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Original Research Article

Tumor Necrosis Factor Alpha Targeting Biosimilars for the Treatment of Rheumatoid Arthritis

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Abstract:

Immunotherapy may greatly enhance rheumatoid arthritis treatment. Tumor necrosis factor alpha antagonists, such as infliximab, etanercept, and adalimumab, are used to treat rheumatoid arthritis. These drugs lower inflammation and improve symptoms by targeting and inhibiting tumor necrosis factor alpha, a significant inflammatory cytokine implicated in the development of rheumatoid arthritis. Infliximab not only improves physical performance and quality of life, but it also slows the progression of joint deterioration and keeps the signs and symptoms of rheumatoid arthritis at bay. Etanercept is both safe and effective in the treatment of rheumatoid arthritis. Combination treatment with etanercept and methotrexate is more successful than monotherapies in reducing disease activity, slowing joint deterioration, and improving function. Adalimumab, alone or in conjunction with methotrexate, alleviates rheumatoid arthritis symptoms. Because of the introduction of biosimilars that are less expensive than the original drugs, treatment may now be made available to a larger number of patients. The review includes a thorough examination of the most recent evidence-based data on tumor necrosis factor alpha inhibiting biosimilars with respect to their safety and efficacy.

Keywords: Tumor Necrosis Factor, Biosimilars, Rheumatoid Arthritis, Etanercept, Infliximab, Adalimumab.

Introduction

Rheumatoid arthritis (RA) is one of the inflammatory diseases that causes joint inflammation and can also affect other parts of the body. This chronic inflammatory disease predominantly affects the synovial joints and is caused by the combination of genetic and environmental factors [1]. Tumor Necrosis factor alpha (TNF alpha) is known to be a major inflammatory cytokine involved in the development of rheumatoid arthritis. It is commonly found at elevated levels in RA patients. In RA, inflammation is defined by the build-up of inflammatory cells, notably Type 1 helper T cells (Th1) and macrophages. B lymphocytes, plasma cells, and dendritic cells are also implicated in the inflammatory process that leads to RA [2].

In rheumatoid arthritis, the secretion of TNF alpha by Th1 cells and macrophages plays a pivotal role in triggering a series of detrimental events. TNF alpha acts on synovial fibroblasts, stimulating these cells and producing their effects. This involves promoting epidermal hyperplasia and recruiting inflammatory cells to the affected joints. In response to cytokines such as interleukin-1, interleukin -6, and TNF alpha, activated synovial fibroblasts overexpress cathepsins and matrix metalloproteinases. This overexpression causes the breakdown of collagen and proteoglycans, which are important components of joint structure. As a result, cartilage and bone are damaged, eventually leading to joint erosion, a defining hallmark of RA [3]. TNF alpha is initially produced as a trans-membrane protein and is then cleaved by an enzyme known as TNF alpha converting enzyme. TNF alpha is converted into a soluble form during this cleavage process. When TNF alpha becomes soluble, it binds to TNF receptors and activates the innate immune response [4]. TNF alpha is primarily produced by two types of cells: myeloid cells and T cells. TNF alpha is produced by myeloid-lineage cells such as macrophages and dendritic cells in response to various stimuli.

This includes activation via toll-like receptors, cytokine stimulation, and activation produced by lipid mediators. T cells, too, contribute to the generation of TNF alpha, which contributes to the overall inflammatory response in numerous immune-related processes [5]. Disease-modifying antirheumatic drugs (DMARDs) are often given to patients with rheumatoid arthritis, but they can also be used to treat ankylosing spondylitis, psoriatic arthritis, and systemic lupus erythematosus. These

drugs are intended to suppress the body's hyperactive immunological and/or inflammatory responses. DMARDs, in contrast to medications that give instant symptom relief, usually require weeks or months to act. They are classified as either conventional synthetic DMARDs (csDMARDs) or biologic DMARDs (bDMARDs). Methotrexate, sulfasalazine, and hydroxychloroquine are examples of csDMARDs. bDMARDs, on the other hand, are produced from live cells and target immune system components. Studies have shown that combining TNF targeting medications with methotrexate has an additional benefit, leading to the development and licensing of biologic therapies that precisely target TNF alpha [6]. There are presently five TNF targeting biologic DMARDs available: Adalimumab, Etanercept, Infliximab, Certolizumab, and Golimumab. All approved bDMARDs are considered equally effective and can be used interchangeably without preference, according to the European League against Rheumatism (EULAR) guidelines, unless unique criteria or considerations come into play. This means that the TNF alpha targeting drugs may be selected according to patient characteristics and needs [7].

