Review of Biosimilars of Adalimumab

V.V. Kaushik

Abstract

A first fully humanized monoclonal antibody approved by US Food and Drug Administration (FDA) in 2002 was Adalimumab. Clinical efficacy and safety of adalimumab has been assessed in various trials in rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, Crohn's Disease, and ulcerative colitis. It is one of the major sales success among biological and still one of the greatest blockbuster amongst monoclonal antibodies. With the advent of patent expiry of the parent drug HUMIRA, several potential biosimilars have debuted in various markets worldwide. Present article will discuss current situation of molecules that are front-runners to become adalimumab biosimilars with particular stress on Indian market and ZRC3197 (Adalimumab Biosimilar).

Introduction

Biologically derived monoclonal antibodies have proven extremely beneficial to a large number of patients across the world.[1] There is an increasing demand for development of biosimilar molecules especially in areas of cancer and autoimmune diseases. Biosimilars are "similar" or "highly similar" to the reference medicinal products (originator products) following the European Medicines Agency (EMA) and the US FDA (Food and Drug Administration) regulatory guidelines. Tumor necrosis factor α (TNF-α) is an important inflammatory cytokine which is produced by activated monocytes or macrophages. TNF plays a key role in the pathogenesis of autoimmune-mediated inflammatory diseases. First synthesized as a transmembrane protein (tTNF) later it is cleaved into a soluble form (sTNF), each having its own biological function.[2] Inhibition of TNF can cause down-regulation of abnormal and progressive inflammatory processes resulting in rapid and sustained clinical remission, improved quality of life, and prevention of target organ damage. TNF-α antagonists are biological agents that bind to TNF-α molecule. These substances were first approved for use in rheumatic diseases and are now widely used. Subsequently, TNF-alpha inhibitors have demonstrated effective therapeutic potential in treating several autoimmune conditions such as rheumatoid arthritis and inflammatory bowel disease.[3]

Currently available anti-TNF agents bind to both the forms of TNF (tTNF, sTNF), thus having limited specificity[4]. Most widely used anti TNF agents include adalimumab, etanercept, infliximab, golimumab and certolizumab.[3] As the patent expiration dates of the innovator drugs are nearing, companies have started developing biosimilars. These agents are similar in safety, efficacy and quality to the original innovator and provide additional advantage to patients in terms of affordability and low cost of therapy, while expanding patient access to therapies. Regulatory guidelines concerning biosimilars have been given by European Medicines Agency (EMA), the US Food and Drug Administration (FDA). In India, biosimilars termed as "similar biologics" are developed in accordance with the guidelines issued by the Central Drugs Standard Control Organization (CDSCO) It has issued specific guidelines on regulatory requirements for market authorization of biosimilars.[5] An iterative process is followed to achieve desired quality for the biosimilar during development when there is no knowledge about the originator process. Biosimilars use the same host system harboring the gene that encodes the same amino acid sequence as that of the targeted originator.[6] However, clinical equivalence of biosimilars has been questioned by some professionals as innovators have undergone several changes since their original formulation, and thus the agents currently administered to patients are not exactly identical but only similar to those approved by regulators.[5] Adalimumab is a fully human monoclonal antibody that acting against TNF. It was originally approved for the treatment of rheumatoid arthritis (RA) in 2002. However, its clinical effectiveness has been demonstrated in several inflammatory conditions such as PsA (Psoriatic Arthritis), plaque psoriasis, inflammatory bowel diseases (Crohn's disease, ulcerative colitis, Paediatric Crohn's disease, and intestinal Behçet's disease), AS (ankylosing spondylitis), axial spondyloarthritis (SpA) and juvenile idiopathic arthritis.[7] This article discusses the present situation of the main candidates of adalimumab biosimilars with focus on Indian biosimilar ZRC3197(Adalimumab Biosimilar).

