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BRIEF REPORT

Real-life Tolerability and Effectiveness of Adalimumab Biosimilar in Ankylosing Spondylitis: the Adalimumab Biosimilar Patient Registry Data

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Objective. Adalimumab is a well-established anti–tumor necrosis factor therapy for patients with ankylosing spondylitis (AS). An indigenously developed biosimilar adalimumab (bADA) (ZRC-3197; Exemptia) is approved for prescribing in India. In this article, we present the effectiveness and tolerability of this bADA in real-life Indian patients with AS from the Adalimumab Biosimilar Patient Registry (ASPIRE) (ISRCTN: 16838474).

Methods. ASPIRE is a postmarketing observational registry for evaluating the real-world experiences of patients with autoimmune inflammatory disorders across multiple centers in India who were prescribed 40 mg of Exemptia subcutaneously every fortnight. For this report, data available until 24 weeks of bADA treatment for patients with AS who were included in the registry were evaluated.

Results. Data from 308 patients with AS from the registry (median age of 35.0 [range 17-68] years, 19% women) were analyzed. In analyzable patients with complete data, there was a gradual and significant decrease ($P < 0.001$) in the primary disease outcome scores (the mean Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] score [n = 107] improved from 6.2 ± 1.54 to 2.1 ± 0.64, and the median visual analogue scale [VAS] score [n = 101] improved from 8 to 2) after 24 weeks of bADA therapy. BASDAI score was lower than 4 in about 94% of patients after 24 weeks of therapy, and 95% of patients achieved BASDAI50 response. The overall global assessment for efficacy and tolerability was 'good' to 'excellent' for a majority of the patients (≥98%), as rated by physicians as well as patients. The therapy was tolerated well, and there were no new unexpected adverse reactions with the biosimilar's use during this study.

Conclusion. This report demonstrates the tolerability and effectiveness of bADA (Exemptia) after its clinical use for 24 weeks in real-world patients with AS from Indian clinical practice.

INTRODUCTION

Ankylosing spondylitis (AS), the most common subtype of spondyloarthritis, is a chronic, progressive, inflammatory disorder of unknown etiology. Introduction of biologics, and particularly, tumor necrosis factor (TNF) antagonists, has been a major breakthrough in the armamentarium of treatment for autoimmune disorders such as AS (1,2). Adalimumab is a fully human, high-affinity, bivalent monoclonal immunoglobulin G1-κ isotype antibody that specifically targets both soluble and membrane-bound TNF; and is approved for the treatment of AS since 2006. Pivotal clinical studies have demonstrated the safety and efficacy of adalimumab in treating patients with AS (1–5).

Despite their clinical benefits, cost remains a concern for biologic treatments, especially in countries like India that need to cater to a large, non-insured patient pool with financial constraints (6). Biosimilars have, thus, emerged and compensated the cost burden and growing demand for originator biologics combined with their patent expiration (7). ZRC-3197 (Exemptia; Cadila Healthcare Ltd.) is one such biosimilar adalimumab (bADA) developed and first approved by Indian regulators (8–10). Comprehensive analytical techniques have characterized and compared the phys-

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icochemical and functional properties of this bADA with those of the originator (11). Biosimilarity between the two products in terms of clinical efficacy and safety has also been demonstrated in a head-to-head comparative clinical trial in patients with rheumatoid arthritis (RA) (12). Based on these results, ZRC-3197 was authorized as a biosimilar in India in 2014 and was made available at almost 20% of the originator's cost (13). Discrete real-life reports from the clinical use of this therapy are suggestive of its effectiveness and tolerability in various autoimmune conditions (14–16).

Although pricing may be a driving force for prescribing biosimilars (6,17), enough emphasis has been put on the need for postmarketing studies and registry data to support their real-world use (10). This article represents one such attempt, from the Adalimumab Biosimilar Patient Registry (ASPIRE), that was undertaken as part of the postmarketing surveillance of the bADA in a larger real-life patient population with various autoimmune conditions, including AS.

Here we report 24-week follow-up data on the clinical effectiveness and tolerability of bADA therapy in a subgroup of real-life Indian patients with AS from this registry. The report also reflects on treatment and usage patterns for such therapies in these patients from Indian clinical practice.