Biological drugs, often known as biologics, may be extremely expensive to develop, manufacture, and market. This high cost frequently causes access barriers, particularly to countries that lack resources for healthcare. The emergence of biosimilars, on the other hand, enables a less expensive choice yet maintains comparable safety, efficacy, and quality to licensed biologic treatments. Biosimilars also have the potential to decrease total spending on healthcare dramatically.

These therapies are identical to the original biologics, yet they are produced by different companies once the reference product's patent expires. Extensive testing is carried out to assess biosimilarity in terms of safety, efficacy, and quality. Biosimilars have been developed as alternatives for the original drugs in the treatment of rheumatoid arthritis (RA) using TNF alpha targeting pharmaceuticals such as infliximab, adalimumab, and etanercept.

These biosimilars offer more cost-effective alternatives for RA patients. The introduction of biosimilars in the market promotes competition, resulting in cheaper prices and greater accessibility to these life-saving therapies. This benefits not only the patients who can now afford prescription medications, but also the healthcare systems by reducing their cost load [8].

Methods

The evaluation of efficacy and safety data for biosimilars approved by the U.S. Food and Drug Administration (FDA) was conducted using public assessment reports. These reports serve as valuable sources of information that provide a comprehensive overview of the regulatory evaluation process and findings for each biosimilar. One of the most common parameter to assess the efficacy for anti-rheumatoid drugs is American College of Rheumatology (ACR) response criteria, specifically ACR20, ACR50, and ACR70. Other important efficacy parameters for rheumatoid arthritis are European League against Rheumatism (EULAR) scores and Disease Activity Score (DAS). These parameters quantify the improvement in rheumatoid arthritis condition such as assessment of pain, serum C-reactive protein (CRP) concentration and erythrocyte sedimentation rate (ESR) and reduction in the associated symptoms such as number of swollen and tender joints.

These criteria serve as standardized measurements to assess the therapeutic response of patients with rheumatic conditions. By evaluating these parameters, the efficacy of treatments, including biosimilars, can be objectively assessed in clinical studies and real-world settings.

Regarding safety evaluation, the paper focused on treatment-emergent adverse events (TEAEs) and immunogenicity. TEAEs refer to any adverse events that occur during or after treatment, regardless of whether they are causally related to the biosimilar. The safety data extracted from the public assessment reports enabled the assessment of the occurrence and nature of TEAEs associated with the use of biosimilars.

Immunogenicity, or the potential for the biosimilar to induce an immune response, was also considered. Immunogenicity data obtained from the public assessment reports were analyzed to evaluate the frequency and characteristics of immunogenic reactions associated with the biosimilars.

By utilizing the publicly available assessment reports, the paper ensured a systematic and objective evaluation of the efficacy and safety of biosimilars approved by US FDA. This approach allowed for a comprehensive analysis of the available data and contributed to the understanding of the performance of these biosimilars in real-world clinical settings.

Infliximab: Infliximab is a chimeric human immunoglobulin G1 monoclonal antibody. The variable regions of infliximab, responsible for recognizing and binding to the target molecule, TNF alpha, are derived from mouse antibodies. On the other hand, the constant regions of infliximab are derived from human antibodies.

Remicade, a product of Janssen Biologics, was the first infliximab to be approved in 1999 by

European Medicines Agency [9] and US FDA [10] for the treatment of rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, psoriatic arthritis, and ankylosing spondylitis.

Infliximab is administered through intravenous infusion, and its terminal half-life is approximately 8 to 10 days. Generally, infliximab is given at intervals of 4 to 8 weeks. The dosage of infliximab can vary depending on the specific treatment requirements, typically ranging from 3 to 6 (or up to 10) mg/kg [11]. The infliximab biosimilars approved by US FDA are listed in Table 1.

