Original Article

A Prospective, Randomized, Double-blind, Comparative Clinical Study of Efficacy and Safety of a Biosimilar Adalimumab with Innovator Product in Patients with Active Rheumatoid Arthritis on a Stable Dose of Methotrexate

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Abstract

Objective: The objective of this study was to compare efficacy, safety, and immunogenicity between the biosimilar adalimumab (AdaliRel) and the reference innovator product in moderate-to-severe rheumatoid arthritis (RA) patients on stable dose of methotrexate (MTX).
Methods: Patients with moderate-to-severe active RA (*n* = 106) on a stable dose of MTX were randomized to biosimilar adalimumab (AdaliRel) (study arm) or reference innovator adalimumab (reference arm) 40 mg every 2 weeks. The primary endpoint was proportion of patients who achieve ACR20 response at week 16. The secondary endpoint was proportion of patients who achieve ACR50, ACR70, absolute values, and changes from baseline in the disease activity score 28 joint (DAS28), health assessment questionnaire-disability index (HAQ-DI), C-reactive protein (CRP), and rheumatoid factor (RF) at week 16 and week 24. Safety was assessed through adverse events (AEs) and laboratory evaluations up to week 34. Antidrug antibodies were assessed to determine immunogenicity.
Results: Out of 106 randomized, 104 individuals were dosed in the study (one subject from each arm was dropped due to consent withdrawal). The number of patients achieving ACR20 response at week 16 was 90.48% in study arm and 90% in the reference arm. The number of patients ACR70 response at week 16 was 13.1% in the study arm and 15% in the reference arm. There was no statistically significant difference between the two treatment arms in terms of number of responders (*P* > 0.05). No difference also was observed in DAS28, HAQ-DI scores, RF, and CRP changes from baseline. There were no clinically meaningful differences in AEs. Immunogenicity profile at week 16 did not indicate any clinically significant concerns.
Conclusion: Biosimilar adalimumab (AdaliRel) and the reference product showed comparable efficacy and safety in RA patients who were on stable dose of MTX.

Key Words: *American College of Rheumatology, biosimilar, biosimilar adalimumab, double-blind, reference adalimumab, rheumatoid arthritis*

Introduction

Rheumatoid arthritis (RA) is an autoimmune disease with a worldwide prevalence of approximately 0.5% to 1% among adults.[1] The reported prevalence of RA in India ranges from 1.4% to 5.2%.[2] When RA is left uncontrolled patients are known to experience joint deterioration, severe disability, decreased quality of life, onset of comorbidities, and premature mortality. Tumor necrosis factor (TNF) inhibitors were the first approved biological disease-modifying antirheumatic drugs (bDMARDs) for treatment of RA. The bDMARD adalimumab is a recombinant human IgG1 monoclonal antibody that binds specifically to TNF-α. Adalimumab has been shown to have significant efficacy with improvements in disease activity, quality of life, and prevention of structural damage and disability.[3] Adalimumab has been extensively studied in combination with methotrexate (MTX) and has been shown to improve outcomes versus placebo

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in subjects with RA who demonstrate an incomplete response to MTX.[4]

Biosimilar adalimumab products that are similar to an already licensed reference product are being developed. Biosimilars offer access to an alternative treatment option and compliance for the chronically ill patients. Biosimilar guidelines allow for demonstrating that proposed biosimilar is highly similar to the reference product and that no clinically meaningful differences exist between the biosimilar and reference product in terms of safety, purity, and potency.[5]

AdaliRel™ (biosimilar adalimumab) from Reliance Life Sciences was developed as biosimilar to reference adalimumab with comprehensive establishment of physicochemical and biological biosimilarity (www.rellife.com/products_AdaliRel.html). The aim of the present study was to establish clinical efficacy and safety of the biosimilar adalimumab with the reference (innovator) adalimumab patients with moderate-to-severe RA who were on stable dose of MTX.

Methods

We conducted a prospective, multi-center, randomized, double-blind, two-arm, parallel group, active-control, comparative clinical study to evaluate efficacy, and safety of biosimilar adalimumab (AaliRel™) (study arm) compared to reference adalimumab in patients with active RA on a stable dose of MTX (CTRI/2012/05/002660).

