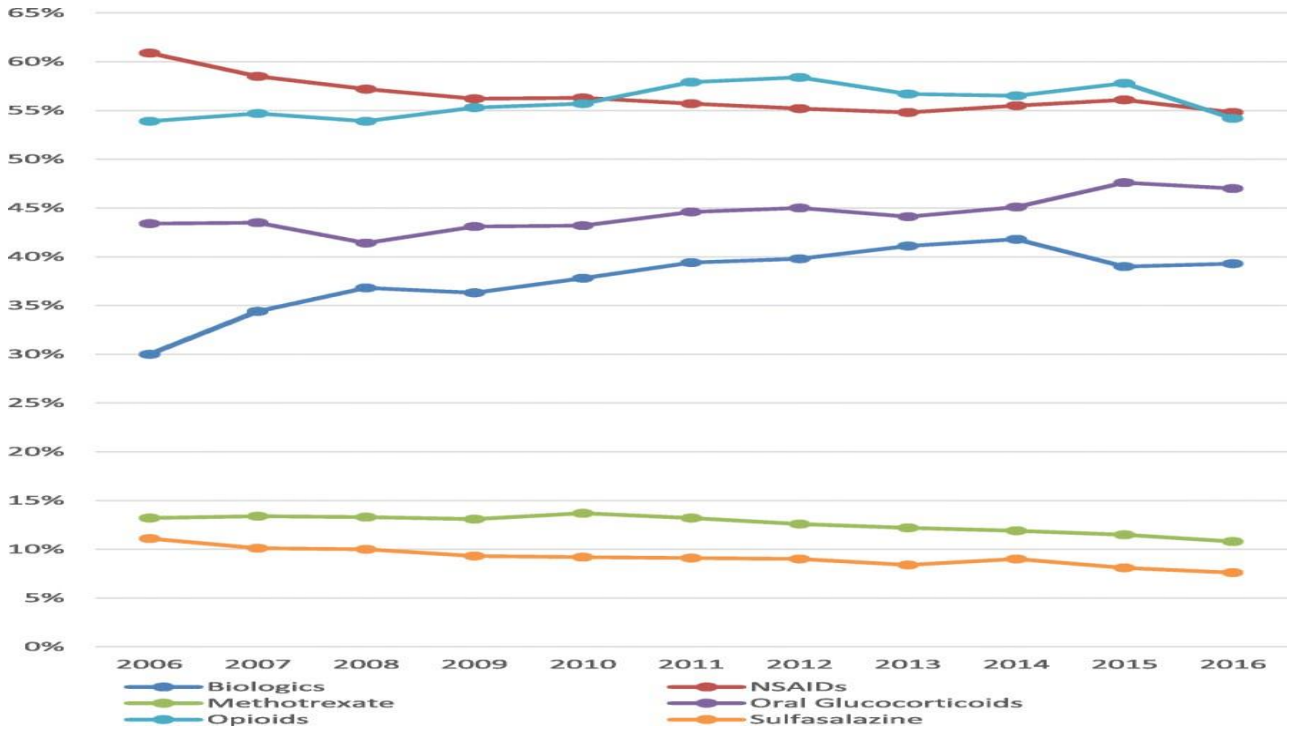

Figure 2

From 2006 to 2016, there was an increase in the usage of TNFi, oral corticosteroids, NSAIDs, and non-biological DMARDs (sulfasalazine and methotrexate). From 2006 to 2016, the use of opioids was steady. Over the past ten years, TNFi alternatives have risen, and better knowledge about the medications' efficacy and safety has made it simpler for clinicians to recommend them. For most patients with AS, the ACR, SAA, and SPARTAN do not advise using non-biological DMARDs, however NSAIDs are still useful and TNFi is advised. Reducing NSAID use raises the danger of long-term use as well as the possibility of renal, gastrointestinal, and cardiac issues.