Adalimumab

Adalimumab was the first fully humanized monoclonal antibody approved by the FDA in 2002. Its sales have increased 20% per year, totaling to USD 8.5 billion.[7] with estimated net profit USD 16 billion in 2016.[8] Adalimumab is a tetramer

Apollo Hospital, Chennai, Tamil Nadu

Table 1: Clinical uses of adalimumab in various autoimmune disorders with dose

Clinical use	Dose	Mean trough levels
Rheumatoid Arthritis	20, 40 and 80 mg subcutaneous dosing every other week and every week	Approximately 5 μg/ml without concurrent methotrexate and 8 to 9 μg/ml with concurrent methotrexate with a dose of 40 mg every other week
		Serum trough levels at steady-state increase proportionally with dose increase
Polyarticular juvenile idiopathic arthritis	24 mg/month (up to a maximum of 40 mg every other week)	5.6 ± 5.6 μg/mL (102 % CV) without concurrent methotrexate and 10.9 ± 5.2 μg/mL (47.7% CV) with concurrent methotrexate (values measured 2 from week 20 to 48)
Crohn's disease	40-160 mg//week	Loading dose of 80 mg adalimumab on week 0 followed by 40 mg adalimumab on week 2 leads to about 5.5 μg/mL trough concentration
		Loading dose of 160 mg adalimumab on week 0 followed by 80 mg adalimumab on week 2 achieves 12 μg/mL trough concentration
Ulcerative Colitis	40-160 mg/week	Same as above

consisting of two light kappa chains and two heavy immunoglobulin G1 (IgG1) chains, with each heavy chain containing one N-glycosylation site.[9] Adalimumab is the result of a partnership between BASF Bioresearch Corporation and Cambridge Antibody Technology which started in 1993. "Phage display" technique was used in the discovery of the drug and it was named D2E7. Manufacturing and development was done by BASF Bioresearch and BASF Knoll respectively. Subsequent manufacturing and commercialization of the drug was done by Abbott. In January 2013, Abbott Laboratories was split into two companies, Abbott Laboratories and AbbVie Inc. Subsequent development and sale of Humira (innovator) was done by AbbVie.

Clinical Indications (Table 1)

Rheumatoid arthritis

Adalimumab was approved by the FDA in 2002 for the treatment of adults with moderate to severe RA and inadequate response to at least one disease-modifying antirheumatic drug (DMARD).[10] Currently, it is indicated in combination with methotrexate (MTX) for treatment of patients with moderate to severe RA and unsatisfactory previous responses to DMARDs or active, severe, and progressive RA. Recommended single dose is 40 mg per subcutaneous route every other week.[11]

Psoriatic Arthritis (PsA) and Psoriasis

Use of adalimumab in patients with PsA was approved in 2005 to relieve the symptoms of arthritis. Additionally, it is also approved in cases of severe psoriasis and chronic plaque psoriasis without arthritis where it is shown to be superior to etanercept and methotrexate.[12]

Ankylosing spondylitis (AS)

In 2006, the EMA and FDA approved the use of adalimumab for reducing the signs and symptoms of AS in cases that do not respond to conventional therapy. Adalimumab effectively relieves spinal, sacroiliac joint inflammation and spondyloarthritis which are typically seen in AS.[13]

Crohn's disease (CD)

Adalimumab was approved in 2007 to reduce the signs and symptoms and induce and maintain clinical remission in adults with moderately to severely active CD and inadequate response to conventional therapy. Patients who do not benefit from treatment with infliximab are also included in the indication.[14]

Juvenile idiopathic arthritis (JIA)

Adalimumab with MTX is indicated for the treatment of moderate to severe polyarticular JIA in patients aged 2 years or older and with unsatisfactory response to one or more DMARDs. It is also indicated in patients as a monotherapy in those having intolerance to MTx. Safety data in patients less than 2 years has not been assessed.[11]

Behcet's disease (BD)

It is first biological approved for use in BD in some countries in patients who are refractory to conventional therapies.

Ulcerative colitis

Adalimumab has been approved for use in patients with moderately to severely active UC and resistant to conventional treatment.[15] Some other approved indications include moderate to severe hidradenitis suppurativa, moderate to severe pediatric Crohn's Disease, intermediate, posterior and panuveitis, non-infectious uveitis.

