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ORIGINAL RESEARCH

# Real-Life Tolerability and Effectiveness of Adalimumab Biosimilar in Rheumatoid Arthritis: ASPIRE Registry Data

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## ABSTRACT

***Introduction***: The TNF-α blocker adalimumab is a well-proven therapy for rheumatoid arthritis (RA). A biosimilar adalimumab (ZRC-3197; Exemptia™), a 'fingerprint match' to reference adalimumab, has been approved for prescription in India since 2014. Here, we report on the effectiveness and tolerability of this biosimilar adalimumab (bADA) from the Adalimumab Biosimilar Patient Registry [ASPIRE; ISRCTN16838474], which contains data from real-life RA patients from India.

***Methods***: ASPIRE is a post-marketing, observational registry that evaluates real-world experience across multiple centres in India. Patients with moderate to severe RA who were prescribed bADA 40 mg subcutaneously every fortnight were enrolled. Patients with complete data available until 24 weeks of bADA treatment were extracted and analyzed for standard disease activity measures and reported adverse events.

***Results***: The registry included 149 patients with RA who had a median age of 41 (22–67) years; 65% of the patients were female. Disease outcome measures, i.e. ESR, DAS-ESR and VAS-pain scores, showed gradual and significant decreases ($p < 0.0001$ for all) in 73 analyzable patients who received 24 weeks of bADA therapy. ACR20, ACR50 and ACR70 responses were achieved in 48%, 48% and 34% of patients after 24 weeks of therapy, respectively, and about 58% and 15% of patients were moderate and good EULAR responders, respectively. Physician and patient ratings for the overall global assessment of efficacy and tolerability were 'good' to 'excellent' for the majority of the patients (≥ 96%). No new safety signals were observed when analyzing this registry data.

***Conclusion***: Real-life data from this post-marketing observational analysis demonstrate the clinical effectiveness and tolerability of 24 weeks of adalimumab biosimilar therapy in Indian patients with RA. This report also reflects upon the treatment strategies and prescription patterns for such therapies in Indian clinical practice.

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## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disorder that is primarily characterized by synovial inflammation and joint destruction leading to functional loss, despite the availability of traditional therapies such as conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). Over the past few decades, biologics have revolutionized the management of RA patients, particularly those with RA resistant to csDMARDs. The most promising agents of this type are the tumour necrosis factor-α (TNF-α) inhibitors [1, 2], such as adalimumab (Humira®; Abbott, USA) which is a fully humanized immunoglobulin (IgG1) monoclonal antibody being successfully used to treat moderate to severe RA since 2002 [2]. Sufficient evidence is already available for its efficacy and safety in reducing RA activity, improving quality of life and preventing structural damage in RA patients [3–6]. However, the accessibility and affordability of biologic therapies are always a concern in less resourceful regions of the world, leading to limited experience in the clinical use of biologics in such areas. This is of particular concern in countries with developing economies such as India, where treatment costs are mostly borne by the patients, which also impacts the prescription patterns and treatment approaches employed by the physicians.

With reference biologics coming off-patent, affordable biosimilar versions of those biologics have entered the market after having passed though rigorous comparative evaluation pathways [7–9]. ZRC-3197 (Exemptia™; Cadila Healthcare Ltd, India); is one such adalimumab biosimilar that has been approved for use in India since 2014 [10, 11]. The physicochemical, functional and clinical comparability of this adalimumab biosimilar (bADA) to reference adalimumab has been demonstrated in detail via standard techniques and clinical trial [12, 13]. Based on those initial results, ZRC-3197 was authorized for clinical use in India. Recently, clinical reports from real-world settings have described the effectiveness and tolerability of this bADA in Indian patients with various immune-mediated chronic inflammatory disorders [14–16].

Other adalimumab biosimilars apart from Exemptia™ are also available in the Indian market. Each of these biosimilars has its own distinct properties, so it is important to monitor the performance of biosimilars during the post-approval phase in real-world clinical practice [11]. More importantly, in countries such as India, the prescription patterns and durations of biologic treatments are influenced more by the patient's relief from symptoms and their ability to pay than the perception of disease severity or outcomes. Hence, the generation of real-world data that allow us to probe these practical patient-centric nuances and outcomes is of the utmost importance when managing these patients.

The Adalimumab Biosimilar Patient Registry [ASPIRE] represents one such attempt undertaken as part of the post-marketing surveillance to evaluate the usage and efficacy of the bADA in various autoimmune arthritic conditions in the real world. In this paper, we report our analysis of the registry's data on the effectiveness and tolerability of the bADA after 24 weeks of clinical use in real-world RA patients. We also reflect upon the treatment and usage patterns of this agent in Indian patients. Data for AS patients are also being reported separately.