Patients with RA who fulfilled the American College of Rheumatology (ACR)/European League Against Rheumatism 2010 classification criteria with score ≥6 were eligible for inclusion if the disease was active as defined by the presence of ≥6 swollen joints, ≥6 tender joints, and C-reactive protein (CRP) ≥10 mg/L. All patients were on treatment with MTX oral or injectable for at least 3 months with no break(s) in treatment of more than 2 weeks in total during this period and were on stable dose between 10 and 25 mg/week for at least 4 weeks before screening. The dose of MTX remained same for the entire duration of the study. Those patients using oral corticosteroids were on a stable dose of up to 10 mg/day prednisolone or equivalent, for at least 4 weeks before screening. Included subjects using NSAIDs were on a stable dose for at least 4 weeks before screening. Patients having active infection, those who had prior use of infliximab, adalimumab, or any biological treatment of RA, those who were on DMARDs other than MTX, and pregnant women were excluded from the study.

Eligible patients were randomized to receive study or reference product as per the randomization schedule on day 1/week 0. The randomization schedule was generated by a statistician. Once a subject was found to be eligible for randomization, the site requested a randomization code for the subject. Randomization was managed centrally. The study and reference adalimumab were administered

to the eligible subjects enrolled in the study as per the subject allocated treatment randomization chart and also they were assigned a seven-digit randomization number in a sequential manner as predecided randomization codes. All study personnel, with the exception of un-blinded statistician, were blinded to the treatment allocation of each patient. Blinding of the allocation of individual patients to one of two treatment arms was ensured throughout the study. Treatment assignment for individual subjects remained double-blind until after the study data were cleaned and the database locked.

The reference product for the study was Humira® (Adalimumab), manufactured by Abbott Laboratories Ltd. Its syringes were imported from England, UK in GTC (Global Temperature Control) validated boxes under controlled temperature conditions of 2-8 degree C.

Patients were treated as per treatment allocation with either study or reference adalimumab till week 16 in a double-blinded manner. The dose of adalimumab in both arms was 40 mg as a single subcutaneous injection every other week.

The primary efficacy endpoint was the proportion of subjects achieving clinical response according to the ACR20 criteria at week 16. A sample size of 105 subjects in a 4:1 ratio (study drug: Reference product) was based on an overall proportion of ACR20 responders of 70% for a power of 80%. Efficacy assessment was performed at week 16 and responders were continued on study drug in an open-label phase up to week 24, while nonresponders were followed up for safety for 10 weeks after the last dose (at week 26). The nonresponders are those subjects who do not achieve desired ACR20 at the end of week 16.

Secondary efficacy endpoints were ACR20 at week 24, ACR50 at week 16 and week 24, ACR70 at week 16 and week 24, absolute values and changes from baseline in disease activity score 28 joint (DAS28) scores, health assessment questionnaire-disability index (HAQ-DI), CRP and rheumatoid factor (RF) at week 16 and week 24. All patients (responders as well as nonresponders) were followed up for 10 weeks after the last dose of adalimumab in both the arms.

All adverse events (AEs) and serious AEs (SAEs) were recorded till the end of the study. Treatment-emergent AEs (TEAEs) were followed till resolution. Immunogenicity sample was collected in nonresponders at week 18 for detection of antibodies against adalimumab. ELISA was used to test for anti-adalimumab antibody using kit from Krishgen Biosystems. The method employs the qualitative sandwich enzyme immunoassay technique.

Statistical analysis

The statistical analysis was performed using the SAS® system. Summary statistics were provided for continuous

variables (e.g., age). Frequency counts were provided for categorical variables (e.g., gender). Analysis was performed in intent-to-treat (ITT), per-protocol (PP), and safety populations as defined in the study. The MTX subgroup analysis was not performed as this was not part of efficacy endpoint analysis. The steroid subgroup analysis was also not performed and was not a part of the efficacy endpoint analysis.

Ethical approval

This study was conducted in compliance with requirements of the Institutional Ethics Committee (IEC) and Drugs Controller General of India (DCGI) and in compliance with International Conference on Harmonization (ICH) - Good Clinical Practice (GCP), Indian Council of Medical Research (ICMR) Ethical Guideline for Biomedical Research and Schedule Y. The study protocol and other study documents for this study were reviewed and approved by the IECs of each of the study sites. Written informed consent was obtained from each all patients.

Results

A total of 106 patients were randomized: 85 patients in the study arm to receive biosimilar adalimumab and 21 patients in reference arm to receive innovator adalimumab (one subject from each arm was dropped due to consent withdrawal). Figure 1 shows the subject disposition. A total of 84 patients were dosed in the study arm, out of which 80 (95.24%) patients completed the double-blind phase, while four (4.76%) patients prematurely discontinued the study; two patients discontinued because of consent withdrawal while the other two discontinued due to AEs. All 80 patients were part of PP and ITT population. Of 20 patients dosed in the reference arm, 19 (95%) completed the double-blind phase while one patient (5%) discontinued due to an AE.