Pharmacodynamics (PD)

Adalimumab is a fully humanized monoclonal antibody composed of variable IgG1 light and heavy chains (constant kappa regions). It does not have any nonhuman component or artificially fused peptide sequences.[16] Being a TNF-α antagonist it binds to TNF-α, and blocks its interaction with the membrane receptors p55 and p75. Out of the 2 subtypes of TNF-α, it has affinity and specificity only for sTNF-α and not for lymphotoxins.[17] Clinical trials have also shown that adalimumab causes significant reductions in the acute-phase reactant levels (such as CRP and fibrinogen), erythrocyte sedimentation rate, concentration of interleukins (IL-1, IL-6, IL-8), concentration of cartilage and synovial remodeling markers, the amount of macrophage colony-stimulating factors, and the concentration of adhesion molecules that account for leukocyte migration, such as intercellular adhesion molecule 1 and vascular cell adhesion molecule 1.[18] Adalimumab also induces lysis of TNF-α-expressing cells in the presence of complement and in CD this is believed to be the main mechanism of action of TNF-α blockers.[19] Also, absolute number and density of epidermal Langerhans cells are reduced in patients with untreated psoriasis

as compared to patients without the disease. Langerhans cells might have anti-inflammatory properties and that also they are involved in the physiological differentiation of keratinocytes. Treatment with adalimumab restores the density of Langerhans cells, and this is believed to be the main mechanism of action of this drug in plaque psoriasis.[19]

Pharmacokinetics (PKs)

Recommended dose of adalimumab is 40 mg per subcutaneous route every other week in RA and initial dose of 80 mg per subcutaneous route, followed by 40 mg every other week in psoriasis. Maximum serum concentration (Cmax) of the drug is 4.7±1.6 mg/mL with the synovial concentration being 31%–96% of the serum levels. Time to Cmax is 131±56 hours and bioavailability of adalimumab is 64%.75 Drug is slowly eliminated in the presence of AAA (Anti-Adalimumab Antibodies) and in individuals older than 40 years. Volume of distribution(Vd) is 4.7-6 L and drug half-life (t1/2) is 2 weeks (10–20 days).[20]

Safety and Pharmacovigilance

Favourable responses to adalimumab is not seen in all the patients. Unfavourable response can be either primary (no response since the beginning of treatment) or secondary (loss of efficacy during treatment) failure. One of the mechanisms of secondary failure is immunogenicity, whereby AAA is produced, which might neutralize the therapeutic action of the drug. AAA production might be related to specific patient characteristics like genetic makeup, comorbid conditions and other concomitant immunomodulators used along with adalimumab.77 AAA production reduces bioavailability and also reduces clinical response to the drug. It has been suggested that measurement of AAA might be useful to predict the response to long-term treatment with adalimumab and to establish the need to adjust the dose of the drug or to change the therapy.[21] An adalimumab sparing effect of MTx has been noted in patients suffering from RA, suggesting a reduced AAA production. However, this association needs to be confirmed. Clinical trials with long-term follow-up and more than 10 years of commercialization has shown that adalimumab is associated with adverse effects, including severe infections, allergic reactions, reactivation of the hepatitis B virus, myocardial infarction, and autoimmune phenomena such as psoriasis, lupus-like syndrome and neoplasms. In addition to decreasing response to adalimumab, AAA also have been associated with lupus-like syndrome.[22] Safety monitoring of biosimilars is critical as their manufacturing process is different than the reference product. Also, many adverse drug reactions are detected only after long term usage in large populations. This further increases the need for stronger post marketing surveillance in case of biosimilars. There is always a doubt about the risk management of biosimilars in emerging markets like India.

Regulatory Requirements

EU had formulated guidelines for biosimilars of monoclonal antibodies in 2012, with special emphasis on clinical and nonclinical development. Also, USFDA has published a preliminary guide for a revision of the development and regulation of biosimilars. In India, biosimilars are approved according to the guides formulated by the CDSCO, a branch of the Ministry of Health and Family Welfare, Government of India. CDSCO established specific guidelines in 2012 listing the regulatory requirements for biosimilars to be approved. Proving that a biosimilar is an identical copy of its reference product, analytical techniques have their own limitations and adalimumab has a complex structure. Thus, it is necessary that comparable clinical efficacy and safety of the must be demonstrated. Firstly, full physicochemical and biological characterization of biosimilars in comparison to the corresponding reference products should be performed. In addition, animal studies and evaluation of PDs and toxicity must be done to demonstrate binding to cell receptors. A specific and selective methods must be designed to detect differences between reference product and the biosimilar in question which is only possible in proper clinical and preclinical testing. It is mandatory to perform clinical PK and PD studies and these should be an independent phase or done at the initiation of phase III trial. Similarity in route of drug administration and dose should also be demonstrated in these studies. For comparing the data equivalence studies are preferred options. Any difference in the effect of treatment should be acceptable to the medical fraternity without having any negative impacts on patient treatment.[23] After the available results, indications of the use of biosimilars should reflect the results of clinical trials demonstrating their efficacy and safety. Additional indications might be extrapolated according to the current guidelines.