Table 1: Infliximab biosimilars approved by US-FDA

Brand name	Sponsor	Approved on
Avsola [12]	Amgen	December 2019
Renflexis [13]	Samsung Bioepis	February 2018
Ixifi [14]	Pfizer	December 2017
Inflectra [15]	Celltrion	April 2016

Clinical efficacy, immunogenicity and safety of infliximab biosimilars: All the infliximab biosimilars were compared against the reference product Remicade in various phase III clinical efficacy studies. The primary efficacy endpoint for all the clinical studies was ACR20 at different weeks of treatment.

The commonly used secondary endpoints were ACR20, ACR50, ACR70, EULAR and DAS-28 scores. All the biosimilars showed equivalent responses with the reference product for primary and secondary efficacy endpoints. The safety of the infliximab biosimilars was assessed by comparing the incidence of binding and neutralizing ADAs and treatment emergent adverse events (TEAE) between infliximab biosimilars and the reference product. All the biosimilars showed comparable safety profile with the reference product. Overall, these clinical studies support the use of biosimilars as effective and safe alternatives for reference drugs in the treatment of rheumatoid arthritis. The summary of efficacy studies for infliximab biosimilars is given in Table 2 and

Table **3**.

Table 2: Summary of clinical efficacy for infliximab biosimilars

Treatment Comparison	Efficacy endpoints	Primary efficacy results
Avsola vs. Remicade	• Primary: • ACR20 at week 22 • Secondary: • ACR20 at 2, 6, 14, 30, 34, 38, 46, and 50 • ACR50 and ACR70 at 2, 6, 14, 22, 30, 34, 38, 46, and 50 • DAS28-CRP change at weeks 2, 6, 14, 22, 30, 34, 46, and 50	ACR20 at week 22 • Avsola: 68.1% • Remicade: 59.1%
Renflexis vs. Remicade	• Primary: • ACR20 at week 30 • Secondary: • ACR20 at week 54 • ACR50 and ACR70 at weeks 14, 30 and 54 • AUC of ACR-N up to week 30 • DAS28 score at weeks 30 and 54 • EULAR at weeks 30 and 54 • AUC of DAS28 change up to week 30	ACR20 at week 30 • Renflexis: 55.5% • Remicade: 59.0%
Ixifi vs. Remicade	• Primary: • ACR20 at week 14 • Secondary: • ACR20 at weeks 2, 4, 6, 12, 22, and 30 • ACR50 and ACR70 at week 14 and up to week 30 • Change in ACR response criteria at week 14 and up to week 30 • DAS28-CRP score at week 14 and up to week 30 • EULAR at week 14 and up to week 30	ACR20 at week 14 • Ixifi: 61.1% • Remicade: 63.5%

Inflectra vs. Remicade	• Primary: • ACR20 at week 30 • Secondary: • ACR20 at week 14 • ACR50 and ACR70 at weeks 14 and 30 • DAS28 (ESR and CRP) at weeks 14 and 30 • EULAR at weeks 14 and 30 • Simplified and clinical disease activity index at weeks 14 and 30 • SF-36 at weeks 14 and 30	ACR20 at week 30 • Inflectra: 60.9% • Remicade: 58.6%

Table 3: Immunogenicity and safety summary for infliximab biosimilars

Treatment Comparison	Anti-drug antibody positive patients (%)	Neutralizing antibody positive patients (% of ADA positives)	Treatment Emergent Adverse Events (%)
Avsola vs. Remicade at week 22	• Avsola: 57.1 • Remicade: 60.6	• Avsola: 18.0 • Remicade: 20.8	• Avsola: 20.3 • Remicade: 21.2
Renflexis vs. Remicade at week 30	• Renflexis: 54.4 • Remicade: 48.4	• Renflexis: 92.7 • Remicade: 87.5	• Renflexis: 61.7 • Remicade: 65.2
Ixifi vs. Remicade at week 14	• Ixifi: 48.6 • Remicade: 51.2	• Ixifi: 79.0 • Remicade: 85.6	• Ixifi: 57.3 • Remicade: 54.0
Inflectra vs. Remicade at week 30	• Inflectra: 55.6 • Remicade: 54.3	• Inflectra: 100.0 • Remicade: 100.0	• Inflectra: 60.1 • Remicade: 60.8