## METHODS

The Adalimumab Biosimilar Patient Registry (ASPIRE) is an ongoing, multicentre, non-interventional, open-label, observational data-collection registry (ISRCTN16838474) that was created to facilitate the evaluation of real-world patients with rheumatic disorders treated with the bADA Exemptia™. This registry was initiated by Cadila Healthcare Ltd in November 2015 across multiple centres in India as part of their postmarketing obligations to the regulatory agencies. Patients with moderate to severe active RA, ankylosing spondylitis, psoriatic

arthritis and juvenile idiopathic arthritis treated with the bADA were included after voluntary consent. Ethics committee approval (Intersystem Biomedica Ethics Committee, 09/02/2018, ref. ISBEC/NR-3/DD-JJ/2018) was sought for data analysis and publication. Patient consent for participation was duly taken. This study was conducted in accordance with the 1964 Declaration of Helsinki and applicable amendments.

Real-world patients with moderate to severe RA who were eligible as per the ACR guidelines and had failed to respond or had responded inadequately to csDMARDs or other biologics were considered for bADA therapy. All patients tested negative for tuberculosis using the Mantoux test (< 5 mm), gamma interferon and chest X-ray; had normal blood counts and liver and renal function; and had elevated ESR and CRP levels. Although not an obvious exclusion criterion, patients were tested for hepatitis B and C and HIV, and seropositive patients were not considered for bADA therapy by physicians in India as per their routice clinical practice patterns in order to avoid any additional risks to these patients. All patients had received standard csDMARD treatment for at least 3 months before the start of bADA therapy as per clinical practice. All these patients were treated with bADA 40 mg subcutaneously every other week as per the centre's routine clinical practice. Most of the patients received stable doses of methotrexate concomitantly at the treating physician's discretion.

Data management was performed by an independent clinical research organization. Electronic case report forms were set up and data were entered for all enrolled patients by all participating centres at baseline and routine follow-up visits. Patient data obtained during routine follow-up visits and investigations performed up to 24–28 weeks after therapy initiation were collected until the data cutoff date of May 2017. Only evaluable patients with complete data were then analyzed. We did not attempt to correct for missing data. Patient demographics (age, sex, race, etc.) and clinical characteristics (disease activity, history of comorbidities and treatment history) were recorded at the time of initiation of bADA therapy. Key efficacy outcomes evaluated for RA patients included American College of Rheumatology (ACR) improvement criteria, i.e. ACR20, ACR50 and ACR70; Disease Activity Score-28 for Rheumatoid Arthritis with ESR (DAS28-ESR), European League Against Rheumatism (EULAR) response criteria, visual analogue scale (VAS) for pain, and overall global efficacy assessment by physician and patient using a 4-point Likert Scale. Safety and tolerability were concluded based on adverse events as reported by the physician or patient. The global tolerability assessment ratings by physician and patient were also based on a 4-point Likert Scale, as follows: excellent (if no adverse event); good (mild adverse event); fair (more than two mild or one moderate adverse event); or poor (serious adverse event requiring hospitalization).

Data were analyzed independently with SAS version 9.4 or later. Descriptive statistics such as *n*, mean, median, standard deviation, range (minimum, maximum) and percentage change were used to summarize continuous variables. Frequencies and percentages were computed for categorical data. Statistical analyses were performed using the Wilcoxon signed rank test to compare efficacy variables at a significance level of 5%.

## RESULTS

As of May 2017, 502 patients with autoimmune inflammatory conditions were included in the ASPIRE registry. From this, data on 149 RA patients were retrieved for analysis. Data collection was attempted for all parameters for the 149 patients who started to receive bADA therapy, but only at their regular clinic visits as per their feasibility. Some patients were either discontinued from the therapy at the physician's discretion, missed a clinic visit, had a delayed follow-up schedule that did not match the required timepoint for data collection, or did not undergo all the clinical and diagnostic tests required for outcome evaluations, as anticipated with routine clinical care and centre-to-centre variation in data collection. Hence, data for all parameters were not available for every patient at the 6-month follow-up visit. Thus, for

the efficacy outcome analysis, the complete data available for 73 patients were considered (i.e. we focussed on patients for whom complete data for weeks 24–28 post adalimumab biosimilar therapy were available). Overall global efficacy and safety assessment results were available for 126 patients at the end of 24 weeks, and are reported here.

