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Review Article

Systemic review of safety and efficacy of approved bio similar for management of rheumatoid arthritis

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ABSTRACT

Biological medicines have opened up new doors to treat many diseases, which include cancers, autoimmune conditions, diabetes, and so on. Stem-cell and gene therapies, insulin, and monoclonal antibodies are all some of the many instances of biological therapies.

Biological Disease-modifying antirheumatic drugs (bDMARDs), such as monoclonal antibodies and receptor Fc-fusion proteins that target the tumor necrosis factor (TNF), are the recent development in treatment for patients with rheumatic conditions.

Patients who are inadequate respondents to stand-alone conventional synthetic DMARDs have significant improvement in symptoms and outcomes with bDMARDs in various rheumatic conditions.

Despite the betterment of the disease, the higher cost when compared to the conventional DMARDs makes bDMARDs less accessible to underprivileged patients. This inequality in the treatment because of the increased cost is being bridged nowadays with the development of lower-cost agents.

This review evaluates the safety and efficacy of the Biosimilars in the treatment of Rheumatoid arthritis.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that involves mostly the joints in the hands, wrists, and knees causing pain. If untreated, RA can lead to extensive damage to the joints and their surrounding connective tissue.

Though RA is a systemic autoimmune condition involving multiple systems, with advanced and aggressive therapeutic interventions, the joints and systemic involvement of RA are being restricted thus improving the quality of patients' life.

Rheumatoid arthritis (RA) is estimated to affect approximately 0.24 to 1 percent of the world population. In 2019, 18 million people worldwide were living with rheumatoid arthritis. Among 70% of them are females, and 55% are older than 55 years.

The financial burden on society due to RA remains substantial.

However, there is no definitive cure for RA, earlier clinching of the diagnosis and initiation of treatment and providing support and rehabilitation can significantly lower the likelihood of severe joint damage and mobility of the patient.

Treatment of RA is classified into two types, Disease-modifying anti-rheumatic drugs (DMARDs) and biological agents.

DMARDs have the dual property of immunosuppression and immune modulation and are classified either as conventional DMARDs or biologic DMARDs.

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Commonly employed conventional DMARDs are methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine.

Biologic DMARDs were introduced in the early 1990s and are usually prescribed after the failure of conventional DMARD therapy (ongoing disease activity or clinical or radiographic disease progression).

By the early 1990s, Biological DMARDs were developed and are being prescribed after the failure (active disease or clinical and or radiological proof of disease progression)of the Conventional DMARDs regimen. The biological DMARDs that are in practice are infliximab, adalimumab, etanercept, rituximab, abatacept, rituximab, tocilizumab, tofacitinib, and a few more in development. Biologic DMARDs are highly specific and are targeted against a specific pathway of the immune system. Some biological DMARDs are monoclonal, and are chimeric humanized fusion antibodies, while the rest are receptors that have been fused to a part of the human immunoglobulin or small molecules such as Janus kinase (JAK) inhibitors.

Biologics are made from a living system that includes humans, plants, animals, bacteria, and other microorganisms; they go through a rigorous, tightly controlled manufacturing process and tend to be patented.

When the patents expire, the field of Biosimilars opens up. Biologics are complex substances that are lab-engineered and have an inherent level of micro-variability. Biosimilars cannot be the exact copies of Biologics, but mimic the active component in the reference parent biologics which will have structural variations.

2. Materials and Methods

This study was carried out as per the approach outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins Julian and Green, 2011a). Furthermore, it is presented in accordance with Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) (Higgins et al., 2015). A detailed search of the Cochrane Central Register of Controlled Trials (CENTRAL), PUBMED and Google scholar was carried out to search all citations of original research studies with key words, Biosimillars in Rheumatoid arthritis; Rheumatoid arthritis and Biosimillars; Safety efficacy of biosimillars were used in search strategy. To detect any missed article during our initial search, a manual check of all the eligible articles references was performed. Two reviewers screened the title, abstract, and complete text in isolation from the selected papers. If there was disagreement between two then another round of search was done. Still, if these was any dispute between two then third author was considered for final decision.

