Clinical use of ZRC3197 (Adalimumab Biosimilar) in Patients with Inflammatory Arthritis: A Real-life Experience

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Abstract

We present our real-life clinical experience of ZRC3197 (Adalimumab Biosimilar) in Indian patients with inflammatory arthritis [spondyloarthropathy (SPA) and rheumatoid arthritis (RA)]. Medical records of these patients were retrospectively retrieved and analysed at our single centre. All the patients had received biosimilar Adalimumab 40 mg every 15 days for initial 3 months. Post 3 months, an 'on-demand modified dosing approach' was followed, wherein BASDAI/DAS28-guided dose reduction or discontinuation of treatment was done. Dose reduction was primarily done by increasing the dosing interval for biosimilar Adalimumab. The 3, 6 and 12 months' follow-up data revealed a significant reduction in disease activity scores (BASDAI/DAS28). At 3 months, BASDAI50% was achieved in 91% and BASDAI 70% was achieved in 45% of SPA patients. At 3 months, 88% showed a reduction in DAS28 > 1.2 from baseline. At 12 months, 94% of the evaluable SPA patients and 58% of evaluable RA patients showed clinical remission or low disease activity. BASDAI/DAS28 score-guided dose reduction led to significantly lesser requirement of biosimilar Adalimumab doses. Biosimilar Adalimumab was well-tolerated with no serious or unexpected side effects. Our analysis suggests that disease activity-guided modified dosing may serve as an effective strategy for patients with inflammatory arthritis, leading to a lower dose requirement for the treatment. Despite the modified dosing, the clinical response following biosimilar Adalimumab was comparable to the published data for the standard Adalimumab treatment in such patients.

Introduction

Tumour necrosis factor (TNF) has been involved in various arthritic disease states like rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). Adalimumab, the first fully human, high-affinity, bivalent, monoclonal immunoglobulin G1-kappa isotype (IgG1-κ) anti-TNF antibody specifically targets both soluble and membrane-bound TNF-α. Inhibition of TNF activity by Adalimumab significantly improves the signs and symptoms, function, and QOL; induces remission; and reduces objectively measured damage in patients with these conditions.[1] Adalimumab [*Humira®; Abbott, US*] has a rapid onset of action and sustained efficacy with long-term treatment, and is well-tolerated, with few patients discontinuing treatment because of adverse events. While the originator Adalimumab (*Humira®*) was first approved globally since 2002 for various autoimmune disorders, the therapy is yet to be available in India. *ZRC 3197(Adalimumab Biosimilar); Cadila Healthcare Ltd., India*) was developed and approved for use in India in 2014. Biosimilarity between originator and biosimilar Adalimumab for physicochemical and functional properties has been validated via a comprehensive set of state-of-the-art analytical techniques.[2] The biosimilarity between the two products in terms of efficacy, tolerability and safety has also been demonstrated in a prospective, randomized, double-blind, active controlled study in patients with rheumatoid arthritis.[3] Currently, for Indian patients suffering from chronic arthritic conditions, a biosimilar Adalimumab *ZRC3197* serves as an accessible and cost-effective Adalimumab therapy option.

Good number of inflammatory arthritis patients does not respond to conventional synthetic disease modifying anti rheumatic drugs (cDMARDS) and they are the candidates for biologic therapy. Various studies have shown efficacy of biologics in very early and early disease in DMARD naive patients as upfront drugs & in established disease refractory to DMARDS. Cost is the major concern of long term biologics use in these patients worldwide. There are few studies that suggest that once patient achieve remission or low disease activity dose of these agents can be reduced to minimize the cost. In this paper, we share our real-life clinical experience on the use of biosimilar Adalimumab *ZRC3197 (Adalimumab Biosimilar)* in patients with inflammatory arthritis. Biosimilar Adalimumab was used in RA, PsA & peripheral SpA patients who were refractory to cDMARDS, while axial SpA patients

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Table 1: Baseline demographic and disease characteristics of the patients

Parameters	Spondyloarthropathy (SpA) [N = 39]	Rheumatoid arthritis (Ra) [N = 51]
Age; years (mean±SD)	38.4 ± 14.5	47.5 ± 12.9
Male: Female	26:13	10:41
Disease duration; yrs (median; range)	7.5 (0.5-36)	7 (0.5-25)
Positive/Negative MT	11/28	10/41
CXR PA (Normal)	39; All	49 [2 pts had old healed TB]
Mean ESR at baseline	-	52.11 ± 33.21
DMARDs naïve patients (%; n)	15%; 6	None
NSAIDs (full dose > 6 weeks) refractory	39; All	-
No. of prior DMARDs (median; range)	1 (0-3)	2 (1-3)
DMARDs failure: Triple/Double/ Monotherapy	-	25/21/5
Patients with prior corticosteroids (n)	3	14
Biologics naïve patients (%; n)	87%; 34	94%; 48