Adalimumab Biosimilars

Several companies are developing candidates for biosimilars of monoclonal antibodies and fusion proteins, with main focus on six reference products with substantial global sales, ie, adalimumab, bevacizumab, etanercept, infliximab, rituximab, and trastuzumab. Clinical trial databases report trials on the development of adalimumab biosimilars (Table 2). There appear to be several front runners in the race to biosimilar adalimumab in Europe/the US. Momenta Pharmaceuticals (Momenta) and generics maker Sandoz have both completed phase III trials with their candidates. But leading the race are biotech major Amgen and Samsung Bioepis, who have both submitted their marketing applications to EMA for approval.[9] Also, FDA has approved Amgen's biosimilar adalimumab in September 2016. Indian generics maker Zydus

Table 2: Biosimilars and nonoriginator biologicals of adalimumab approved or in development

Company	Status of Biosimilar
AET BioTech/BioXpress Therapeutics, Germany/Switzerland	Biosimilar in pipeline. Development partnership announced in November 2012
Amgen, USA (ABP 501)	Approved by US FDA in September 2016 and submitted to EMA for approval in December 2015
Boehringer Ingelheim, Germany (BI695501)	Phase III study expected to be completed in December 2016
Coherus Biosciences, USA (CHS1420)	Pharmacokinetic study completed in August 2014
Fujifilm/Kyowa Hakko Kirin (Fujifilm Kyowa Kirin Biologics), Japan (FKB327)	Ongoing phase III trial
LG Life Sciences/Mochida Pharmaceutical, South Korea, Japan (LBAL)	Phase I trial expected to be completed in March 2015
Momenta Pharmaceuticals/Baxalta (Baxter spinoff USA) (M923)	Phase III trial started in October 2015
Merck KGaA (Merck Group), Germany (MSB11022)	Phase III trial expected to complete in September 2017
Oncobiologics/Viropro, USA (ONS3010)	Phase III trial expected to start in 2016
Pfizer, USA (PF6410293)	Phase I completed in 2014
PlantForm, Canada	Clincal trials began in 2014. Expected to be launched in 2016
Samsung Bioepis, South Korea (SB5)	Submitted to EMA for approval in July 2016
Sandoz, Switzerland (GP2017)	Started phase III clinical trial in December 2013, expected to be completed in April 2016
Zydus Cadila, India (ZRC3197 (Adalimumab Biosimilar))	Launched in India in December 2014

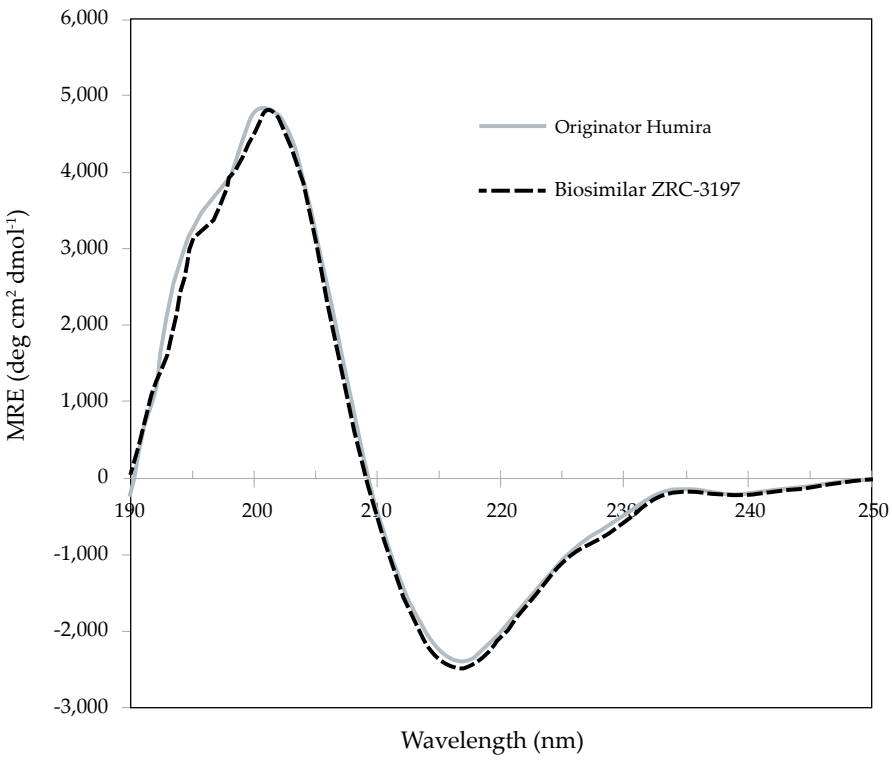


Fig. 1: Comparison of the secondary structure of the biosimilar ZRC-3197 with respect to the originator HUMIRA by CD spectroscopy[25]

