

EDITORIAL

Biosimilars in Rheumatology- Name Changers or Game Changers?

Rohini Handa

The therapeutic juggernaut in Rheumatology shows no signs of slowing. The 'spas' of yesteryears have made way for the 'biologic infusion centres' of today. The arrival of biologics pari passu with better understanding of disease mechanisms has contributed to this tectonic shaft. The kind of upbeat optimism ushered by the biologic disease modifying drugs (DMARDs) is similar to the one that greeted the introduction of corticosteroids. Complementing the biologic DMARDs are better measurement tools to quantify disease activity in rheumatic diseases. Subjective impressions have yielded to objective measurements. Disease assessment tools like DAS 28 (disease activity score), SDAI (simplified disease activity index), CDAI (clinical disease activity index) etc are no longer confined to the realm of research. They are employed in the day to day management of patients. The modern day treatment is 'response driven' rather than 'routine care' whereby one sets a predefined threshold of disease activity (target) for a patient and escalates treatment till the target is achieved (treat to target). Older drugs like methotrexate have undergone a makeover and higher doses administered subcutaneously in combination with other DMARDs like hydroxychloroquine, sulfasalazine or leflunomide are advocated. Better pain management and emphasis on quality of life (QoL) are an integral part of this changed paradigm. Durable remission is now a clinical reality in several rheumatic diseases and hope for 'drug free' remission does not seem unrealistic.

The agents of change, the biologic DMARDs, have entered adulthood.

The first patients were enrolled in anti-TNF trials nearly 25 years ago and Remicade® and Enbrel® introduced nearly two decades ago. This was followed by a spate of other introductions and as of now 9 biologics are approved for rheumatoid arthritis (RA). These include anti-TNF agents (infliximab, etanercept, adalimumab, golimumab, certolizumab), IL-1 antagonist (anakinra), IL-6 antagonist (tocilizumab), costimulation modulator (abatacept) and B cell depleting therapy (rituximab). Tofacitinib and baricitinib, targeted synthetic DMARDs, are not included under the category of biologic DMARDs. Other biologics available are belimumab, secukinumab, ustekinumab and denosumab. The list continues to expand rapidly both in terms of new drugs and new indications. The introduction of biologics was not without unique challenges-medical, regulatory and social. Infections like tuberculosis emerged and screening protocols were adopted and adapted to tackle this situation. The high costs put health care budgets under strain. Access in resource poor countries emerged as an important issue. The expiry of patents and the emergence of biosimilars has further changed the therapeutic landscape of Rheumatology. Biosimilars are associated with substantial cost savings and improved access.

A biosimilar is defined by WHO as a bio-therapeutic product which is similar in terms of quality, safety and efficacy to an already licensed

reference bio-therapeutic product, with similarity defined as '*the absence of a relevant difference in the parameter of interest*'.¹ Minor differences in clinically inactive components are allowed since non-identity is the norm while dealing with biopharmaceuticals. The 'art' for a biosimilar is to demonstrate that it is as close as possible to its reference product in all relevant functional and structural aspects, again within current technical and scientific possibilities and its inherent variability.² The objective is not to re-establish benefit for the patient.

Biosimilar development is an evolving landscape from a clinical trial, regulatory and access point of view, which increases the challenges associated with implementing a successful development programme.³ The entire field is in a state of transition and transformation as guidelines and norms are refined and fine tuned in light of new knowledge. The debate on extrapolation of indications, switching and interchangeability, nomenclature and traceability, and trial design for biosimilars continues to engage the attention of industry, academia, governments and professional medical bodies. Since biosimilars are complex molecules, the regulatory pathways are very different from generics and include a comparability exercise based on totality of data. The European Medicines Agency (EMA) and US Food and Drug Administration (FDA) have defined pathways for regulatory approvals.^{4,5}

In India, the regulatory bodies responsible for approval of 'similar biologics' are the Department of Biotechnology (DBT – under the Ministry of Science and Technology), through its Review Committee on Genetic Manipulation (RCGM), and the Central Drugs Standard Control Organization (CDSCO – under the Ministry of Health and Family Welfare). The CDSCO is the national regulatory authority in India that evaluates safety, efficacy and quality of drugs in the country while RCGM is responsible for overseeing the development and preclinical evaluation of recombinant biologics. These bodies have released revised guidelines on similar biologics in August 2016.⁶ One key feature of the revised 2016 document is the need for post marketing studies, which are intended to further reduce the residual risk of the 'similar biologic'. CDSCO calls for specific post marketing safety data 'through a pre-defined single arm study of generally, more than 200 evaluable patients and compared to historical data of the reference product. The study should be completed preferably within 2 years of the marketing permission/manufacturing license unless otherwise justified.' The primary aim of the Phase IV study is safety while the secondary endpoint is efficacy and immunogenicity. The document clarifies that 'if immunogenicity is evaluated in clinical studies, it is not mandatory to carry out additional non-comparative immunogenicity studies in post marketing studies.'

The first 'similar biologic' approved and marketed in India was a hepatitis B vaccine in 2000. In recent years over 50 biopharmaceutical products have been approved for marketing in India, with more than half of them being 'similar biologics'.⁷ In this supplement of JAPI, data about the adalimumab biosimilar ZRC-3197 is presented. ZRC3197 was approved as a similar biologic of adalimumab by the Drug Controller General of India (DCGI) on December 9, 2014 and, as such, was the first adalimumab biosimilar approved by a regulatory agency.