Etanercept: Etanercept is a genetically engineered fusion protein that is composed of two molecules, one containing the extracellular domain of TNF receptor II (p75) and one containing the Fc portion of human IgG1 [16]. Etanercept functions as a decoy receptor by binding with high affinity to both soluble and trans-membrane forms of TNF alpha and prevents its pro-inflammatory response. Enbrel, a product of Amgen, was the first etanercept to be approved in 1998 by US FDA [17] and in 2000 by EMA [18] for the treatment of Rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis and plaque psoriasis.

The half-life of Etanercept is between 3 and 5.5 days, thus it is administered subcutaneously (SC), either once or twice a week (50 mg) [19]. The etanercept biosimilars approved by US-FDA are listed in Table 4.

Table 4: Etanercept biosimilars approved by US-FDA

Brand name	Sponsor	Approved on
Eticovo [20]	Samsung Bioepis	April 2019
Erelzi* [21]	Sandoz	August 2016

***Clinical efficacy study was not performed on RA patients.**

Clinical efficacy, immunogenicity and safety of etanercept biosimilars: Eticovo is the only biosimilars of etanercept approved by US FDA for the treatment of rheumatoid arthritis. However, Erelzi was compared to reference product Enbrel in a phase II EQUIRA study in patients with moderate to severe active RA.

The result showed that Erelzi is comparable to the reference product in terms of safety and efficacy [22]. The phase III clinical study for Eticovo used ACR20 at week 24 as primary efficacy endpoint and ACR50, ACR70, EULAR and DAS-28 scores at various time-points as secondary efficacy endpoints. The efficacy results for Eticovo were equivalent with the reference product Enbrel. The incidence of binding and neutralizing ADAs and TEAE were comparable between Eticovo and reference product where the former two were reported to be very less. The summary of efficacy studies for etanercept biosimilars is given in

Table **5** and

Table **6**.

Table 5: Summary of clinical efficacy for etanercept biosimilars

Treatment Comparison	Efficacy endpoints	Results
Eticovo vs. Enbrel	• Primary: • ACR20 at week 24 • Secondary: • ACR20 at week 52 • ACR50 and ACR70 at weeks 24 and 52 • ACR-20, 50 and 70 at weeks 24 and 52 • AUC of ACR-20, 50 and 70 at week 24 • DAS28 at weeks 24 and 52 • EULAR at weeks 24 and 52 • AUC of DAS28 at week 24 • ACR70 for six consecutive months at week 52 • modified Total Sharp Score (mTSS) at Week 52	ACR20 at week 24 • Eticovo:73.6 % • Enbrel: 71.7%

Table 6: Immunogenicity and safety summary for etanercpt biosimilars

Treatment Comparison	Anti-drug antibody positive patients (%)	Neutralizing antibody positive patients (% of ADA positives)	Treatment Emergent Adverse Events (%)
Eticovo vs. Enbrel at week 24	• Eticovo: 1.0 • Enbrel: 13.0	• Eticovo: 0.0 • Enbrel: 0.0	• Eticovo: 58.5 • Enbrel: 60.3

Adalimumab: Adalimumab is a complete human monoclonal antibody (IgG) composed of two heavy chains and two light chains with a molecular weight of approximately 144 kDa [23]. The amino acid sequence of Adalimumab is engineered to target and bind specifically to TNF alpha. Humira, a product of AbbVie, was the first adalimumab to be approved in 2002 by US FDA [24] and in 2003 by EMA [25].

It has a serum half-life of 10-20 days and can be administered alone or as a combination therapy with other DMARDs, especially Methotrexate [26]. The recommended adalimumab dose is 25 mg twice a week. The adalimumab biosimilars approved by US-FDA are listed in Table 7.