The demographic and clinical characteristics for all of the RA patients included in the registry are presented in Table 1 to provide an overall patient profile. The median age for the RA group was 41 (22–67) years and 65% of that group were females. The duration of disease was > 6 years. Before the initiation of bADA treatment, the majority of the patients (87%) had received prior csDMARDs, mostly methotrexate (78%); about 8% of the patients had received biologics such as infliximab and etanercept; and 40% of the patients were on NSAIDs. Comorbid conditions included vitiligo or hypertension (in 0.5% each), obesity and coronary artery disease (in 2%), and diabetes (in 1.5% of these patients). About 70% of the patients continued to receive methotrexate concomitantly with bADA therapy. The baseline DAS28-ESR score was 7.16 (4.7–7.7) and the baseline VAS-pain scale score was 9.0 (5–10) for the group.

**Table 1** Baseline demographic and clinical characteristics of the RA patients

| Patient characteristic | RA ($N$ = 149) |
|---|---|
| Male:female, *n* (%) | 35:65 |
| Age (years) | 42.1 ± 9.5 |
| BMI (kg/m$^2$) | 26.0 ± 3.5 |
| CRP | 26.7 ± 23.4 |
| Duration of disease | 6.4 ± 5.4 |
| VAS-pain | 8.5 ± 0.8 |
| DAS28-ESR | 7.1 ± 0.4 |
| **Prior csDMARDs [yes], *n* (%)** | **129 (86.6%)** |
| Methotrexate | 116 (77.8%) |
| Hydroxychloroquine | 3 (2.0%) |
| Leflunomide | 1 (0.7%) |
| Sulfasalazine | 1 (0.7%) |
| Others | 8 (5.3%) |
| Prior biologics [yes], *n* (%) | 12 (8%) |
| Nonsteroidal anti-inflammatory drugs | 60 (40.2%) |

Data presented as mean ± standard deviation or number of patients (percentage)

The disease outcome measures evaluated, i.e. ESR, single joint count (SJC), total joint count (TJC), patient global assessment (PGA), DAS-ESR and VAS-pain scores, showed gradual decreases over the treatment period of 24 weeks for the 73 patients with complete data. The improvements in these scores after 24 weeks of bADA therapy are presented in Table 2. There were significant decreases ($p < 0.0001$ for all) in the ESR, DAS28-ESR, and VAS-pain scores at 24 weeks as compared to the baseline. The mean change in DAS28-ESR post 24 weeks was − 3.53 ± 0.68, and the percentage change was − 48.6 ± 7.58.

At the 24-week follow-up, 48% of the patients achieved ACR20 and ACR50 responses and 34% of the patients achieved an ACR70 response. About 58% of the patients achieved a moderate response and 15% of the patients achieved a good response as per the EULAR criteria. The physician and patient global efficacy assessment ratings were 'good' to 'excellent' for the majority of the treated group (≥ 96% patients; $n$ = 126) (Table 3).

In general, the most commonly reported adverse events (in about 10% of patients) were abdominal discomfort, abdominal pain, accelerated hypertension, arthralgia, body tinea, chest pain, diarrhoea, dizziness, dyspepsia, dyspnoea, fungal infection, gastritis and headache, which were in line with the approved prescribing information for adalimumab biosimilar and consistent with the safety profile of adalimumab. Infections were reported in 2% of the population, with tuberculosis in 5 patients. No injection-site reactions or pneumonia events were noted in the registry database. Treatment was discontinued in 12 out of 149 patients (8%) owing to adverse events or a lack of efficacy. No new safety signals were observed when analyzing this registry data. The

**Table 2** Summary of disease outcome measures after 6 months of adalimumab biosimilar therapy in RA patients

| Parameter | Baseline | At 6 months | *Change from baseline (mean ± SD) [*n* = 73] | |
|---|---|---|---|---|
| | | | Change | % Change |
| DAS28-ESR | 7.10 ± 0.43; 7.16 (4.7, 7.7) | 3.72 ± 0.57; 2 (2.72, 5.71) | − 3.53 ± 0.68 | − 48.6 ± 7.58 * |
| ESR | 100.3 ± 12.36; 102.0 (60,130) | 27.6 ± 11.25; 26 (10, 72) | − 74.2 ± 12.76 | − 72.8 ± 10.90 * |
| SJC | 11 ± 2.7; 11.0 (3, 22) | 3 ± 2.1; 3.0 (8, 16) | − 8 ± 2.72 | − 72.7 ± 3.2* |
| TJC | 13 ± 3.3; 14.0 (1.5, 10) | 3 ± 2.4; 3.0 (6, 21) | − 10 ± 2.9 | − 90.9 ± 2.93* |
| PGA | 7 ± 1.4; 6.66 (4, 21) | 6 ± 1.8; 6.9 (1, 18) | − 1 ± 1.74 | − 14.28 ± 2.23* |
| VAS-pain | 8.5 ± 0.79; 9.0 (5, 10) | 2.5 ± 0.91; 2 (0, 6) | − 6.2 ± 1.09 | − 71.4 ± 11.00 * |