A total of 119 studies were identified from Google scholar, Pubmed and Cochrane central register. Among these studies, 56 matched as per inclusion and Exclusion criteria. 37 studies were found to be duplicate studies so and out of total 119 studies, 19 were analyzed

2.1. Inclusion criteria

1. Original literature with Human models with established Arthritis disease
2. Randomized control trials, Comparative studies
3. Studies in English language.

2.2. Exclusion criteria

1. Duplicate studies
2. Studies with no relevance with current study or keywords
3. Case reports
4. Studies which cannot be extracted from true source
5. Animal studies
6. Other language.

Information source and search criteria:

1. Pubmed, Cochrane Central Register of Controlled Trials, Google Scholar will be undertaken
2. The search is confined to papers in English, these papers will be screened by abstract,linked
3. With key words : *Rheumatoid arthritis, *Biosimillars, *Biosimillars in Rheumatoid arthritis.

3. Result

3.1. Randomized studies of rituximab and its biosimillar were reviewed

From a Phase I Randomised Controlled Trial in RA from Won Park et al., CT-P10, a biosimilar of rituximab (RTX) was compared to a clinical profile of RTX.

A 56-Week Open-Label Study in patients with Rheumatoid Arthritis, RCT Phase I, 87 patients were enrolled, DAS28 and EULAR response were noted, Rituximab compared to Biosimilar CT-P10.

In this study, comparable efficacy and safety profiles were assessed in subjects who were switched from RTX to CT-P10 and patients who were those maintained on CT-P10 during the complete treatment duration.

According to Dae Hyun Yoo et al.,[1] CT-P10 is a biosimilar of innovator rituximab (RTX), which is used to treat patients of rheumatoid arthritis (RA) who have not responded well to anti-tumor necrosis factor agents. The aim of the study was to compare the clinical profile of CT-P10 versus RTX in subjects with RA who received up to two courses of therapy and were under followup for 72 weeks. The results up to week 72 of a Phase I Randomized Controlled Trial were analyzed. In 154 patient, DAS28 response was noted with Rituximab Biosimilar CT-P10 compared to Innovator Rituximab in Patients with Rheumatoid Arthritis:. In subjects with RA,

efficacy, safety, and other clinical data were not different between CT-P10 and RTX after up to two courses of treatment over 72 weeks.

In Won Park et al.,[2] This multinational, randomized, double-blind trial, was designed to demonstrate equivalence in pharmacokinetics and efficacy between CT-P10 and innovator rituximab (RTX) in patients with rheumatoid arthritis (RA). Adults with active RA were treated with CT-P10, United States-sourced RTX (US-RTX; Rituxan®), or European Union-sourced RTX (EU-RTX; MabThera®) at weeks 0 and 2. It is a randomized controlled Phase 3 trial, 372 Patients with Rheumatoid Arthritis participayted and DAS28-CRP score was assesed. CT-P10 and RTX were similar in of efficacy and displayed equivalent pharmacodynamic, immunogenicity, and safety profiles up to week 24.

In Chang Hee Suh et al.,[3] purpose of this study was to asses long-term clinical outcomes of extended treatment with CT-P10, a rituximab biosimilar, compared with rituximab reference molecule sourced from the USA and the EU (US-RTX and EU-RTX) in rheumatoid arthritis (RA) for up to 48 weeks. In this multinational, randomized, double-blind trial, 372 adults with active RA given up to two courses of CT-P10, US-RTX, or EU-RTX along with methotrexate. Efficacy was assessed by Disease Activity Score 28-joint count (DAS28) and American College of Rheumatology (ACR) response rates. Pharmacokinetics, pharmacodynamics, immunogenicity, and safety were also evaluated. CT-P10 was equivalent to EU-RTX and US-RTX in terms of efficacy, pharmacokinetics, pharmacodynamics, immunogenicity, and safety up to week 48.