Cadila launched its similar biologic in India in December 2014 under the brand name Exemptia™. It is the first company anywhere in the world to launch a biosimilar of adalimumab (Table 2).

American biopharmaceutical company Amgen initiated a Phase III clinical trial of an adalimumab biosimilar candidate in patients with severe RA (ABP 501). Positive results were recently communicated that demonstrate equivalence to reference product relative to efficacy, comparative safety, immunogenicity, and effectiveness. Safety and PKs of Boehringer Ingelheim's biosimilar candidate, BI695501, have already been investigated with the drug being in Phase III studies. Coherus and Pfizer, Inc. announced that their adalimumab biosimilar candidates have achieved the primary end point of PK similarity relative to the reference product in clinical trials conducted in healthy individuals. Sandoz, started a Phase III study of its biosimilar candidate GP2017 in patients with moderate to severe plaque psoriasis.[24] SB5, Samsung Bioepis' Humira® biosimilar candidate, is currently being evaluated in a Phase III study. Another adalimumab biosimilar candidate currently undergoing a Phase III clinical study is FKB327, by Fujifilm Kyowa Kirin Biologics Co.

ZRC3197 (Adalimumab Biosimilar)

Cadila Healthcare Ltd. launched what it called the first adalimumab biosimilar, ZRC-3197 on December 9, 2014. This agent was produced in genetically manipulated CHO cells containing adalimumab heavy and light chain genes (DE27). The primary and secondary structure of ZRC-3197 are similar to those of adalimumab and also in terms of purity and heterogeneity. CDSCO approved the drug and it is sold under the name Exemptia™ for the treatment of RA, JIA, PsA, and AS (CTRI/2013/10/004040). Guidelines of CDSCO and also of International Conference on Harmonization-Good Clinical Practice were followed during the clinical trial.

Using set of orthogonal analytical techniques ZRC-3197 was extensively characterized for physicochemical and functional properties of the monoclonal antibody in comparison with the originator HUMIRA. High

Table 3: Relative distributions of different glycan species variants of adalimumab obtained with the biosimilar ZRC-3197 and originator HUMIRA® by UHPLC method[25]

Glycan Variants	% Relative distribution of glycan variants	
	Originator HUMIRA	Biosimilar ZRC-3197
G0F-N	2.27	1.61
G0	0.65	0.94
G0F	74.50	73.86
Man5	3.75	1.20
G0FB	0.86	0.29
GI	0.04	0.06
GiF	11.11	14.30
Gi'F	3.74	4.81
GIFB/Man6	1.49	0.15
G2F	1.31	2.27
G2FB	0.21	0.08
AIF	0.06	0.44

level of similarity was revealed in physicochemical characterization of the biosimilar ZRC-3197 as compared to HUMIRA. Peptide mapping, amino acid sequencing, N- and C-terminal sequencing, and molecular mass determination using a wide range of MS techniques revealed that the primary structure and molecular identity of the biosimilar ZRC-3197 were identical to the originator HUMIRA. Also, CD spectroscopy and MS revealed that ZRC-3197 had indistinguishable protein secondary structure and S–S cross-links as compared to originator HUMIRA (Figure 1). Predominantly β structure of protein and correct formation of S–S cross-links was seen in both the products further confirming the structural conformity of the two products. Aggregates of monoclonal antibodies can enhance immunogenicity and affect in-vivo safety and efficacy of the medicinal products. Hence, purity of the biosimilar ZRC-3197 was also assessed by a set of orthogonal analytical methods in comparison with originator. HP-SEC, one of the methods to characterize the protein aggregates, was applied to assess the purity of the samples. This analysis showed that biosimilar ZRC-3197 had a highly similar level of purity with a very low level of aggregates (0.5%), as observed with the originator. Other studies like SDS-PAGE and CE-SDS analysis, also showed indistinguishable pattern of size heterogeneity and level of purity between ZRC-3197 and HUMIRA. Hence in terms of purity and molecular integrity both these products were similar.[25]

