

# Real-life Safety Profile of ZRC3197 (Adalimumab Biosimilar) in Indian Patients with Common Rheumatic Diseases

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## Abstract

The advent of biologic therapies has brought in significant improvement in the outcome of patients suffering from chronic inflammatory arthritis. High costs and unavailability have however, limited their utility in some parts of the world. These limitations have been overcome to a good extent by the introduction of biosimilar versions of original products, which are gaining momentum, of late. Adalimumab (Humira<sup>®</sup>), a TNF- $\alpha$  inhibitor has been successfully used in patients with inflammatory arthritis for more than a decade now. ZRC3197 (Adalimumab Biosimilar) was developed in India and approved for use since 2014. Ongoing evaluation of safety in real-world setting outside the context of controlled clinical trials is pivotal in ensuring long-term safety of such biologic therapies. We share the real-life safety profile of biosimilar Adalimumab in patients with chronic inflammatory arthritis and other autoimmune conditions from a tertiary care centre in south India.

## Introduction

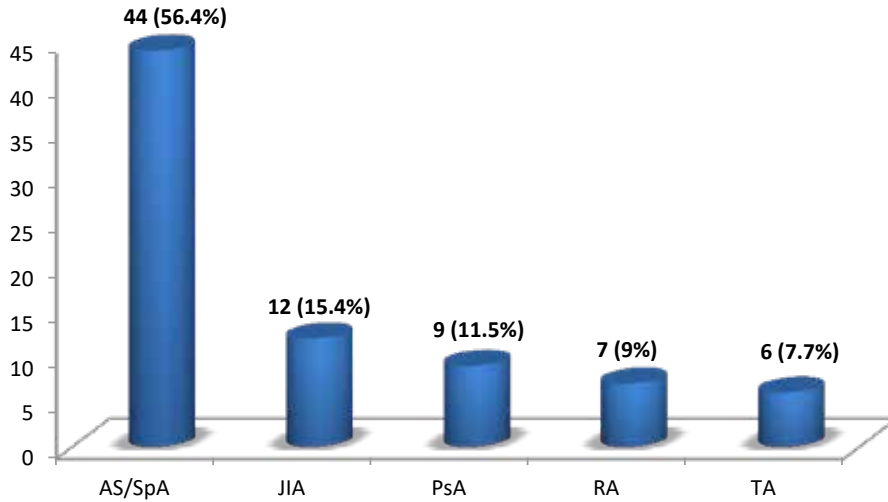
The past few decades have witnessed significant advances in the management of chronic inflammatory arthritis. Introduction of biologic therapies, with tumour necrosis factor inhibitors (TNFi) being the initial molecule to be used in clinical practice, has revolutionised the therapeutic approach in patients with chronic arthritis, especially in those who have been resistant to therapy with conventional disease modifying anti-rheumatic drugs (cDMARDs). Adalimumab (Humira<sup>®</sup>; Abbott, US), a fully humanized monoclonal antibody, is one such TNF- $\alpha$  blocking agent, that has been evaluated in various clinical trials and approved for use in rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA) and juvenile idiopathic arthritis (JIA).<sup>1</sup> Use of innovator biologics like Adalimumab continue to remain limited owing to their high costs and

restricted access to patients in some parts of the world.<sup>1-4</sup> As the patents of existing reference biologics begin to expire 'biosimilar' versions of these molecules are being approved by regulatory authorities to be used in clinical practice. Biosimilars are highly similar copies of originator biologics, that undergo a well-defined and stringent regulatory approval processes requiring rigorous analytical, non-clinical and clinical studies.<sup>2</sup> Biosimilars have improved the patients' affordability and accessibility to treatments, primarily owing to their reduced costs.<sup>3-5</sup>

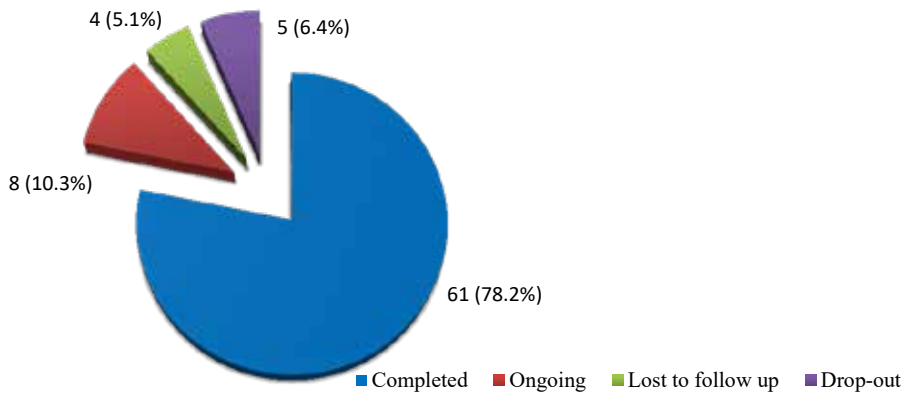
ZRC3197 (Adalimumab Biosimilar); Cadila Healthcare Ltd., India has been developed and approved for use in India since 2014. It is obvious that the increased access to

biologic therapy through biosimilars is required to be accompanied by high quality and comparable efficacy and safety to the reference product. Clinical development of a biosimilar thus focuses on a rigorous head-to-head comparison with the reference molecule.<sup>2</sup> The physicochemical and functional properties of biosimilar adalimumab ZRC3197 (Adalimumab Biosimilar) were demonstrated to be comparable to the originator adalimumab (Humira<sup>®</sup>) using standard analytical techniques.<sup>6</sup> The biosimilarity of ZRC3197 (Adalimumab Biosimilar) to Humira<sup>®</sup> in terms of efficacy and safety was also demonstrated in a controlled context by a prospective, double-blind, multicentre, active controlled, clinical study in patients with Rheumatoid Arthritis (RA).<sup>7</sup>