It is developed and marketed by Zydus Cadila (India) in India as Exemptia™. The manufacturers used comprehensive analytical techniques to characterize the physicochemical and functional properties of ZRC-3197 and demonstrate indistinguishable primary and secondary structures (finger print match) with the originator product.⁸ When analyzed, in parallel, the biosimilar ZRC-3197 and the originator HUMIRA® were observed to show a high degree of sameness of the carbohydrate structure and charge heterogeneity profile. Both showed highly comparable key functional properties, as assessed by in vitro cell-based assay and surface plasmon resonance technique. The biosimilar ZRC-3197 exhibited highly similar tumour necrosis factor alpha neutralizing activity as well as binding affinity for FcγRIIIa receptor compared to that of the originator product.⁸

The regulatory trial for ZRC-3197 included 120 patients drawn from 11 sites in India.⁹ The trial sponsors calculated the sample size based on an assumed ACR 20 response rate of 55% at week 12 and margin of 28.5% with 80% power and two-sided 5% level of significance. In this multicentre, prospective, randomized, double-blind, active controlled parallel arm study, patients with moderate to severe RA were given 40 mg of either test adalimumab (Exemptia) or reference adalimumab (Humira) by subcutaneous route every other week for 12 weeks. The primary endpoint was proportion 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 proportion of patients with an ACR50 and ACR70 response in two treatment groups at week 12. Safety outcomes were also assessed. After 12 weeks, patients treated every other week with test adalimumab (Zydus Cadila) had statistically similar response rates as compared to reference adalimumab (AbbVie): ACR20 (82% vs. 79.2%;

P > 0.7); ACR50 (46%, vs. 43.4%; P > 0.7); ACR70 (14% vs. 15.1%; P > 0.8). The change in DAS28-CRP score was -2.1 ± 1.09 and -2.1 ± 1.21 , in test and reference products, respectively. It was statistically significant compared to baseline, but not significantly different between the two products. Three serious adverse events and no death was reported during the study.⁹ Exemptia is now approved for treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis/spondylarthrititis (SpA), Crohn's disease, ulcerative colitis and hidradenitis suppurativa.

In this supplement, Sharma et al. discuss the use of biologics and biosimilars in Rheumatology practice while Kaushik et al. focus on the global adalimumab biosimilar programme. Sharma et al. report their experience with the use of Exemptia™ in 90 patients with RA and SpA. Kapoor et al present data on switching in 15 patients with SpA, who were switched to Exemptia™ after failing infliximab and/or etanercept. Mathew and colleagues from Christian Medical College, Vellore share safety data of 116 patients administered biosimilar adalimumab (Exemptia™) from December 2014 till August 2016. Trial patients are required to fulfill stringent inclusion criteria while the patients in clinical practice are a variegated lot with overlaps and comorbidities. As such, post marketing studies and registry data are crucial in giving patients, regulators and doctors the confidence in using these biosimilars. This real world data bridges the gap between the trial and target populations and adds to the growing body of literature on the safety and efficacy of this adalimumab biosimilar.

Improved understanding the pathobiology of autoimmune rheumatic diseases has ushered in the era of biologic treatments. Several targeted therapies and designer drugs are available and many more are in the pipeline. One major challenge is the burgeoning

cost of these treatments. Biosimilars hold promise and potential to expand access to these highly effective treatments. Since medicine cannot be practiced in isolation from societal needs and resource availability, the need of the hour is to strike a balance between efficacy, safety, access and cost. While cutting costs, we should not cut corners. Rigorous trial design, ethical data collection, transparency in data presentation and continued pharmacovigilance are the key mantras to promote physician and patient confidence in biosimilars. Bio-originators and biosimilars can co-exist. Indeed, biosimilars have the power to be real game changers rather than mere name changers. The interest of our patients will neither be served by outright rejection nor by unquestioned acceptance but by insistence on a data driven approach

that is evidence based!

Conflict of Interest

RH has served as speaker, consultant, advisory board member for Abbott India, Pfizer, Ranbaxy, Sun, IPCA, GSK, Dr Reddy's Laboratories Ltd, BMS India, Janssen, Piramal Life Sciences, Panasonic Health Care, Roche, Sanofi, Eli Lilly, Zydus.

References

1. WHO Expert Committee on Biological Standardization. Sixtieth Report. WHO Technical Report Series 977.
2. Schneider CK. Biosimilars in rheumatology: the wind of change. *Ann Rheum Dis* 2013; 72:315-8.
3. Goel N, Chance K. Biosimilars in rheumatology: understanding the rigor of their development. *Rheumatology* 2017; 56:187-97.
4. European Medicines Agency. Guideline on similar biological medicinal products. 2014. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf.
5. U.S. Food and Drug Administration. Guidance for industry. Scientific considerations in demonstrating biosimilarity to a reference product. 2015. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>
6. Revised Guidelines on Similar Biologics: Regulatory Requirements For Marketing Authorization In India, 2016. Available at <http://www.cdscn.in/forms/list.aspx?lid=1812&ld=1>.
7. Generics and Biosimilars Initiative. GaBi online. <http://www.gabionline.net/Biosimilars/General/Similar-biologics-approved-and-marketed-in-India>.
8. Bandyopadhyay S, Mahajan M, Mehta T, Singh AK, Parikh A, Gupta AK, et al. Physicochemical and functional characterization of a biosimilar adalimumab ZRC3197. *Biosimilars* 2015; 5:1-18.
9. Jani RH, Gupta R, Bhatia G, Rathi G, Ashok Kumar P, Sharma R, et al. A prospective, randomized, double-blind, multicentre, parallel-group, active controlled study to compare efficacy and safety of biosimilar adalimumab (Exemptia; ZRC-3197) and adalimumab (Humira) in patients with rheumatoid arthritis. *Int J Rheum Dis* 2016; 19:1157-1168.