Among the 84 patients who received study biosimilar adalimumab their mean age was 42.5 ± 11.62 years, 68 (81%) were female and 16 (19%) were male. Their mean weight was 57.8 ± 16.06 kg, mean body mass index (BMI) was 22.9 ± 4.13 kg/m^2, and the mean CRP value was 30.3 ± 22.48 mg/L. Out of 20 patients who received reference adalimumab their mean age was 47.1 ± 10.54 years, 18 (90.0%) were female, mean weight was 58.4 ± 12.32 kg, mean BMI was 24.5 ± 5.51 kg/m^2, and the mean CRP value was 36.9 ± 40.45 mg/L.

Efficacy

The number of patients who achieved an ACR20 response at week 16 was 76 (90.48%) in the study arm and 18 (90%) patients in the reference arm in the PP population [Table 1]. There was no significant difference in the number of responders at week 16 between two treatment arms.

In the secondary endpoint analysis, the total number of patients (PP population) achieving clinical response as per
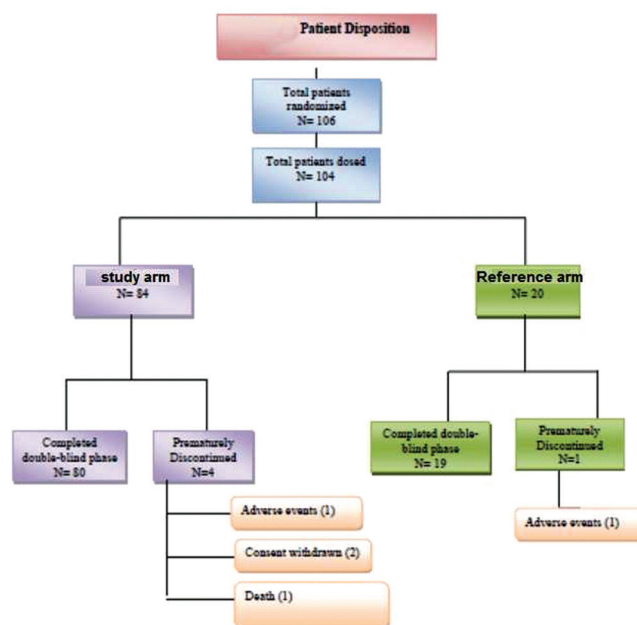

Figure 1: Patient disposition

ACR50 criteria at week 16 was 39 (46.43%) in the study arm and 9 (45%) in the reference arm [Table 1]. There was no significant difference between two treatment arms.

The total number of responders (PP population) achieving clinical response as per ACR70 criteria at week 16 were 11 (13.1%) in the study arm and 3 (15%) in the reference arm [Table 1]. There was no significant difference between two treatment arms.

HAQ-DI scores at baseline and at week 16 in the study arm and reference arm is depicted in Figure 2. In PP population, the mean HAQ-DI score in the study arm at baseline was 15.298 which reduced to 7.225 at week 16. The mean HAQ-DI score in the reference arm at baseline was 14.650 and reduced to 7.684 at week 16. There was no significant difference observed for reduction of HAQ-DI scores between study and reference groups at week 16.

Figure 3 shows DAS 28 scores at baseline and week 16. DAS28 score of higher than 5.1 is indicative of high-disease activity, and DAS28 below 3.2 indicates low-disease activity. The baseline mean DAS28 score in the study arm was 5.5 which decreased to 3.6 at week 16. Similarly, the baseline mean DAS28 score in the reference arm was 5.6 which decreased to 3.6 at week 16. Mean difference in the DAS28 scores was −1.8 and −2.0 in the study and reference arms, respectively.

In the study arm, the mean RF titers at baseline were 456.7 IU/ml which decreased to 213.7 IU/ml at week 16. In the reference arm, the mean RF titers decreased from baseline of 400.67 IU/ml to 137.01 IU/ml at week 16. The mean change was −255.74 in the study arm and −270.51 in the reference arm [Table 1].