Variable	**Overall Population (*N* = 14,729)**	**Males (*N* = 7842)**	**Females (*N* = 6887)**
Medication			
Biologics	5795 (39.3%)	3384 (43.2%)	2411 (35.0%)
Cox-2 inhibitor	1154 (7.8%)	569 (7.3%)	585 (8.5%)
Sulfasalazine	1122 (7.6%)	528 (6.7%)	594 (8.6%)
Methotrexate	1591 (10.8%)	695 (8.9%)	896 (13.0%)
Acetaminophen	425 (2.9%)	118 (1.5%)	307 (4.5%)
NSAIDs	8065 (54.8%)	3970 (50.6%)	4095 (59.5%)
Muscle Relaxants	4273 (29.0%)	1823 (23.2%)	2450 (35.6%)
Anticonvulsants	2859 (19.4%)	1110 (14.2%)	1749 (25.4%)
Opioids	7980 (54.2%)	3897 (49.7%)	4083 (59.3%)
Oral Glucocorticoids	6928 (47.0%)	3251 (41.5%)	3677 (53.4%)
Injectable Glucocorticoids	4832 (32.8%)	2115 (27.0%)	2717 (39.5%)

Table 3

FACTORS BEHIND MARKET SHARE SHIFT

Pricing and Reimbursement considerations

The use of biological treatments for ankylosing spondylitis is typically cost-effective for the European healthcare system, but the high patient volume and high budgets make it quite expensive. The introduction of biosimilars is anticipated to result in significant savings and improved availability and affordability.

1. Cost-effectiveness and Financial Burden:

- Biological products for Ankylosing Spondylitis treatment are cost effective.
- However, increasing number of patients and impact on budget make them a significant financial burden.

2. Expected Savings from Biosimilars:

- Introduction of biosimilars on the market will impact cost savings significantly.
- These savings are related to improved affordability and access to treatment.

3. Biosimilar Availability:

•Four out of the six International Nonproprietary Names (INNs) had authorized biosimilars by the EMA.

•However, biosimilar of Humira was not there in the observed countries, despite earlier authorization.

4. Price Differences:

•Price differences between manufacturers' prices of reference biological products in selected countries ranged from 25% to 70%.

•Retail prices showed differences between 60% to 95%.

•Differences were most notable for rituximab and less notable for tocilizumab.

5. Biosimilar Prices:

- Three INNs' producers and retail costs for biosimilar were determined:rituximab, and Infliximab, etanercept

•Manufacturers' prices differed between **26% and 75%**, while retail prices differed between **40% and 92%** for biosimilars.

While four out of the six International Nonproprietary Names (INNs) had authorized biosimilars, biosimilar Adalimumab was notably absent from all price lists, suggesting potential data exclusivity issues. On the other hand, biosimilar rituximab was available in eight countries, and biosimilar etanercept in nine countries.

- Among the analyzed countries, Lithuania and Estonia were the only ones lacking published prices for the selected medicinal products, indicating potential challenges in pricing transparency in those countries.
- The study found significant variability in price information across the countries, suggesting disparities in pricing and reimbursement policies for biological products.
- The differences in manufacturers' prices ranged from 22% to 69%, indicating variations in the cost of production and distribution across different regions.
- Retail prices showed even greater variability, ranging from 62% to 95%. This wide range indicates differences in pricing strategies, markups, and healthcare system regulations among the countries.
- Noteworthy was the wide-ranging prices for reference biological products (RBPs) such as rituximab, with tocilizumab showing relatively minimal variability-signaling variances in competition and market trends for diverse products.
- Spain and France emerged as the front-runners in published biosimilar prices, demonstrating a much better availability and market rivalry potential in these countries. Lithuania and Estonia, in contrast, were the only nations where no biosimilar prices were reported, which hints at an apparent access barrier and minimal market competition for biosimilars in these regions.
- Moreover, the analysis uncovered the differences in pricing approaches employed by different countries, adding to the discrepancies in retail costs. This implies that aspects like health system regulations, negotiation strategies, and market dynamics have a bearing on the ultimate prices of biologicals.
- Rituximab compared to etanercept displayed greater price divergences at the retail level, mainly due to contrasts in market rivalry, biosimilar supply, and pricing approaches relative to each country.