While initial biosimilarity is proved, ongoing evaluation of safety in real-world clinical settings and outside clinical trials is the need of the hour for biosimilar therapies.<sup>2</sup> Pharmacovigilance databases and post-marketing registries are being used as important tools to monitor long-term safety of these treatments.<sup>2,5</sup> Evidence-based information and real-life experience from actual clinical practice supports the physicians for informed choices and improved patient care. With this single tertiary care centre, retrospective data review, we have attempted to share our experience on the real-life safety profile of ZRC3197 (Adalimumab Biosimilar)



**Fig. 1: Indications for initiating ZRC3197 (Adalimumab Biosimilar)**



**Fig. 2: Adherence to biosimilar adalimumab treatment**

following its clinical use in patients with inflammatory arthritis and other autoimmune conditions.

## Materials and Method

All patients initiated on ZRC3197 (*Adalimumab Biosimilar*) in the departments of Clinical Immunology and Rheumatology and Pediatric Rheumatology, Christian Medical College, Vellore, during the period of December 2014 till August 2016, and had continued treatment for at least 3 months were included in this study. As a standard protocol, all patients undergo a high-resolution computed tomography (HRCT) thorax and Quantiferon TB Gold / Mantoux test as part of the screening protocol prior to TNFi administration in the institution. A retrospective electronic medical records (EMR) review was conducted for all the included patients after obtaining consent

from the institutional review board. All these patients had assessments done every 3 months up to 1 year of biosimilar Adalimumab treatment.

Safety information including serious adverse events (SAEs) and non-serious adverse events (AEs) as reported and recorded in the EMR, from the first dose of biosimilar adalimumab through 70 days (5 half-lives) after the last dose, was collected. SAEs were defined as fatal or immediately life threatening, requiring hospitalisation, resulting in persistent or significant disability/incapacity, congenital anomaly or requiring medical or surgical intervention to prevent a serious outcome. Safety data retrieved is presented using descriptive statistics; frequency (percentage) or number of observations/events.

## Results

A total of 116 patients had received ZRC3197 (*Adalimumab Biosimilar*) during the study period. However, complete EMR data could be retrieved only for 78 patients, of which 50 (64.1%) were males. The indications for use of biosimilar included AS/spondyloarthritis, JIA, PsA, RA and refractory Takayasu Arteritis (TA) who had failed conventional immunosuppression (Figure 1). Majority of the patients were biologics naïve [69 (88.5%) patients]. Treatment adherence amongst these patients is shown in Figure 2. Sixty-one (78.2%) patients had completed the biosimilar adalimumab treatment, while it was ongoing for 8 (10.3%) patients at the time of analysis. Remaining nine patients (11.5%) either dropped out or were lost to follow up. From the 78 EMRs retrieved, 4 non-serious AEs (5.1%) – nausea (1), injection site reactions (1) and abdominal pain (2); and 3 SAEs (3.8%) – psoriasis flare, pneumonia and TB reactivation (initiated elsewhere) were recorded. Tuberculosis reactivation was reported only in 1 patient's record.

## Discussion

The safety profile of adalimumab originator molecule has already been evaluated by various controlled clinical trials, as well as open-label and observational studies.<sup>1</sup> Clinical use of adalimumab for more than a decade now has not revealed any new safety signals. Infections, injection site reactions, headache and musculoskeletal pain remain the most commonly observed AEs with adalimumab use. The most common SAEs reported have been tuberculosis reactivation, opportunistic infections and malignancies.<sup>1,8</sup> The clinical study comparing biosimilar adalimumab and originator adalimumab has also shown a comparable distribution of AEs between the two treatments. Pyrexia, headache and cough were the most common AEs, and pyrexia, dizziness and cough were the only three SAEs reported in this study.<sup>7</sup> Findings from the current analysis

reveal a real-time safety profile of biosimilar adalimumab similar to that already seen in a context of its controlled clinical trial. Tuberculosis reactivation was reported only in one patient, for whom the biosimilar therapy was initiated at another centre. The patient had subsequently been admitted at our centre for further management. Hence, the importance of a stringent pre-biologic therapy screening needs to be emphasized in all patients being initiated on these molecules.

Overall, the safety observed during clinical trial of biosimilar adalimumab also seems to be translated in real-life clinical practice. The safety profile exhibited by biosimilar adalimumab from this analysis also continues to be in line with the published literature for the originator adalimumab, and reveals no new unexpected safety signals.

Being a retrospective chart review

study, the significant amount of missing data and lack or under reporting of events cannot be ignored. The data was also not sufficient to conclude on the short-term efficacy of treatment. Nevertheless, this analysis provides vital information on the real-time safety of biosimilar adalimumab in patients from routine clinical practice. Well-designed, prospective studies with long-term follow-up shall further contribute to these findings.

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