Table 1: American College of Rheumatology 20, 50, 70 responders and rheumatoid factor, C-reactive protein reduction at week 16

ACR responders at week 16			
Variable	Study adalimumab (*n*=84), *n* (%)	Reference adalimumab (*n*=20), *n* (%)	Difference in proportions between groups
ACR20	76 (90.48)	18 (90)	0.91% (95% CI: −23.96%-25.54%)
ACR50	39 (46.43)	9 (45)	−0.78% (95% CI: −25.545%-24.14%)
ACR70	11 (13.1)	3 (15)	2.21% (95% CI: −22.75%-26.73%)
Reduction in mean RF titers at week 16			
RF	Baseline	Week 16	Mean change
Study adalimumab (SD)	456.7 IU/ml (893.2773)	213.7 IU/ml (575.2733)	−255.74 IU/ml
Reference adalimumab (SD)	400.67 IU/ml (481.0402)	137.01 IU/ml (262.3418)	−270.51 IU/ml
Reduction in mean CRP at week 16			
CRP	Baseline	Week 16	Mean change
Study adalimumab (SD)	30.39 mg/L (22.4767)	14.61 mg/L (21.9404)	−16.37 mg/L
Reference adalimumab (SD)	36.93 mg/L (40.44797)	7.35 mg/L (7.036458)	−29.94 mg/L

ACR20: The ACR definition of improvement which requires at least a 20% improvement in TJC, SJC, and in three of five core set measures, namely patient's assessment of pain, patient's global assessment of disease activity, physician's assessment of physical function, patient's assessment of physical function, and acute-phase reactant value, ACR50: ACR definition of improvement which requires at least 50% improvement in TJC, SJC and three of five core set measures, ACR70: ACR definition of improvement which requires at least 70% improvement in TJC, SJC and three of five core set measures, CI: Confidence intervals, TJC: Tender joint count, SJC: Swollen joint count, ACR: American College of Rheumatology, RF: Rheumatoid factor, SD: Standard deviation, CRP: C-reactive protein
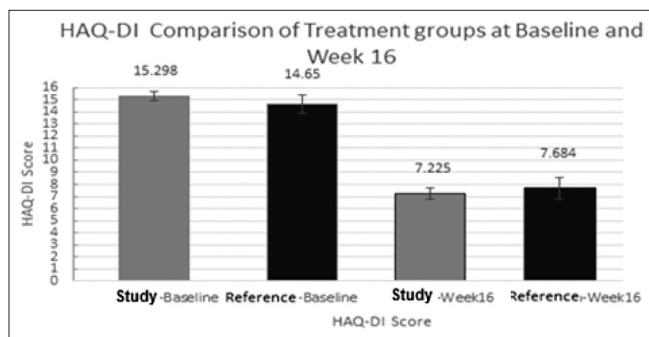

Figure 2: Health assessment questionnaire-disability index at week 16. Population (*n* = 104)

Figure 3: DAS28 at week 16. Population (*n* = 104)

The mean CRP at baseline was 30.29 mg/L and 36.93 mg/L in study and reference arm, respectively. The mean CR*P* values reduced to 14.61 mg/L and 7.35 mg/L in both arms, respectively, at week 16. The mean change was −16.37 in the study arm and −29.94 in the reference arm [Table 1].

Safety analysis

As depicted in Table 2, there were 32 (38.1%) patients in the study arm and 10 (50%) patients in the reference arm who had at least one AE in the study. There were 19 (22.6%) patients in the study adalimumab arm and 6 (30%) patients in the reference arm with at least one TEAE related to study medication. The most common AEs was pyrexia seen in 5 (5.95%) patients in the study arm and urinary tract infection 3 (15%) in the reference arm. One (1.19%) patient in study arm and 1 (5%) patient in reference arm discontinued the study prematurely due to AEs.
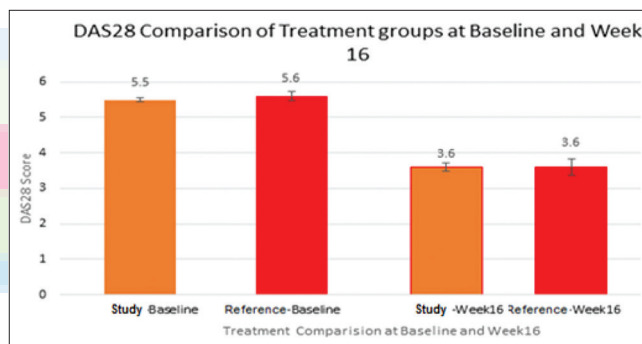
In this study, 17 SAEs were reported. As per the MedDRA coding, these 17 SAEs were coded into a total of 18 SAE terms of which, 15 were reported in the biosimilar arm and three were reported in the reference arm. Out of 15 SAE reported in biosimilar arm, seven were possibly related, six were unrelated and two were unknown. Out of 3 SAEs reported in the reference arm, two were possibly related and one was unrelated to reference drug.