Data presented as: mean±standard deviation; median (min-max); percentage (%) of patients; N = total number of patients; n = number of analysable patients

who did not show response to full dose of NSAIDS even after 6 weeks duration. Majority of our RA patient population had received full dose of combination cDMARDS (25/51 triple therapy and 21/51 double therapy with corticosteroids for 3 months and despite that, had a persistent high disease activity) before starting treatment. Our findings also suggest using an *on-demand modified dose reduction* regimen for Adalimumab therapy in these patients.

Patient Selection, Data Collection and Analysis

This was a single-centre, retrospective review of real-life data on the clinical use of biosimilar Adalimumab in patients with inflammatory arthritis. Medical records retrieval was performed from electronic database of Niramaya Health Care (Dedicated Rheumatology Centre), Jaipur, Rajasthan. Records were evaluated for patients with inflammatory arthritis – spondyloarthropathy (SPA) and rheumatoid arthritis (RA) - who had received treatment with *ZRC3197 (Adalimumab Biosimilar)* and, for whom, data was available for more than 3 months of follow-up. Records with less than 3 months of follow-up data were excluded from the analysis.

Retrieved medical records confirmed that all patients were prescribed *ZRC 3197 (Adalimumab Biosimilar)* 40 mg dose every 15 days, for 3 months of the treatment initiation [*recommended therapy*]. Disease activity was monitored through BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) scores in SPA patients and by DAS28 (Disease Activity Score) in RA patients. After 3 months of standard therapy, an *on-demand modified dosing* approach was considered which involved patient-wise BASDAI/DAS28-guided dose reduction or discontinuation of biosimilar Adalimumab primarily by increasing the dosing interval. Data, as available, on the disease activity monitored every 3 months for up to at least 1 year was analysed. Use of concomitant medications viz. DMARDs and corticosteroids (particularly for RA patients), was also evaluated. Descriptive statistics were used to analyses the collected data. All collected data were grouped into two patient categories: SPA and RA. Continuous variables were summarized using mean (standard deviation) or median (range) and categorical variables were summarized using frequency counts and percentages. Two-sided paired Student's t test was used for comparing treatment outcomes with a 5% level of significance.

Results & Discussion

A total of 90 patients' records, meeting the evaluation criteria, were retrieved and analysed: 39 patients had SPA; 51 patients had RA. Baseline demographic and disease characteristics of these patients are presented group-wise in Table 1. The median disease duration for the SPA and the RA group was 7 years and 7.5 years, respectively. All SPA patients were refractory to a full dose NSAIDs treatment and 15% of these patients was DMARDs naïve. All RA patients had failed prior DMARDs therapy. Most of the patients (87-94%) were biologics naïve. All patients were prescribed biosimilar Adalimumab and BASDAI/DAS-guide dose reduction by increasing dosing interval was done for all patients. Methotrexate was administered concomitantly in 12 patients with SPA and 44 patients with RA, while steroids were given to 14 patients with RA. Other DMARDs given to these patients included sulfasalazine, hydroxychloroquine and leflunomide. Clinical characteristics of the patients are presented group-wise in Table 2. The patient pool included a total of 9 juvenile cases: 7 patients with juvenile AS and 2 patients with juvenile idiopathic arthritis.

Disease activity outcome and treatment details for all patients are presented group-wise in Table 3. A significant reduction in disease activity scores was achieved for both, the SPA and RA patients, at 3, 6 and 12 months after the start of biosimilar Adalimumab treatment. Figure 1 shows a diagrammatic presentation of disease activity over 12 months after the initiation of biosimilar Adalimumab treatment for various patient subgroups. Results for the SPA group excluding patients with psoriatric arthritis (PsA) were comparable to the total SPA patient group. The reduction in disease activity scores was not significant in the patients with PsA, however, the group size was also too small to conclude.