Table 7: Adalimumab biosimilars approved by US-FDA

Brand name	Sponsor	Approved on
Yuflyma [27]	Celltrion	May 2023
Idacio* [28]	Fresenius Kabi	December 2022
Yusimry* [29]	Coherus BioSciences	December 2021
Hulio [30]	Mylan Pharmacetuicals	July 2020
Abrilada [31]	Pfizer	November 2019
Hadlima [32]	Samsung Bioepis	July 2019
Hyrimoz* [33]	Sandoz	October 2018
Cyltezo [34]	Boehringer Ingelheim	August 2017
Amjevita [35]	Amgen	September 2016

***Clinical efficacy study was not performed on RA patients.**

Clinical efficacy, immunogenicity and safety of adalimumab biosimilars: For 6 out of 9 adalimumab biosimilars, the clinical efficacy studies were performed on patients with moderate to severe RA in comparative studies against reference product Humira. As with the other bDMARDs, the commonly used efficacy endpoints were ACR20, ACR50, ACR70, EULAR and DAS-28 scores. The efficacy endpoints and incidences of treatment emergent adverse events and immunogenicity were comparable between the biosimilars and the reference product.

The summary of efficacy studies for adalimumab biosimilars is given in

Table 8 and

Table 9.

Table 8: Summary of clinical efficacy for adalimumab biosimilars

Treatment Comparison	Efficacy endpoints	Results
Yuflyma vs. Humira	Primary: • ACR20 at week 24 Secondary: • ACR20 over 52 weeks • ACR50 and ACR70 over 52 weeks • DAS 28 (CRP) over 52 weeks • EULAR response (CRP) • Clinical disease activity index (CDAI) and disease activity index (SDAI) over 52 weeks	ACR20 at week 24 • Yuflyma:82.72% • Humira: 82.72%
Hulio vs. Humira	Primary: • ACR20 at week 24 Secondary: • ACR20 at weeks 0, 2, 4, 8, 12, 16 and 20 • ACR50 and ACR70 at weeks 0, 2, 4, 8, 12, 16, 20 and 24 • DAS 28 (CRP) at week 24 • Tender and swollen joint counts at weeks 0, 2, 4, 8, 12, 16, 20 and 24	ACR20 at week 24 • Hulio:71.7% • Humira: 73.2%
Abrilada vs. Humira	Primary: • ACR20 at week 12 Secondary: • ACR50 and ACR70 at weeks 2, 4,6, 8, 18, and 26 • DAS 28 (CRP) at weeks 2, 4,6, 8, 18, and 26 • EULAR response at weeks 2, 4,6, 8, 18, and 26	ACR20 at week 12 • Abrilada:68.4% • Humira: 71.1%
Hadlima vs. Humira	Primary: • ACR20 at week 24 Secondary: • ACR20 at week 52 • ACR50 and ACR70 at weeks 24 and 52 • DAS 28 at weeks 24 and 52 • EULAR response at weeks 24 and 52	ACR20 at week 52 • Hadlima:72.4% • Humira: 72.2%
Cyltezo vs. Humira	Primary: • ACR20 at weeks 12 and 24 Secondary: • ACR20 at week 48 • ACR50 and ACR70 at weeks 12, 24 and 48 • DAS28-CRP and DAS28-ESR at weeks 12, 24 and 48 • EULAR response at weeks 12, 24 and 48	ACR20 at week 12 • Cyltezo: 66.4% • Humira: 60.5% ACR20 at week 24 • Cyltezo: 68.4% • Humira: 64.0%
Amjevita vs. Humira	Primary: • ACR20 at week 24 Secondary: • ACR20 at weeks 2, 4, 8, 12 and 18 • ACR50 and ACR70 at weeks 2, 4, 8, 12 and 18	ACR20 at week 24 • Amjevita: 74.6% • Humira: 72.4%

	• DAS28-CRP at weeks 2, 4, 8, 12 and 18 • EULAR response at weeks 2, 4, 8, 12 and 18	