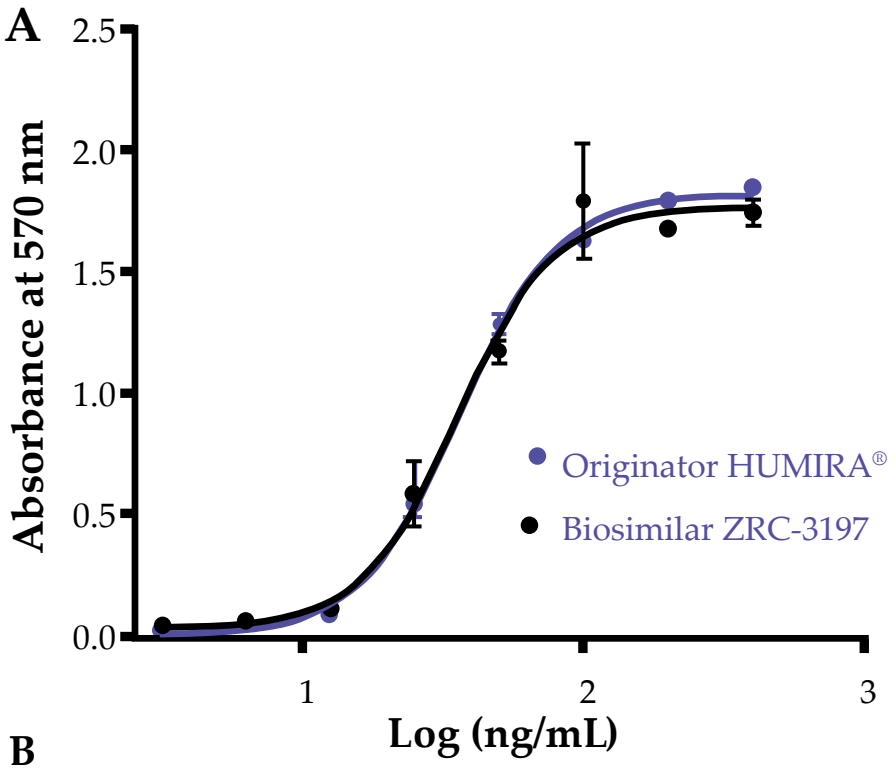
Table 4: Comparison of monosaccharide contents between the biosimilar ZRC-3197 and originator HUMIRA[25]

Monosaccharides	Concentrations of monosaccarides (µg sugar/mL protein sample)	
	Originator Humira	Biosimilar ZRC-3197
Fucose	97	105
Galactosamine	<12.5	<12.5
Glucosamine	389	374
Galactose	25	30
Mannose	297	311

HP-IEC, cIEF, and MS were used to assess the charge heterogeneity profile of ZRC-3197 and compared with the originator HUMIRA as different type and level-of-charge heterogeneity and post-translation modifications can substantially affect the in vitro and in vivo properties of monoclonal antibodies. HP-IEC and cIEF analysis, respectively, showed that ZRC-3197 had highly comparable charge variants (Lys-variants) and nearly identical pI value(s) for the major and minor charged species variants with respect to the originator HUMIRA. Highly similar levels of Met-oxidation and deamidation of certain Gln/Asn amino acids were seen ZRC-3197 and HUMIRA on MS analysis of the peptide fragments derived from various proteolytic enzyme digestions along with similar very low levels of oxidation and deamidation. However, in CDR regions no such modifications were seen in both the compared products. Hence, in the absence of any detectable modifications in the CDR regions, it can be predicted that the two products will not show any difference in binding affinity to TNF-α. In general, a high level of sameness of the charge heterogeneity pattern and amino acid modifications, in particular was observed between the biosimilar ZRC-3197 and originator HUMIRA.[25]