PATIENTS AND METHODS

The Adalimumab Biosimilar Patient Registry (ASPIRE) is an ongoing, multicenter, noninterventional, open-label, and observational data collection registry (ISRCTN: 16838474) to evaluate real-life patients with autoimmune rheumatic conditions who are treated with bADA (Exemptia). The registry was initiated in November 2015 across multiple centers in India by Cadila Healthcare Ltd. as part of their postmarketing regulatory obligations. Independent ethics committee approval was sought for the data analysis and publication.

Eligible patients diagnosed with AS, who had voluntarily consented to receive bADA as their preferred biologic at the participating centers were included in the registry. All patients tested negative for tuberculosis (Mantoux and interferon gamma release assay), hepatitis B and C, and human immunodeficiency virus tests and had normal blood counts, normal liver and renal functions, and an elevated erythrocyte sedimentation rate and C-reactive protein level. Patients had received standard nonsteroidal anti-inflammatory drug (NSAID) treatment for at least 3 months before biologic therapy as per routine clinical care. Patients received 40 mg of bADA subcutaneously every other week along with concomitant, stable doses of methotrexate (MTX) or other disease-modifying antirheumatic drugs (DMARDs) and/or NSAIDs as per the treating physician's discretion.

An independent clinical research organization was involved for data management, including setting up electronic case report forms and data collection was done from participating centers at baseline and routine follow-up visits. All data available up to 24 to 28 weeks after the start of bADA therapy for all enrolled patients were entered into the system by the study centers. Data, available from the routine follow-up visits of the patients and from investigations performed, were collected until the data cutoff date of May 2017, and evaluable patients with complete data were analyzed. No imputation was done for missing data.

Demographic and clinical characteristics were recorded, as received, at the time of initiation of bADA therapy. Key efficacy outcomes included Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), visual analogue scale (VAS) score, and global efficacy assessment ratings by the physician and patient using a 4-point Likert scale. Safety and tolerability data were based on adverse events recorded by the physician or patient. The global tolerability assessment ratings by the physician and patient were also based on a 4-point Likert scale as follows: excellent: no adverse event; good: mild adverse event; fair: more than two mild or one moderate adverse event; and poor: serious adverse event requiring hospitalization. Data were analyzed independently with SAS version 9.4 (SAS Institute, Inc) or later. Descriptive statistics, such as n, mean, median, SD, range (minimum to maximum) and percentage change, were used for summarizing the continuous variables. Frequency and percentages were computed for categorical data. Statistical analyses were performed using the Wilcoxon signed rank test to compare efficacy variables at a 5% significance level.

RESULTS

As of the cutoff date for the data analysis (May 2017), 502 patients with various autoimmune inflammatory disorders, such as RA (149 patients), juvenile idiopathic arthritis (JIA) (26 patients), psoriatic arthritis (PsA) (19 patients), and AS (308 patients), were included in the registry. Data for the JIA and PsA

Table 1. Baseline demographic and clinical characteristics of patients with AS[a]

Patient Characteristic	AS (n = 308)	Patients Analyzable for Disease Outcome Scores (n = 107)
Sex (male female), %	81:19	82:18
Age, y	36.5 ± 10.58	37.8 ± 9.7
BMI, kg/m^2	25.0 ± 4.03	25.7 ± 3.7
ESR, mm/hour	98.0 ± 18.09	103.98 ± 10.6
CRP, mg/L	41.4 ± 55.63	38.3 ± 26.4
Proportion of patients with elevated CRP levels	228 (74%)	77 (72%)
Duration of disease, y	5.75 ± 3.7	4.60 ± 1.6
DMARDs (yes)	177 (57.47%)	8 (5.5%)
VAS (pain)	8.3 ± 0.85	8.57 ± 0.6
BASDAI	6.3 ± 1.39	6.2 ± 1.54

Abbreviation: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BMI, body mass index; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; VAS, visual analogue scale.
[a]Data are presented as mean ± SD or number of patients (percentage) unless otherwise indicated.