- Italy exhibited the most considerable difference in etanercept prices, with the biosimilar being priced 45% less costly than the reference product - scaling down costs somewhat significantly for patients and health care systems in Italy.
- On the contrary, Spain recorded the least significant distinction in etanercept prices, with just a 10% divergence in retail costs. The abundance of multiple biosimilar solutions in Spain suggests sensible market competition and cost gain potentials for patients.
- The wide range of prices for reference biological products (RBPs), such as rituximab, which showed a great deal of variability - indicating differences in competition and market trends for various products. Whereas Spain and France had the most competitive prices for biosimilars, countries such as Lithuania and Estonia revealed virtually nonexistent biosimilar prices, indicating an apparent lack of access and minimal market competition for biosimilars in those regions.
- This analysis revealed the various pricing approaches utilized by different countries, thus contributing to the wide discrepancies in retail costs. This implies that factors such as health system regulations, negotiation strategies, and market dynamics have an influence

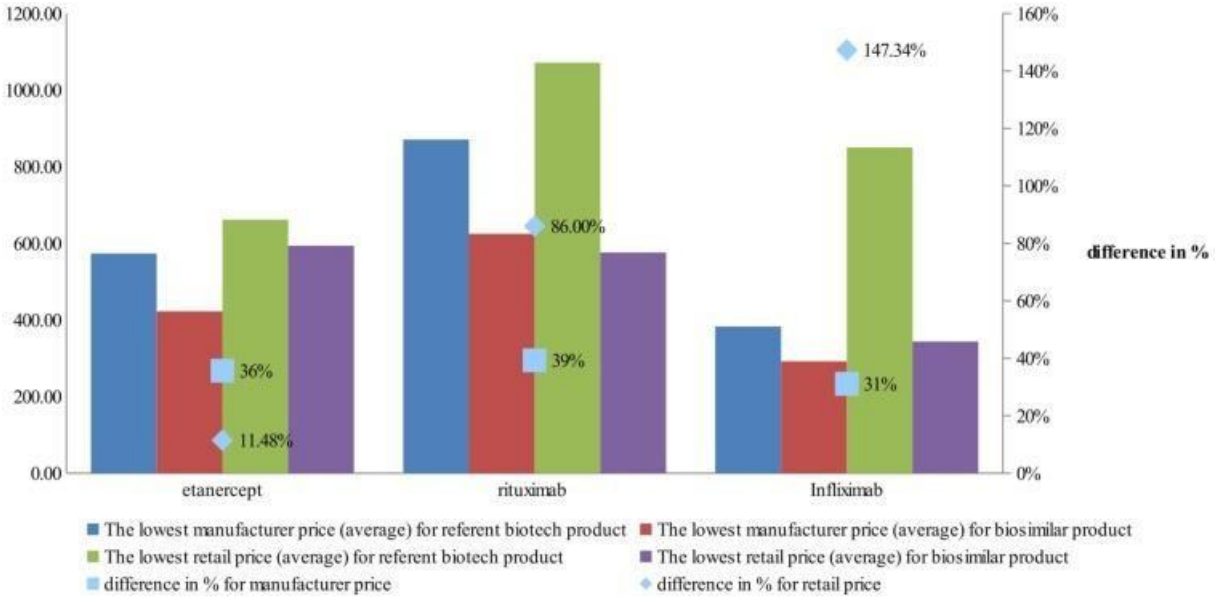

Figure: 3

- Rituximab had greater price disparities at the retail level in comparison to etanercept. This is due to the differences in market competition, biosimilar supply, and pricing tactics for each country.
- Italy recorded the most substantial difference in etanercept prices, with the biosimilar

costing approximately 45% less than the reference product - thereby making it more affordable to the patients and health systems.