In Vikram Murlidhar Haridas et al.,[4] The purpose was to demonstrate pharmacokinetic (PK) similarity between DRL_RI, a proposed rituximab biosimilar, and two originator molecules (Rituxan® [RTX-US] and MabThera® [RTX-EU]) and compare their pharmacodynamics (PD), efficacy, safety, and immunogenicity in rheumatoid arthritis (RA) patients with poor response to methotrexate (MTX)-based therapy and treatment naive. In this randomized, double-blind, parallel-group study, 276 patients with moderate-to-severe active RA were randomized to receive DRL_RI, RTX-US, or RTX-EU on days 1 and 15. DRL_RI demonstrated equivalence with RTX-EU and RTX-US, the originator products, with comparable efficacy, PD, safety, and immunogenicity.

In Seung Cheol Shim et al.,[5] the aim was to assess the efficacy and safety of CT-P10, a rituximab biosimilar after a single switch, during a multinational, randomized, double-blind Phase 3 trial involving patients with RA. Patients received 48 weeks' treatment with CT-P10 or United States- or European Union-sourced originator rituximab (US-RTX and EU-RTX, respectively. Efficacy was assessed with Disease Activity Score using 28 joints (DAS28), American College of Rheumatology (ACR) response rates, and quality of life-related parameters. Pharmacodynamics, immunogenicity and safety were also analyzed. At week 72, similar improvements were noted by disease activity parameters including DAS28 and ACR response rate in the four extension period treatment arms. Quality of life change at week 72 vs baseline were similarly demonstrated during the extension period in all groups. Newly developed anti-drug antibodies were found in two patients following study drug infusion in the extension period. Similar pharmacodynamic and safety profiles were observed across groups. Study showed that long-term use of CT-P10 up to 72 weeks was effective and well tolerated. Furthermore, change from originator rituximab to CT-P10 in RA was well tolerated and did not result in any clinically meaningful change in terms of efficacy, pharmacodynamics, immunogenicity and safety.

3.2. Randomized studies on adalimumab were reviewed

In Stanley B Cohen et al.,[6] aim was to demonstrate clinical equivalence of adalimumabbiosimilar candidate BI 695501 with Humira. Subjects with active rheumatoid arthritis on stable methotrexate were randomized to BI 695501 or Humira in a double-blind, parallel-group, study. At week 24, 645 patients were re-randomised to continue BI 695501 or Humira, or switch from Humira to BI 695501. The coprimary endpoints were the proportion of patients achieving the American College of Rheumatology 20% response criteria (ACR20) at weeks 12 and 24. Further efficacy and safety endpoints and immunogenicity were assessed up to week 58.BI 695501 demonstrated similar efficacy, safety and immunogenicity to Humira; switch from Humira to BI 695501 had no impact on efficacy, safety and immunogenicity.

In Rajendrakumar H Jani et al.[7] In this study, efficacy, tolerability and safety of biosimilar adalimumab (Exemptia; ZydusCadila) was compared with originator adalimumab (Humira; AbbVie) in patients with moderate to severe rheumatoid arthritis (RA). In this multicentre, prospective, randomized, double-blind, active controlled parallel arm study, 120 subjects with moderate to severe RA were given 40 mg of either test adalimumab (Exemptia) or originator adalimumab (Humira) by subcutaneous route every other week for 12 weeks. The primary endpoint was percentage of responders in two treatment groups by American College of Rheumatology 20 (ACR20) at week 12. The secondary endpoints were change in Disease Activity Score of 28 joints - C-reactive protein (DAS28-CRP) and percentage of patients with an ACR50 and ACR70 response in two treatment groups at week 12. Safety outcomes were also assessed;The results demonstrated biosimilarityin tyerms of efficacy, tolerability and safety of test adalimumab (Exemptia) and originatoradalimumab (Humira) in patients with moderate to severe RA.