Glycosylation- type and degree also plays an important role in vivo efficacy and half-life of monoclonal antibody products. On a comparative basis carbohydrate structure of the biosimilar ZRC-3197 and originator HUMIRA was also compared. Both ZRC-3197 and HUMIRA showed presence of G0F carbohydrate moiety, as the predominant variant (approximately 70%–75%) among the other glycan variants (Table 3). Other minor glycan variants also did not show any significant differences. UHPLC analysis also revealed a very low level of sialylated (A1F) variant like in ZRC-3197 as that seen in originator HUMIRA. Monosaccharide analysis also revealed similar levels of fucose, glucosamine, mannose, and galactose in both the products (Table 4). Peptide mapping by MS showed a common glycosylation site at the position Asn301 on the heavy chain of biosimilar ZRC-3197 and HUMIRA. More than 98% glycosylation occupancy of the heavy-chain components of the two products was shown in CE-SDS analysis. In toto, these results clearly demonstrated homogeneity of carbohydrate structures of the biosimilar ZRC-3197 as compared to that of the originator HUMIRA.[25]

Ability of ZRC-3197 to bind (neutralizing activity) to TNF with respect to HUMIRA was assessed in an in-vitro cell based assay using L929 cell line since primary mechanism of adalimumab involves binding of TNF-α. This test showed that biosimilar ZRC-3197 had nearly identical EC50 value with a potency ratio of approximately 100%, as compared to that of the originator HUMIRA. Also, SPR analysis, showed that biosimilar ZRC-3197 had comparable affinity (KD value) to TNF-α as HUMIRA. The two products also showed highly comparable rates and extent of association (*ka*) and dissociation



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Samples	EC_{50} ng/mL	Relative potency
Originator HUMIRA®	35.66	-
Biosimilar ZRC-3197	35.50	100.40%

Fig. 2: r-HuTNF-α neutralizing activity by cell-based L929 assay: comparison between the biosimilar ZRC-3197 and originator HUMIRA®. TNF-neutralizing activity was estimated by a MTT reduction assay on L929 cells[25]

(*kd*) between TNF-α and adalimumab (Figure 2). Assessment of affinity for of adalimumab Fcγ receptors was also assessed as it also functions through this receptor. SPR analysis showed that ZRC-3197 had a highly comparable KD values (*ka* and *kd*) for Fcγ RIIIa receptor in comparison with the originator HUMIRA. Also a highly comparable affinity constant for FcRn receptor for ZRC-3197 was also observed as compared to that of the originator HUMIRA. Hence, main functional properties of the biosimilar ZRC-3197 and originator HUMIRA were similar.[25]

After thorough characterization of physicochemical and functional properties of the biosimilar ZRC-3197, a comparative animal toxicity study revealed no significant differences between the biosimilar ZRC-3197 and originator HUMIRA. Single dose injection in rats exhibited an overlapping pharmacokinetics profile in ZRC-3197 compared to that of the originator HUMIRA. A multi-centric, prospective, randomized, double-blind, active controlled parallel study arm in patients with rheumatoid arthritis between the ages of >18 and <65 years also revealed comparable efficacy and safety of ZRC-3197. In this phase III study, 120 patients were recruited with the primary end points being PDs (efficacy) of adalimumab (ZRC-3197) and adalimumab (Humira) in patients with RA compared to baseline, and the aim was to determine the proportion of patients who attained ACR20 in both groups on day 84. Results showed that the biosimilar exhibited high levels of similarity relative to efficacy, safety, and tolerability in patients with RA compared to the reference product. As biosimilar ZRC-3197 exhibited highly similar level of efficacy, safety, and tolerability of the drug in rheumatoid arthritis patients, as compared to that of the originator HUMIRA, Cadila Healthcare, Ahmedabad, Gujarat, India, received the marketing authorization for ZRC-3197 from Directorate General of Health Services, CDSCO, in India. It is marketed in India under the brand name ZRC3197(Adalimumab Biosimilar).[25] Also, ZRC3197(Adalimumab Biosimilar) was extrapolated to all the indications of adalimumab and is used to treat auto immune disorders such as rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, and ankylosing spondylitis.[26]

Conclusion

Adalimumab, the fully human anti-TNF alpha monoclonal antibody, was first approved globally in 2002 and since then has been the most preferred therapy to treat patients suffering from auto immune disorders. However, the therapy was not available to patients in India till 2014. It is estimated that more than 12 million patients in India suffer from these chronic conditions which progressively deteriorate and lead to lifelong pain and in some cases, even disability. ZRC3197(Adalimumab Biosimilar) can provide affordable treatment at low cost and has comparable efficacy as demonstrated in previous studies.

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