- Spain experienced the lowest difference in etanercept prices, with a mere 10% divergence in retail costs. The abundance of biosimilar options available in Spain serves to demonstrate the potential of competitive market pricing and cost savings for patients.
- For rituximab, Spain again demonstrated a smaller price difference (15% at the retail level) compared to Hungary (43% at the retail level), indicating different pricing dynamics and potential cost advantages in Spain.

Regulatory pathways and approval processes

Biological products, including generics, biosimilars, and biosimilar substitutes, have been approved by the FDA through multiple approvals. A Biological License (BLA) is used to demonstrate the safety and efficacy of a product used in clinical trials.

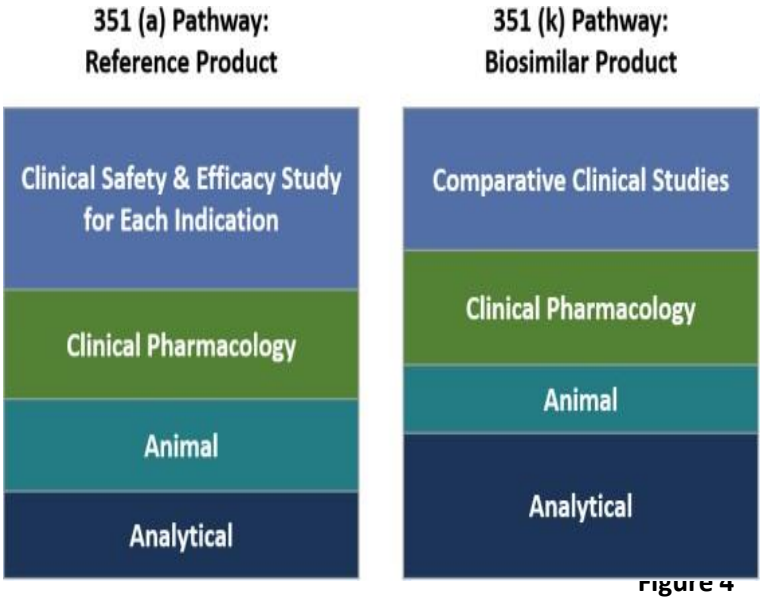

Figure 4

Biosimilars are very similar to reference products, with no discernible differences in safety or effectiveness. The shortened biosimilar approval pathway reduces development time and costs while maintaining safety and effectiveness standards. Manufacturers of biosimilars provide comparative data, such as analytical characterization, animal studies, and clinical comparisons to the reference product. The sum of these data supports the conclusion that a biosimilar is very similar to the reference product. Biosimilar manufacturers can avoid extensive clinical trials by relying on the FDA's determination of efficacy and safety for the reference product, resulting in faster access and moretherapeutic options.

Physicians and Patients Perspective towards biological treatment

- **Scientific evidence:** The proven effectiveness of the drugs had a significant influence on prescription decisions. However, there was a lack of consensus among rheumatologists regarding the evidence for biologics, leading to differing interpretations.
- **Subjective judgments, experience of the prescriber:** In addition to scientific evidence, subjective judgments and the experience of the prescriber played a significant role. The knowledge and experience of the prescriber were rated as important factors. Social knowledge, such as input from colleagues and professional networks, also influenced prescription decisions.
- **Organizational factors:** Organizational factors, including available resources, cost-effectiveness, and treatment guidelines, played a role as well.
- **Patient attitudes and preferences:** The study highlighted the importance of patient attitudes and preferences in the decision-making process, although they were rated relatively low in influence. Patient involvement and shared decision-making were mentioned as important factors, considering the chronic nature of Ankylosing Spondylitis and the long-term relationships between patients and physicians.

Unmet Needs in the treatment of Ankylosing Spondylitis with Biological products.

- **Ineffectiveness in some patients**: Biological drugs are not effective in all patients with AS. In some cases, patients may not respond to treatment at all, while others may experience only a partial response.
- **Adverse side effects**: Biological drugs can have several adverse side effects, including infections, infusion reactions, and autoimmune reactions. These side effects can be serious and may require patients to discontinue treatment.
- **High cost:** Biological drugs are expensive, and this can be a barrier to access for some patients.
- **Limited availability:** Biological drugs are not available in all countries, and even in countries where they are available, they may not be covered by insurance.
- **Patient education:** Patients need to be educated about the risks and benefits of biological

drugs, as well as how to manage any side effects.