In Ahmadreza Jamshidi et al.,[8] This study objective was to compare efficacy and safety of test-adalimumab (CinnoRA®, CinnaGen, Iran) to the innovator product (Humira®, AbbVie, USA) in adult patients with active rheumatoid arthritis (RA). In this randomized, double-blind, active-controlled, non-inferiority trial, a total of 136 patients with active RA were randomized to receive 40 mg subcutaneous injections of either CinnoRA® or Humira® every other week, while receiving methotrexate (15 mg/week), folic acid (1 mg/day), and prednisolone (7.5 mg/day) over a period of 24 weeks. Physical examinations, vital sign, and laboratory tests were performed in patients at baseline and at 12-week and 24-week visits. The primary endpoint in this study was the percentage of patients achieving moderate and good disease activity score in 28 joints-erythrocyte sedimentation rate (DAS28-ESR)-based European League Against Rheumatism (EULAR) response. The secondary endpoints were the percentage of patients achieving American College of Rheumatology (ACR) criteria for 20% (ACR20), 50% (ACR50), and 70% (ACR70) responses along with the disability index of health assessment questionnaire (HAQ), and safety. CinnoRA® was demonstrated to be non-inferior to Humira® in terms of efficacy at week 24 with a comparable safety profile to the originator product.

In Roy M Fleischmann et al.[9] is a randomized, double-blind comparative study of the adalimumab (ADL) biosimilar PF-06410293, (ADL-PF), and originator ADL sourced from the European Union (ADL-EU) in patients with active RA. Therapeutic equivalence was assessed based on ACR20 responses at week 12 (primary endpoint). It was reported that long-term safety, immunogenicity, and efficacy of ADL-PF in patients who continued ADL-PF treatment throughout 78 weeks or who change from ADL-EU to ADL-PF at week 26 or week 52 was equivalent. Eligible patients (2010 ACR/EULAR RA diagnosis criteria for ≥ 4 months; inadequate response to MTX, ≤ 2 doses non-ADL biologic), stratified by geographic regions were randomized (1:1) in treatment period 1 (TP1) to ADL-PF or ADL-EU (40 mg subcutaneously, biweekly), both with MTX (10-25 mg/week). After 26 weeks (start of TP2), patients receiving ADL-EU were re-randomized to stay on ADL-EU or switch to ADL-PF for 26 weeks. At week 52 (start of TP3), all patients received open-label treatment with ADL-PF for 26 weeks and were followed after last treatment dose upto week 92. To evaluate maintenance of response after transition or remaining on ADL-PF, ACR20, DAS28-4(CRP), and other measures of clinical response/remission were assessed through week 78 as secondary endpoints. Three groups were evaluated: biosimilar, week 26 switch, and week 52 switch. There were no clinically meaningful differences in safety, immunogenicity, and efficacy for patients who were maintained on ADL-PF for 78 weeks and those who had changed from ADL-EU at week 26 or week 52.

In Stanley Cohen et al.,[10] ABP 501 is a Food and Drug Administration-approved biosimilar to adalimumab; structural, functional and pharmacokinetic evaluations have demonstrated that both are highly similar. These results are from a phase III study comparing efficacy, safety and immunogenicity between ABP 501 and adalimumab. In this randomized, double-blind, active comparator-controlled, 26-week equivalence study, 526 patients with moderate to severe active rheumatoid arthritis (RA) despite methotrexate were randomized (1:1) to ABP 501 or adalimumab (40 mg) every 2 weeks. Primary endpoint was risk ratio (RR) of ACR20 between groups at week 24. Primary hypothesis that the treatments were similar would be confirmed if the 90% CI for RR of ACR20 at week 24 was between 0.738 and 1.355, demonstrating that ABP 501 is equivalent to adalimumab. Secondary endpoints included Disease Activity Score 28-joint count-C reactive protein (DAS28-CRP). Safety was analyzed via adverse events (AEs) and laboratory evaluations. Antidrug antibodies were assessed to detect immunogenicity. Results from this study demonstrated that ABP 501 is equivalent to adalimumab in clinical efficacy, safety and immunogenicity in patients with moderate to severe RA.

3.3. Randomized studies on infliximab were reviewed

Josef S Smolen et al.,[11] already reported 54 weeks results from the phase III study of SB2, a biosimilar of reference infliximab (INF), in terms of efficacy, safety and immunogenicity. This transition period analyzed results in patients with rheumatoid arthritis (RA) who shifted from INF to SB2 with those in patients who maintained treatment with INF or SB2. Patients with moderate to severe RA despite methotrexate treatment were randomized (1:1) to receive SB2 or INF at weeks 0, 2 and 6 and every 8 weeks thereafter until week 46. At week 54, patients previously receiving INF were randomized (1:1) to switch to SB2 (INF/SB2 (n=94)) or to continue on INF (INF/INF (n=101)) up to week 70. Patients who have already received SB2 continued on SB2 (SB2/SB2 (n=201)) up to week 70. Efficacy, safety and immunogenicity were assessed up to week 78. The efficacy, safety and immunogenicity profiles remained similar among the INF/SB2, INF/INF and SB2/SB2 groups up to week 78, with no treatment-emergent adverse events or clinically relevant immunogenicity after switching from INF to SB2.