Table 2. Summary of AS disease-outcome scores at 6 months of biosimilar adalimumab therapy in patients with AS

Parameters	n[a]	Baseline, Mean ± SD, Median (Range)	6 mo, Mean ± SD, Median (Range)	Change From Baseline, Mean ± SD[b]	
				Change	% Change
BASDAI	107	6.2 ± 1.54, 6.85 (1.15-8.25)	2.1 ± 0.64, 2.05 (0.20-4.60)	−4.8 ± 0.85	−69.37 ± 9.30
VAS (pain)	101	8.3 ± 0.98, 8.0 (4-9)	2.4 ± 0.65, 2 (2-5)	−6.2 ± 0.81	−72.3 ± 7.60

Abbreviation: AS, ankylosing spondylitis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; VAS, visual analogue scale.
[a]n = number of evaluable patients with data recorded.
[b]$P < 0.001$, calculated using the Wilcoxon signed rank test.

subgroups were not analyzable because of the small sample size, whereas data for the RA subgroup is reported separately. Data for 308 patients with AS were considered for analysis and are reported here.

Data were collected for all patients only as available from their regular clinical visits that matched their feasibility and the physician's advice. In some cases, bADA therapy was discontinued as per the treating physician's discretion, whereas some patients missed their visit or had a delayed follow-up not coinciding with the data collection schedule for the study, and some patients did not undergo all clinical and diagnostic evaluations as anticipated on their visits because of a center-specific follow-up approach. Hence, not all data and outcome measures were completely reported for each patient who entered the registry at the end of 24 weeks. As a result of this, complete data available for 100 odd patients were evaluated for efficacy outcome analysis. Overall global efficacy and global safety assessments reporting at 24 weeks was performed for 250 odd patients and reported.

Demographic and clinical characteristics that were entered into the registry for the patients with AS are presented in Table 1 so as to provide an overall patient profile. The median age for the group was 35.0 (range 17-68) years, and the BMI was 25.35 (range 12.60-30.00); 19% of the patients were women. The median duration of disease was 5.2 (range 0.3-26) years. About 29% of patients received concomitant DMARDs, mostly MTX and sulphasalazine. Comorbid conditions included uveitis, psoriasis, and vitiligo in 5% of patients. The baseline VAS score ranged from 4 to 10, and the mean BASDAI score was 6.3 ± 1.39.

The AS disease outcomes for about 100 analyzable patients at 24 weeks after therapy are presented in Table 2; baseline characteristics for these patients are also included in Table 1. The BASDAI and VAS (pain) showed a gradual and significant ($P < 0.001$) decrease over the 24 weeks of the treatment period. The mean BASDAI scores improved from 6.2 ± 1.54 to 2.1 ± 0.64 (mean change of –4.8 ± 0.85), and VAS scores improved from 8.3 ± 0.98 to 2.4 ± 0.65 (mean change of –6.2 ± 0.81) at the end of 24 weeks of therapy. About 94% of patients had a BASDAI score lower than 4, and 95% of patients achieved at least a BASDAI50 response. The global assessment for efficacy by physicians and patients was "excellent to good" in 98% of patients (n = 250; Table 3).

In general, common adverse events such as headache, nausea, fatigue, arthralgia, and rashes were reported by 10% to 15% of the patients, whereas the infection rate was 5% to 10%. Events of tuberculosis were reported in 2% of the population, and there were no injection-site reactions received in the registry database. Therapy was discontinued in 9% of patients because of adverse events and in 2% of patients because of lack of efficacy. No new safety findings were observed during this registry evaluation period. The global tolerability assessment ratings were good to excellent for 98% to 100% of patients (n = 251; Table 3).

DISCUSSION

Unlike generic and originator biologics, whose approvals are primarily based on rigorous, randomized, placebo-controlled studies, biosimilars are mostly approved based on the totality of evidence generated from limited head-to-head clinical comparisons with their originators. Hence, despite the potential pharmacoeconomic edge offered, there is a lot of attention from regulators and

Table 3. Summary of overall effectiveness and tolerability of biosimilar adalimumab in patients with AS at 6 months [a,b]

Rating	Overall Assessment of Tolerability		Overall Assessment of Efficacy	
	Physician's Global Assessment (n = 251)	Patient's Global Assessment (n = 251)	Physician's Global Assessment (n = 250)	Patient's Global Assessment (n = 250)
Excellent	170 (67.73)	177 (70.52)	171 (68.40)	201 (80.40)
Good	81 (32.27)	72 (28.69)	75 (30.00)	43 (17.20)
Fair	0	2 (0.80)	4 (1.60)	5 (2.00)
Poor	0	0	0	1 (0.40)

Abbreviation: AS, ankylosing spondylitis.
[a]Data are presented as number of patients in the specified category (percentage).
[b]n = total number of evaluable patients with data recorded.

health care providers as well as payers on the real-life use of biosimilars, validation for extrapolating indications, and their relative immunogenicity and switchability from originators (10,18). Real-life analyses such as this one bridge the gap between the use of such therapies in limited, controlled clinical comparisons and in actual patients at large.