The BASDAI/DAS28 score-guided dose reduction/increase in dosing interval led to a significantly lesser number of biosimilar Adalimumab doses, as compared to theoretical requirement per the recommendations (Table 3). About

Table 2: Clinical characteristics and diagnosis of patients

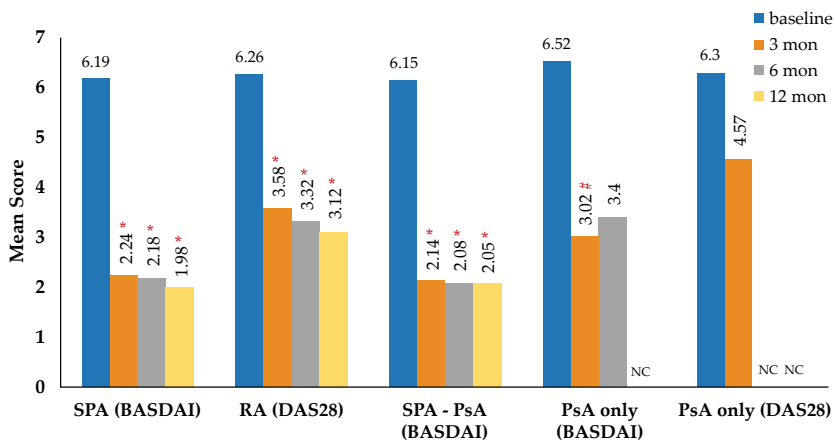
Spondyloarthropathy (SPA)	**N = 39**
Diagnosis	
Ankylosing Spondylitis	13
Juvenile Ankylosing Spondylitis	7
Inflammatory Bowel disease	2
Psoriatic Arthritis (PsA)	8
Spondyloarthropathy, unclassifiable	9
Axial SPA	12
Peripheral SPA	7
Axial + Peripheral	15
HLA B27: Positive/Negative/NA	23/8/8
Rheumatoid Arthritis (RA)	**N = 51**
Diagnosis	
Rheumatoid Arthritis	49
Juvenile Idiopathic arthritis, polyarticular	2
RF and ACCP Positive	20
Only RF Positive	33
Only ACCP Positive	32

Data presented as: n = number of analysable patients

Table 3: Disease activity outcomes and biosimilar adalimumab treatment details

Description	**SPA N = 39**	**RA N=51**
Disease activity score	BASDAI	DAS28
Baseline	6.19±1.05 (n=35)	6.26±1.0 (n=47)
3 months	2.24±1.15 * (n=35)	3.58±0.93 * (n=44)
6 months	2.18±1.18 * (n=25)	3.32±1.21 * (n=42)
12 months	1.98±0.91 * (n=15)	3.12±1.16 * (n=31)
Actual Duration of ZRC3197(Adalimumab Biosimilar) treatment: Median (range)	5 (2-19) months	6 (2.5-18 months)
ZRC3197(Adalimumab Biosimilar) (40 mg) - Total NUMBER of Doses		
Standard/Recommended: 40 mg (1 dose) every 15 days calculated for actual duration of treatment above*:*	10 (4-38); 13.5±7.79	12 (5-36); 15.4±8.89
Actual:	10 (4-27); 11.1±5.12.4 *	11 (5-30); 12.6±6.4 *
Number of patients requiring overall ≥ 3 ZRC3197(Adalimumab Biosimilar) doses less than Standard regimen	14 out of 39 patients (36%)	21 out of 51 patients (41%)
Number of Patients receiving Steroids: *baseline vs. 3 months vs. 6 months vs. 12 months*	Not available	14 vs. 8 vs. 4 vs. 3
Mean steroid dose reduction		4.14±1.8 mg (baseline) 1.23±2.89 mg (12 mon) *

Data presented as: mean±standard deviation; median (min-max); percentage (%) of patients; number of analysable patients; *Paired Student's T test. P<0.001. Statistically significant reductions as compared to baseline/standard.



Data presented as: mean±standard deviation; median (min-max); percentage (%) of patients; number of analyzable patients.
*Paired Student's T test; * P<0.001; # p< 0.05 Statistically significant reductions as compared to baseline/standard; NC = not calculable.*

Fig.1: Disease Activity Scores over 12 months in patients with inflammatory arthritis treated with biosimilar adalimumab

36% of SPA patients and 41% of RA patients required ≥ 3 doses less than the standard recommended regimen. For the RA group, number of patients requiring steroids dropped, and the mean steroid dose was also significantly reduced over 12 months. These results also include the 9 juvenile patients, further indicating towards the efficacy of biosimilar Adalimumab in these patients too.

Clinical response at 6 months and 12 months following a modified-dose regimen for biosimilar Adalimumab in our patients is summarized in Table 4. At 3-month follow-up, 91% of SPA patients achieved BASDAI50% and 45% achieved BASDAI70% responses. Majority (94%) of the evaluable patients' records revealed SPA patients in clinical remission or low disease activity (LDA) at 12 months. For the RA group, clinical remission as defined by DAS28 < 2.6 was achieved in 11% of patients. However, clinical response (defined as reduction in DAS28 > 1.2 from baseline) was achieved in 88% of these patients. Clinical remission (DAS28 < 2.6) or LDA (DAS28 < 3.1) was observed in 58% of the RA patients at the end of 12 months post biosimilar Adalimumab treatment.