Data are presented as mean ± standard deviation or median (range)
*DAS28-ESR* Disease Activity Score–28 for Rheumatoid Arthritis with ESR, *TJC* total joint count, *SJC* single joint count, *PGA* patient global assessment, *VAS* visual analogue scale, *n* number of patients with evaluable observations/data
*$p < 0.0001$; Wilcoxon signed rank test

**Table 3** Summary of overall effectiveness and tolerability of adalimumab biosimilar in patients with RA at 6 months

| Rating[a] | Overall assessment of tolerability | | Overall assessment of efficacy | |
|---|---|---|---|---|
| | Physician's global assessment *n* = 126 | Patient's global assessment *n* = 126 | Physician's global assessment *n* = 126 | Patient's global assessment *n* = 126 |
| Excellent | 43 (34%) | 85 (67%) | 22 (17%) | 50 (40%) |
| Good | 81 (64%) | 37 (29%) | 100 (79%) | 72 (57%) |
| Fair | 2 (2%) | 4 (3%) | 4 (3%) | 4 (3%) |
| Poor | 0 | 0 | 0 | 0 |

Data presented as number of patients in the specified category (percentage)
*n* total number of patients with evaluable observations/data
[a] 4-point Likert Scale rating

global tolerability assessment ratings were good to excellent for ≥ 96% of patients.

## DISCUSSION

Real-world evidence from the clinical use of high-end therapies, especially biosimilars, outside of clinical trials is required for the continuous appraisal of drug safety and efficacy in treated patients [11]. While most biosimilar products pass through rigorous analytical nonclinical and clinical comparisons with the originator before they are approved for use, they are still only similar to and not identical to or the same as the originator [17], and they are evaluated for approval differently by different authorities [18]. Hence, postmarketing surveillance studies or registries that monitor the real-world clinical use of an approved biosimilar provide additional validation of its effectiveness and safety [8, 11]. Healthcare professionals usually have limited clinical information on a new product when they need to make an informed decision about whether to use that

product. The availability of real-world data such as that examined in this report can help healthcare professionals to make a more informed and thus confident decision regarding biosimilar use and whether switching to a biosimilar from the originator is worthwhile, which could help to avoid the nocebo (negative placebo) effect [8, 18].

In our study, 24 weeks of bADA therapy led to significant improvements in the disease outcome measures, i.e. ESR, DAS-ESR and VAS-pain scores ($p < 0.0001$ for all). About 48%, 48% and 34% of the patients achieved ACR20, ACR50, and ACR70 responses, respectively. The mean change in DAS28 at 24 weeks was − 3.53, and good and moderate EULAR responses were obtained in 15% and 58% of patients, respectively. Several pivotal clinical trials have demonstrated the efficacy of reference adalimumab in patients with RA, in terms of ACR criteria and the DAS-based EULAR response, when given subcutaneously every other week [3–5]. Patients with active RA who received adalimumab 40 mg every other week in pivotal double-blind studies achieved ACR20 response rates of 63% and 65%, ACR50 response rates of 52% and 39%, and ACR70 response rates of 24% and 21% at 6 months [6]. The landmark ARMADA trial pointed to an ACR20 response in 67.2%, an ACR50 response in 55.2% and an ACR70 response in 26.9% of RA patients receiving 40 mg adalimumab for 24 weeks [3]. In another 26-week phase III study, 46.0% of RA patients achieved ACR20, 22.1% achieved ACR50 and 12.4% patients achieved ACR70 [4]. In a large, open-label trial in approximately 6000 RA patients previously treated with other anti-TNF agents, 12 weeks of adalimumab therapy was associated with ACR20 and ACR50 responses in about 60% and 33% of patients, respectively; 76% had a moderate and 23% had a good EULAR response. In addition, 12% achieved DAS28 < 2.6, indicating clinical remission [5]. A head-to-head clinical comparability trial of bADA versus reference adalimumab reported statistically similar response rates in both treatments at the end of 12 weeks: an ACR20 response in 82% vs. 79.2% patients, an ACR50 response in 46% vs. 43.4% patients, and an ACR70 response in 14% vs. 15.1% patients, respectively [13]. A report of the real-world use of bADA from a single Indian centre reported a reduction in DAS28 of > 1.2 from baseline in 88% of the treated RA patients. At 6 months, the mean DAS28 score dropped to 3.32 from 6.26 at baseline. At 12 months, 58% of the patients showed clinical remission or low disease activity [16].