Out of 15 patients in biosimilar arm, 8 (9.52%) had SAEs from infections and infestations class. The other SAEs were observed from cardiac disorders, gastrointestinal disorders, general disorders and administration site conditions, psychiatric disorders, renal and urinary disorders (i.e., 1 [1.19%] subject in each SOC class). All three patients in reference arm had SAEs from infections and infestations class. One death was reported in the biosimilar arm for which cause of death attributed by the physician was aspiration pneumonia due to upper gastrointestinal bleed with neutropenic sepsis. No subject

Table 2: Summary of adverse events		
Variable	Study adalimumab (*N*=84) Number (%) Events	Reference adalimumab (*N*=20) *n* (%) E
Subjects with Adverse Events		
At least one Adverse Event	32 (38.1%) 54	10 (50%) 18
At least one TE Adverse Event Related to Study Drug	19 (22.62%) 29	6 (30%) 9

in either treatment arm had abnormal clinically significant laboratory parameters at baseline and week 16.

Immunogenicity profile was done at week 16. Only one subject in study arm was positive for antibodies, who also was declared as clinical responder at week 16. Thus, the immunogenicity profiling did not indicate any clinically significant concerns.

Discussion

The introduction of TNF inhibitors (TNFi) has brought a paradigm change in the management of RA. The 2015 ACR guidelines for the management of RA proposes the usage of DMARDs with TNFI in the treatment of moderate-to-severe RA.[6] Combining results from different clinical studies, adalimumab has demonstrated up to 7 years of efficacy among long-standing RA patients when used in combination with MTX.[7] The percentage of patients achieving clinical remission continues to increase after two or more years of continuous treatment with combination therapy.[7] Real world data from Japan showed that DMARD-naïve and biologic naïve patients with RA who had risk factors to develop structural progression also significantly benefitted from adalimumab, in terms of reduction is disease activity and acute phase reactants.[8] In a health economic outcome study, there was a large reduction of days lost in the combination group (adalimumab/MTX) in comparison with MTX alone, at year 1 and a difference maintained to year 2. The combination therapy was much more successful in maintaining the quality of work than MTX alone.[9]

However, the major limitation for routine usage of TNFi patients in resource constraint countries is its high cost which most patients cannot afford. Biosimilars therefore positively impact the most vulnerable patient groups, including those with low incomes, senior citizens, and patients with multiple chronic diseases by increasing accessibility and reducing out of pocket costs.[10]

We conducted the present study with the intention to bridge the unmet medical need; to test the efficacy and safety of biosimilar biologic DMARD for the management of a disease that is refractory to manage at times[11] to provide a low cost, effective, and safe biologic DMARD.

We found that there was no significant difference between two treatment arms in terms of number of responders for the primary endpoint and both drugs were clinically equivalent. The total number of responders achieving clinical response as per ACR50 and ACR70 criteria at week 16 was also comparable. The mean reduction of HAQ-DI score, DAS28 score, RF, and CRP levels in the study arm and reference arm also showed no significant difference. The safety results of the study show that the study biosimilar adalimumab is safe to administer in patients with active RA. Biosimilar adalimumab has also been shown in a previous multicenter randomized trial from India to be safe and efficacious, however, the primary endpoint was assessed at 12 weeks while we assessed at week 16.[12] A large multicentric randomized trial recruiting patients from the UK, Spain, and the US also found that biosimilar adalimumab (ABP 501) is equal in efficacy, safety and immunogenicity to reference adalimumab in patients with moderate-to-severe RA.[3]

The strength of our study is that it is double-blind, randomized controlled trial. One limitation, however, is the short duration of follow-up. Thus, to conclude this study has further provided data on the clinical comparability between biosimilar adalimumab and innovator product among Indian patients with active RA. These results will bridge the unmet medical need to provide a cost-effective biosimilar alternative for management of active RA.

Conflicts of interest

All the authors (Dr Prasad Apsangikar, Dr Sunil Chaudhry, Dr Manoj Naik, Dr Jamila Joseph and Dr Shashank Deoghare) are employees of the sponsor Reliance Life Sciences Pvt ltd. There are no conflicts of interest.

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