Patient-tailored dose reduction of anti-TNF- α agents has been reported to successfully preserve a stable LDA in patients with AS.[4] About 74% patients in this prospective, observational cohort maintained reduced dose or dosing frequency after 6 months of anti-TNF therapy; and most of the patients (94%) maintained a low LDA at 24 months. For patients who received Adalimumab, the mean dose over time corresponded to almost 66% of the standard dose.[4] A retrospective report from an Indian centre has also recently confirmed the efficiency of on-demand modified dose regimen for TNF-α blocker in significantly improving disease activity, clinical response and quality of life in AS patients.[5] Findings from our analysis also supports such findings, wherein disease activity-guided dosing led to a significant reduction in the Adalimumab dose requirements.

At 12 months, Adalimumab treatment was associated with

Table 4: Clinical response at 3 months and 12 months of biosimilar adalimumab treatment

Description	Spondyloarthropathy (SPA) N = 39	Rheumatoid Arthritis (RA) N=51
Duration of follow-up in months:	6 (3-18) months 8.68 ± 5.4 months	12 (3-18) months 10.8±4.5 months
At 3 months	n = 35	n = 44
Disease activity	32 (91%) patients [BASDAI 50%] 16 (45%) patients [BASDAI 70%]	5 (11%) patients [DAS28 < 2.6] 9 (20%) patients [DAS28: 2.6 – 3.1] 39 (88%) patients [Reduction in DAS28 > 1.2 from baseline]
At 12 months F/U	n = 16	n = 31
Patients in Remission or low disease activity	15 (94%) * [BASDAI < 4]	18 (58%) [DAS28 < 3.1]

*Data presented as: mean±SD, median (range), number of analysable patients (n, %) with F/U data available. *One patient, BASDAI = 4 at 12 months F/U.*

BASDAI50% responses in 40% and 65% of AS patients, respectively, with or without prior anti-TNF therapy.[6] A retrospective analysis in Japanese patients with RA revealed clinical remission (DAS28 < 2.6) in 35% of patients at 6 months and 38% of patients at 12 months after Adalimumab treatment. A significant decrease in mean DAS28 score at 52 weeks was also reported.[7] A prospective, observational real-life experience in spondyloarthritides patients reported >70% clinical responders (BASDAI 50%; DAS > 1.2 reduction) and clinical remission in 33% (axial) and 13% (peripheral) of these patients after 1 year of standard Adalimumab treatment.[8] Despite a modified-dose regimen, the clinical response to biosimilar Adalimumab observed in our patients also appears in line with the published efficacy of Adalimumab therapy.

In our analysis, one patient with PsA developed bacterial pneumonia after 4 months of biosimilar Adalimumab therapy start and had discontinued the treatment. Three RA patients reported adverse events, each, of persistent cough; abdominal TB; miliary TB, and discontinued treatment. One patient developed drug-induced lupus after 2 doses of biosimilar Adalimumab treatment. Overall, biosimilar Adalimumab appeared to be well-tolerated in these patients with no serious or unexpected side effects. However, since this is a retrospective data review, lack/under reporting of events or loss of follow-up may also be accounted for lesser adverse events.

Although no analysis for cost-effectiveness of biosimilar Adalimumab was performed, the approach of modified dosing with reduced frequency that resulted in a comparatively lesser number of dose requirements is indirectly suggestive a reduced treatment costs in these patients.

Challenges and Strengths

This was a retrospective data review design, limited by a small patient pool from a single centre. The groups were neither randomized nor controlled, and the lack of event reporting or amount of missing data cannot be ignored. Details on disease progression was also not be assessable. Nevertheless, such analyses provide insightful details on the clinical characteristics and treatment patterns for patients derived from an unselected, unbiased real-life pool of routine clinical practice. This study also provides first-hand information on the clinical effectiveness and safety profile of biosimilar Adalimumab in routine clinical care in Indian patients. As the emphasis on real-world studies in developing evidence-based documentation continues to grow, knowledge gained from such a study can serve as a useful guide for designing future post-marketing studies and registries.

Conclusions

ZRC3197(Adalimumab Biosimilar) serves as an accessible and cost-effective anti TNF-α therapy for patients with inflammatory arthritis in India. Disease activity score-guided modified dose reduction of biosimilar Adalimumab may serve as an effective treatment strategy in these patients leading to a lower dose requirement. Biosimilar Adalimumab also demonstrates clinical response comparable with published data on Adalimumab, and maintains a low disease activity in such patients. Though retrospective in nature and limited by amount of data; this real-life evaluation provides useful insights for future prospective studies to further evaluate the clinical use of biosimilar Adalimumab.

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