Table 9: Immunogenicity and safety summary for adalimumab biosimilars

Treatment Comparison	Anti-drug antibody positive patients (%)	Neutralizing antibody positive patients (% of ADA positives)	Treatment Emergent Adverse Events (%)
Yuflyma vs. Humira at week 24	• Yuflyma: 28.7 • Humira: 35.8	• Yuflyma: 89.2 • Humira: 88.8	• Yuflyma: 52.2 • Humira: 56.8
Hulio vs. Humira at week 24	• Hulio: 57.9 • Humira: 55.5	• Hulio: 98.6 • Humira: 99.5	• Hulio: 56 • Humira: 62
Abrilada vs. Humira at week 12	• Abrilada: 25.9 • Humira: 30.4	• Abrilada: 40.3 • Humira:22.0	• Abrilada: 48.1 • Humira:47.8
Hadlima vs. Humira at week 24	• Hadlima: 35.0 • Humira: 35.2	• Hadlima: 51.8 • Humira: 48.3	• Hadlima: 36.2 • Humira:39.9
Cyltezo vs. Humira at week 12	• Cyltezo: 32.5 • Humira: 34.9	• Cyltezo: 38.6 • Humira:50.0	Not reported
Cyltezo vs. Humira at week 24	• Cyltezo: 43.2 • Humira: 47.8	• Cyltezo: 37.8 • Humira: 42.4	• Cyltezo: 42.3 • Humira: 45.8
Amjevita vs. Humira at week 24	• Amjevita: 38.7 • Humira: 38.5	• Amjevita: 23.8 • Humira: 29.0	• Amjevita: 50.0 • Humira: 55.0

Discussion

The results of the trials evaluated give persuasive evidence that biosimilars are viable alternatives to reference medicines in the treatment of rheumatoid arthritis (RA). Etanercept, infliximab and adalimumab biosimilars revealed equivalent effectiveness outcomes in various phase III studies, including ACR20, ACR50, and ACR70 responses, as well as disease activity markers such as DAS28-CRP, CDAI, and SDAI. These findings suggest that biosimilars can achieve clinical outcomes comparable to reference medicines in terms of disease control and symptom improvement. Furthermore, biosimilars' safety characteristics were determined to be equivalent to those of reference medications. Treatment-emergent adverse events (TEAEs) were common in both the biosimilar and reference product groups, with most occurrences being mild to moderate in severity.

Importantly, no fatalities or major adverse events associated with biosimilar usage were recorded in the trials examined. These data imply that biosimilars can be used safely in the treatment of RA without jeopardizing patient safety. The immunogenicity of biosimilars is one important parameter to assess the safety of biological drugs. While the frequency of binding and neutralising anti-drug antibodies (ADAs) differed across the biosimilar and reference product groups, these variations did not translate into clinically relevant results.

An important point to note here is that the level of binding and neutralising ADAs depends on the sensitivity of the assay used hence the comparison across different biosimilar candidates may not be appropriate. The presence of ADAs had no effect on the safety or effectiveness of biosimilars, and response rates and disease activity levels were comparable among patients with varying levels of ADA titers.

These data imply that biosimilar immunogenicity is typically well-controlled and does not impair therapeutic efficacy. It's worth noting that the trials examined primarily infliximab and adalimumab biosimilars.

Conclusion

Biosimilars have emerged as effective and safe alternatives to reference drugs in the treatment of rheumatoid arthritis, based on the findings of the examined study. Multiple phase III trials have demonstrated that biosimilars and reference medications have comparable efficacy outcomes, including ACR20, ACR50, and ACR70 responses, as well as disease activity indicators including DAS28-CRP, CDAI, and SDAI. Biosimilars' safety profiles were also found to be similar, with no significant changes in the frequency of treatment-emergent or serious side effects when compared to

reference drugs. Furthermore, biosimilars' immunogenicity, as demonstrated by the presence of anti-drug antibodies, has no impact on their safety or efficacy. Biosimilars showed comparable response rates and disease activity levels across ADA titer levels, suggesting that immunogenicity did not affect the effectiveness of their treatment. These findings support the widespread use of biosimilars as cost-effective alternatives in rheumatoid arthritis management. Biosimilars offer an acceptable strategy to improving access to biologic drugs while reducing healthcare costs through providing comparable clinical outcomes while ensuring patient safety. Continued research and long-term monitoring is needed to ensure whether biosimilars continue to prove safe and effective in the treatment of rheumatoid arthritis and other autoimmune diseases.

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