Multiple clinical studies have already proven the efficacy of adalimumab in improving outcomes in patients with AS (1,3–5,19). In pivotal studies, BASDAI50 responses were reported in 42.3% and 57.2% of patients after 24 weeks and 12 weeks of adalimumab therapy, respectively (3,5). A real-life report described a BASDAI score lower than 4 in 83.1% of patients with AS after 12 weeks of adalimumab therapy (19). In our study too, the median BASDAI score reduced from 6.85 to 2.05 and the VAS score improved from 8.0 to 2.0 after 24 weeks of therapy. More than 90% of our patients achieved a BASDAI score lower than 4 and a BASDAI50 response after 24 weeks of therapy, with an overall assessment of efficacy as 'excellent to good' in almost all (98%) of them. Although our findings are numerically higher than those reported in controlled clinical trials, they are in concurrence with the real-life report (19).

Our results are reflective of the current Indian scenario, in which biologics are used more as on-demand or debulking agents to often target a flare or high disease activity rather than as conventional long-term disease-controlling agents. Clinicians prescribe biologics for a fixed duration, which also varies between practitioners, depending on the aggression required to target remission on a case-to-case basis. As a result, the discontinuation of a biologic is abrupt in many cases or sometimes tapered based on clinical improvement (20). Moreover, although biosimilars such as bADA may offer considerable cost-effectiveness (6,13), the continuation of therapy is still influenced by its affordability for patients in India because most of them bear their own treatment expenditures, and such therapies are not insured.

Hence, after biologic discontinuation, patients are maintained on stable DMARDs, and the biologic is reintroduced depending on the deterioration of the disease. This implies that not all patients who were entered in the registry continued to receive the bADA therapy for the entire 6 months, although those who might have shown clinical improvement in earlier visits could have discontinued the therapy and not contributed to the 24-week outcome measurements. Patients could have also missed a follow-up schedule or could have had a delayed visit not coinciding with the registry's data collection time point, which, in turn, could have resulted in numerically higher outcome measure scores, as discussed above. Additionally, patients who discontinue the treatment because of lack of efficacy (reported in about 2% of our group) also cannot be ignored. Nevertheless, the registry captured all comers and evaluated the real-time use of bADA therapy in Indian patients with AS with such custom-made approach. The current results may also be reflective of the concomitant use of DMARDs, the real-life non-randomized patient pool, and more importantly, the real-time observational nature of this analysis influenced by a center-specific data collection approach and missed follow-ups.

Injection-site reactions (about 10%) and nonserious infections are the most common side effects with adalimumab use (1,3). The safety profile of bADA was shown to be comparable with that of the originator in patients with RA (12); real-life use of bADA was associated with about 4% to 5% serious and non-serious events such as nausea, and injection-site reactions, psoriasis flare, and pneumonia and tuberculosis reactivation (14). Patients with AS enrolled in this registry did not report any unexpected serious or nonserious events with bADA use. The recorded side effects, including rash, fever, serious infections, and pneumonia, are in line with the established safety profile of adalimumab. Nevertheless, missing data or underreporting of events because of the observational real-life data collection, a well-counseled patient pool, data type of medical records, or the succinate buffer base used in this biosimilar product (21) could have contributed to the overall lower reporting rate of adverse reactions or injection-site reactions.

Despite the limitations associated with the real-life observational design of this data collection registry, real-world evidence for the clinical effectiveness and tolerability of the biosimilar molecule has been demonstrated. Significant improvement in AS disease outcome scores with good to excellent tolerability of the bADA, compared with those of the originator, was observed. Registries such as this one allow us to step out of the controlled clinical trial environment and evaluate the performance of such products in large real-time patient cohorts.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published and had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Gharia.
Acquisition of data. Kapoor, Kaushik, Jain, Rao.
Analysis and interpretation of data. Gharia.

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