In Stanley B Cohen et al.[10] Aim of this study was to assess the long-term efficacy, safety, and immunogenicity of the infliximab biosimilar, PF-06438179/GP1111 (PF-SZ-IFX), in patients with rheumatoid arthritis (RA) who remained onbiosimilar treatment throughout 78 weeks or who changed from originator infliximab (Remicade®) sourced from the EU (IFX-EU) at week 30 or week 54 in the REFLECTIONS B537-02 study. In this phase III, double-

blind, active-controlled study, patients with moderate-to-severe active RA were initially randomized to PF-SZ-IFX or IFX-EU, each with methotrexate (treatment period [TP] 1; N = 650). At week 30, patients receiving PF-SZ-IFX continued PF-SZ-IFX; patients receiving IFX-EU were re-randomized to continue IFX-EU or switch to PF-SZ-IFX (TP2; n = 566). From weeks 54 to 78, all patients received open-label treatment with PF-SZ-IFX (TP3; n = 505). Efficacy, safety, and immunogenicity data were assessed during TP3. Results upto week 78 continue to support the efficacy, safety, and immunogenicity of PF-SZ-IFX in patients with moderate-to-severe active RA. There were no differences that can be said as clinically menaingful between groups, independent of a single treatment transition from IFX-EU to PF-SZ-IFX at week 30 or week 54.

Jung Yoon Choe.,[12] compared the efficacy, safety, immunogenicity and pharmacokinetics (PK) of SB2 to the infliximab originator product (INF) in subjects with moderate to severe rheumatoid arthritis (RA) despite methotrexate therapy. This was a phase III, randomised, double-blind, multinational, multicentre parallel group study. 584 Patients with moderate to severe RA despite methotrexate therapy were randomized in a 1:1 ratio to receive either SB2 or INF of 3 mg/kg. The primary end point to assess the efficacy was the American College of Rheumatology 20% (ACR20) response at week 30. Inclusion of the 95% CI of the ACR20 response difference within a ±15% margin was needed for equivalence. SB2 was similar to INF in terms of ACR20 response at week 30. SB2 was found comparable safety profile, immunogenicity and PK to INF.

Stanley B Cohen et al.,[13] evaluated the efficacy, safety, pharmacokinetics (PK), and immunogenicity of PF-06438179/GP1111 (IxifiTM/Zessly®), an infliximab biosimilar, vs infliximab (Remicade®) originator product sourced from the European Union (infliximab-EU) in biologic-naïve patients with moderate to severe active rheumatoid arthritis (RA) despite methotrexate therapy. This was a double-blind, active-controlled, randomized, multinational study. This study reported results from the initial 30-week treatment period. Patients (N = 650) were stratified by geographic region and randomized 1:1 to PF-06438179/GP1111 or infliximab-EU (3 mg/kg intravenous at weeks 0, 2, and 6, then every 8 weeks). Dose enhancement to 5 mg/kg was allowed beginning at week 14 for patients with inadequate RA response. The primary endpoint was American College of Rheumatology criteria for ≥ 20% clinical improvement (ACR20) response at week 14. Therapeutic equivalence was proven if the two-sided 95% CI for the treatment difference was within the symmetric equivalence margin of ± 13.5%. Statistical analysis was also performed with a two-sided 90% CI using an asymmetric equivalence margin (- 12.0%, 15.0%). PF-06438179/GP1111 and infliximab-EU showed similar efficacy, safety, immunogenicity, and PK with or without dose enhancement in patients with moderate to severe active RA on background methotrexate.