- **Monitoring:** Patients who are taking biological drugs need to be monitored closely for signs of infection, infusion reactions, and autoimmune reactions.
- **Compliance:** Patients need to be compliant with their treatment regimen to achieve optimal results.

These unmet needs highlight the need for further research into new and more effective treatments for AS. There is also a need to develop strategies to improve the safety and affordability of biological drugs.

Why Biosimilars failed in US.

The growth of specialty biologics has contributed to the increasing pharmaceutical spending in the US. Biosimilars, which are intended to provide cost savings and increase market competition, have faced challenges in the US market. The lack of market penetration and limited price reductions of biosimilars can be attributed to various factors.

Patent Thicket Challenge

One significant challenge is the existence of a patent thicket, which makes it difficult for biosimilars to enter the market. While biosimilar sales are expanding rapidly in Europe, the US has experienced slower adoption. European countries have employed a winner-takes-all bidding approach to enhance their negotiating power and achieve significant cost savings. However, such a strategy has not been effectively implemented in the US.

Rebate Trap

The rebate trap is another obstacle to biosimilar approval. The discount system between manufacturers, pharmacy benefit managers (PBMs), and payers creates incentives to prioritize more expensive original biologics over biosimilars. The substantial discounts offered by originator biologic manufacturers discourage the placement of biosimilars on formularies, resulting in lower coverage and utilization of biosimilars.

Efforts to address the rebate trap have not been successful, and transparency regarding discounts remains a challenge. Despite the potential cost savings biosimilars can offer, the fear of premium increases has hindered the implementation of certain policies aimed at promoting biosimilar adoption.

Prescriber inertia

It is influenced by factors such as investment incentives and coverage by insurers or formularies, also impacts the adoption of biosimilars. Furthermore, reimbursement procedures for drugs administered in clinical settings may discourage healthcare providers from switching to biosimilars, as they may result in lost revenue due to lower reimbursement rates.

Interchangeability

It refers to the ability to switch between the original biologic and its biosimilar, is a crucial consideration. The unique characteristics of biologic pharmaceuticals, such as protein glycosylation, make it necessary to ensure safety and efficacy when switching between products. Although studies have generally shown no significant differences between biosimilars and original biologics, concerns about immunogenicity, safety, and efficacy persist among healthcare professionals.

The concept of interchangeability, if achieved, could impact the adoption of biosimilars. It would allow pharmacists to substitute a biosimilar without notifying the prescriber, similar to generic drugs. However, the uncertainty surrounding the consequences of interchangeability has led to apprehension among healthcare providers.

Overall, the slow adoption of biosimilars in the US can be attributed to challenges such as patent barriers, the rebate trap, prescriber inertia, and concerns about interchangeability. Despite the potential cost savings and the need for increased market competition, the US market has struggled to fully embrace biosimilars. Regulatory modifications, further research, and policy changes may be necessary to address these challenges and promote the wider utilization of biosimilars in the US healthcare system.

6. CONCLUSION

The introduction of biologic therapies transformed the treatment of Ankylosing Spondylitis (AxSpa). Previously, NSAIDs' were in the market, but their efficacy was limited. TNF inhibitors (TnFi's) improved symptoms, inflammation, and imaging findings significantly. Biosimilars were created as less expensive alternatives to biologics with comparable quality and effectiveness. IL17A-i such as Secukinumab and Ixekizumab have also been approved for the treatment of AS. TNF inhibitors have demonstrated long-term efficacy as well as the ability to slow radiographic progression. IL-17 inhibitors inhibit inflammation and have the potential to slow radiographic progression. Bimekizumab has shown promise in inhibiting both IL-17A and IL-17F.

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