Results from our analysis are in line with the published literature for adalimumab therapy discussed above. The slightly higher ACR50 and ACR70 response rates in our study as compared to the above reports may reflect only the good responders rather than the whole group. We also acknowledge that rates of ACR20 response and good EULAR response appear to be slightly lower than expected in these patients. However, the overall assessments pointed to good to excellent efficacy. The physician and patient global assessment accounting for efficacy outcomes (EULAR response) could have been subjective, i.e. a not so good improvement score may have been given by patients if they perceived a minor improvement in pain. On the other hand, the results of overall assessment (as presented in Table 3) were based on a 4-point Likert scale, wherein patients independently expressed that their overall confidence in the treatment was very high, which may reflect the suggested discrepancy.

It is important to note that only patients for whom complete data were available for 24 weeks were included in the analysis of efficacy outcomes. Hence, patients with delayed or missed follow-up details could have contributed to the lower overall values for ACR20 and EULAR good response. More importantly, this may be reflective of the prescription pattern and clinical management practices of Indian physicians for this patient pool. Biologics are employed more often as induction or debulking agents than as long-term disease-controlling therapies in clinical practice in India. Hence, biologics are initiated for a fixed duration, depending on how aggressively the treating physician approaches remission control, and are then discontinued or tapered off, only to be reintroduced for disease flares [19]. Hence, not all of the patients received therapy for all 6 months, while those who showed

improvement during previous visits could have discontinued the therapy and would therefore not have been accounted for in 6-month outcome results. There is also a possibility that the cumulative good initial responses of patients who continued to receive the therapy may have led to the higher improvement scores (ACR50, moderate EULAR response) at 24 weeks. The prescription duration and the treatment approach of the physician are also often influenced more by the affordability of the treatment to the patient than the needs of the patient per se. Patient feedback about symptoms is an important influence on the usage of expensive therapies. Hence, in some cases there was an abrupt discontinuation of therapy, after which the patients were usually maintained on a conventional therapy while biologics were applied as rescue agents when there was a disease flare. Data from this registry are thus indicative of the clinical practice and usage patterns of the biosimilar in the real world in India.

The most common adverse events associated with adalimumab use are injection-site reactions, infections, and tuberculosis reactivation [6]. The safety profile of bADA was shown to be comparable to that of the originator and did not reveal any unexpected safety signals in the head-to-head comparison [13]. Real-world data from a single centre also did not yield any new findings relating to bADA use [14]. This registry has not prompted any unfavourable, unexpected safety concerns with the use of bADA in these patients. The reported side effects (fever, nausea, fungal infection, abdominal pain, headache, etc.) were in line with the established safety profile of adalimumab in RA patients. The low rates of injection-site reactions and adverse events may be attributable to the underreporting of adverse events owing to the non-randomized and well-informed patient pool, to missing data due to delayed or lost follow-up, to the open-label, observational, centre-specific data collection approach used by the registry, or to the succinate buffer base used in this biosimilar product [20]. This could also be reflective of the shorter and more varied durations of treatment (associated with real-world prescription patterns) analyzed in this study. In real world, often, patients with lesser risks are chosen for adalimumab use and hence, the safety data that has emerged out might have been limited. Nevertheless, most of the patients reported good to excellent tolerability overall.

Though limited by the real-world, open-label, non-interventional, observational nature of the study, registries like this offer an important monitoring tool for biosimilar treatments following regulatory approval. Data supporting the effectiveness and safety of biosimilars outside the controlled trial environment can help to reassure healthcare professionals of the dependability, interchangeability, and switchability of such products.

## CONCLUSION

The post-marketing real-world clinical use of the adalimumab biosimilar Exemptia™ led to significant improvements in disease outcome scores, and the biosimilar showed good-to-excellent tolerability in Indian patients with RA. The results achieved with Exemptia™ were comparable to those attained with the reference adalimumab. Registries like the one used in the present work are important tools for probing the real-world prescription patterns and treatment strategies used in such patients from a country that has distinctive clinical practices.

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***Data Availability.*** The datasets obtained and/or analyzed during the current study are available from the corresponding author on reasonable request.



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