3.4. Studies on etanercept were reviewed

Paul Emeryet al.,[14] compared the efficacy and safety of SB4 (an etanerceptbiosimilar) with originator product etanercept (ETN) in subjects with moderate to severe rheumatoid arthritis (RA) despite methotrexate (MTX) therapy. This is a phase III, randomized, double-blind, parallel-group, multicentre study with a 24-week primary endpoint. Patients with moderate to severe RA despite MTX treatment were randomized to get weekly dose of 50 mg of subcutaneous SB4 or ETN. The primary endpoint assessment was the American College of Rheumatology 20% (ACR20) response at week 24. Other efficacy endpoints as well as safety, immunogenicity and pharmacokinetic parameters were also analyuzed: SB4 was shown to be similar with ETN in terms of efficacy at week 24. SB4 was well tolerated with a lower immunogenicity profile. The safety profile of SB4 was equivalent with that of ETN.

Sang Cheol Bae et al.,[15] evaluated equivalence in efficacy and safety of biosimilar HD203 with innovator etanercept (ETN) plus methotrexate (MTX).Patients with active RA received 25 mg HD203 or ETN subcutaneously twice-weekly with MTX for 48 weeks in a phase III, multicentre, randomised, double-blind, parallel-group design. The primary end point was the percentage of patients achieving the American College of Rheumatology 20% response (ACR20) at week 24 for per-protocol study completer set (PPS). Secondary end points included ACR response criteria, ACRn, European League against Rheumatism (EULAR) response, change in Disease Activity Score 28 (DAS28), patient-reported outcomes, safety and immunogenicity. The study met its primary objective of demonstrating equivalent efficacy of HD203 and ETN. HD203 was well tolerated, with safety comparable with ETN in this study population with RA.

Hiroaki Matsuno et al.,[16] evaluated the equivalence between LBEC0101 (etanerceptbiosimilar) and the etanerceptoriginator product (ETN-RP) in terms of efficacy and safety, including immunogenicity in patients with active rheumatoid arthritis despite methotrexate treatment. This phase III, multicentre, randomised, double-blind, parallel-group, 54-week study was performed in Japan and Korea. The primary efficacy endpoint was the change from baseline in the disease activity score in 28 joints based on erythrocyte sedimentation rate (DAS28-ESR) at week 24. American College of Rheumatology 20% (ACR20) response rate, adverse events (AEs), pharmacokinetics and development of antidrug antibodies (ADAs) were also assessed. The clinical efficacy of LBEC0101 was similar to ETN-RP. LBEC0101 was well tolerated and had a comparable safety profile to ETN-RP.

Table 1: Reference product and their biosimillars with authorization date

S. No	Active Substance	Reference product (authorisation date)	Biosimilar product (authorisation date)	
1.	Infliximab	Remicade (1999)	Inflectra (2013) Flixabi (2016) Amgevita (2017) Cyltezo (2017) Imraldi (2017)	Remsima (2013) Zessly (2018) Hyrimoz (2018) Idacio (2019) Kromeya (2019)
2.	Adalimumab	Humira (2003)	Solymbic (2017) Halimatoz (2018) Hefiya (2018) Hulio (2018)	Amsparity (2020) Hukyndra (2021) Liomyris (2021) Yuflyma (2021)
3.	Golimumab	Simponi (2009)	None	
4.	Certolizumab pegol	Cimzia (2009)	None	
5.	Etanercept	Enbre l(2000)	Benepali (2016) Nepexto (2020)	Erelzi (2017)

In Janusz Jaworski et al.,[17] EQUIRA study was conducted in patients with moderate-to-severe rheumatoid arthritis and inadequate response to disease-modifying anti-rheumatic drugs. This was a phase III, double-blind study. Eligible patients were randomized 1:1 to receive subcutaneous 50 mg SDZ ETN or ETN, once-weekly, for 24 weeks. At week 24, patients with at least moderate EULAR response in the SDZ ETN group continued SDZ ETN treatment, and those in the ETN group were shifted to receive 50 mg SDZ ETN, for up to 48 weeks. Subjects received concomitant methotrexate at a stable dose (10-25 mg/week) and folic acid (≥ 5 mg/week). Similarity between SDZ ETN and ETN for change from baseline in disease activity score including 28 joint count C-reactive protein (DAS28-CRP) at week 24 (primary endpoint) and comparable safety and immunogenicity profile of SDZ ETN and ETN have previously been demonstrated at week 24. Therefore, 48-week results of the study after a single switch from ETN to its biosimilar at week 24 were presented. The 48-week results from the EQUIRA study showed that switch from ETN to SDZ ETN in subjects with moderate-to-severe rheumatoid arthritis does not affect the efficacy, safety, or immunogenicity of etanercept.

4. Discussion

Biologics are a revolutionary therapeutic tool for patients in debilitating and life-threatening states but are limited by their higher costs and less access to the poor population.

Thankfully the options widened to newer and cheaper alternatives that have started to enter the market. Biosimilars are medicines that resemble previously approved reference biologics currently on the market. Biosimilars have the potential to join the race in the treatment of RA for economically challenged patients and enable accessibility to the general population like generic medications. Biosimilars are biological components that are highly similar to the existing bDMARDs which are already approved by the U.S. Food and Drug Administration (USFDA), Table 1.

Only minor changes in clinically inert substances are allowed in Biosimilars. Biosimilars cannot be the exact copies of Biologics, but mimic the active component in the reference parent biologic.

4.1. We entered the time of biologic medicines

With a growing aged population and increased demand for treating chronic illnesses, biologic use is steadily on the rise. Biosimilars will start to play a significant part in the management of RA as nowadays the treatment strategies of any diseases are mainly governed by the value and cost. The introduction of newer Biosimilars in the coming years would save patients as much as $250B globally and increase the accessibility to biologic therapy for the additional 1.2M RA patients by the year 2025. This will broaden the therapeutic options for patients who are chronically ill and who were denied or being managed only with conventional treatments and utilize the extended advantage of biologic medicines.

4.2. Current status of biosimillar in rheumatology in India[18]

The Biosimilars have been approved and accepted in India widely. The very first Biosimilar approved was Hepatitis B Vaccine in the year 2000. Twenty-five or more Biosimilars are currently available in the Indian pharmaceutical market. The following list enumerates the list of approved Biosimilars in Rheumatology in India.(Table 2)

The purpose of the review is to assess the safety and efficacy of biosimilars to the reference molecule. All the studies reviewed showed comparable results with not much difference in safety and efficacy profile. Assessment markers like DAS SCORE, ACR SCORE, and CRP were used in most of the studies and were found to improve.

Table 2: Biosimillars approved in India in Rheumatology till date

S.No.	Biosimilar	Active moiety	Originator	Approved Indication	Launch date in India	Company
1.	Etacept	Etanercept	Enbrel	AS, RA, PsA, Ps	April 2013	Cipla
2.	Intacept	Etanercept	Enbrel	AS, RA, PsA, Ps	Mar. 2015	Intas
3.	Infimab	Infliximab	Remicade	AS, RA, PsA, Ps, IBD	Sep. 2014	Epirus
4.	Exemptia	Adalimumab	Humira	AS, RA, PsA, Ps, IBD	Dec 2014	Zydus
5.	Reditux RA	Rituximab	Mabthera	Leukemia, Lymphoma, RA	Apr 2007	Dr Reddy's

5. Conclusion

The advanced development and technology in Rheumatology have paved the way for earlier detection and diagnosis, and the use of Biologic DMARDs and their Biosimilar counterpart will grow in the coming days. Though with strict guidelines, usage of Biosimilars will be affordable.

Development and treatment strategies with Biosimilars must be well-informed and documented to the Physicians and Rheumatologists. A careful approach has to be followed.

The full potential of the Biosimilars must be explored by the physicians as it can provide extended therapeutic benefits which would increase the effectiveness of healthcare services worldwide.

Biosimilars may also considerably bring down the cost of biologics and, consequently, increase the utilization of biologic treatments.

Biosimilars can provide the comparative results as biologics effectively at minimum cost of the treatment and also open up newer and multiple prescriptions that could reduce the cost burden on society.

6. Source of Funding

None.

7. Conflict of Interest

None.

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