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

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Background /Objective & Methods

- Rheumatoid arthritis is an autoimmune, debilitating condition, leading to functional loss despite traditional therapies. Anti TNF biologics like adalimumab have improved the management of these patients, however, their accessibility and cost remain a concern in growing economies like India.
- A biosimilar adalimumab (Exemptia) which is comparable to the originator (Humira) in clinical efficacy as well as safety, is developed and approved for use in RA in India.
- ASPIRE is post-marketing surveillance registry evaluating the real-life clinical use of this bADA in RA patients in India. The study is also reflective of the real-time prescription patterns and clinical practice of managing such patients in India.

Background /Objective & Methods

- The Adalimumab Biosimilar Patient Registry (ASPIRE) is an ongoing, multicenter, non-interventional, 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 post marketing regulatory obligations.
- 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.

Background /Objective & Methods

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- 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 routine 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.

Background /Objective & Methods

- 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.

- 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.

Result

- 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 time point 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.

Result

- Thus, for the efficacy outcome analysis, the complete data available for 73 patients were considered (i.e. we focused 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 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.

Result

- 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.

Baseline demographic and clinical characteristics of the RA patients

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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)

Result

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- RA disease outcome measures i.e. ESR, DAS-ESR and VAS-pain scores showed a gradual and significant decrease ($p<0.0001$ for all) in 73 patients after 24 weeks of bADA therapy.

- ACR20, ACR50, and ACR70 responses were achieved in 48%, 48% and 34% of patients.

- More than 96% ‘Good to excellent’ rating for overall global assessment for efficacy and tolerability by physician and patients.

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

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

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Summary of overall effectiveness and tolerability of adalimumab biosimilar in patients with RA at 6 months				
Ratinga	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 specific category (percentage)
total number of patients with evaluable observation/ data
a 4-point likert scale rating

Result

- 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 with the reported with the biosimilar treatment.

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

Conclusion

- The post-marketing real-world clinical use of the adalimumab biosimilar ExemptiaTM led to significant improvements in disease outcome scores, and the biosimilar showed good-to-excellent tolerability in Indian patients with RA.

Abridged Prescribing Information

COMPOSITION: Exemptia™ (Adalimumab) 40 mg /0.8 mL single use pre filled syringe and 20mg /0.4 mL single use pre filled syringe **DESCRIPTION:** EXEMPTIATM (Adalimumab) is a recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor (TNF-α).EXEMPTIATM is supplied as a sterile, preservative-free solution of Adalimumab for subcutaneous administration. The solution of EXEMPTIATM is clear and colorless. **MECHANISM OF ACTION**: Adalimumab binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF-α receptors. Adalimumab also lyses surface TNF expressing cells in vitro in the presence of complement. Elevated levels of TNF-α is found in the synovial fluid of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitispatients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. **INDICATIONS & DOSAGE:** Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis: The recommended dose of EXEMPTIATM for adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), or ankylosing spondylitis (AS) is 40 mg subcutaneously administered every other week. Methotrexate (MTX), other non-biologic DMARDs, glucocorticoids, nonsteroidal anti-inflammatory drugs (NSAIDs), and/or analgesics may be continued during treatment with EXEMPTIA™. Juvenile Idiopathic Arthritis: Exemptia™ dosing in JIA is based on weight; for 10 kg (22 lbs) to <15 kg (33 lbs): 10 mg s.c. every other week. For 15 kg (33 lbs) to < 30 kg (66 lbs): 20 mg s.c. every other week and for ≥ 30 kg (66 lbs): 40 mg s.c. every other week. Plaque Psoriasis or Non-Infectious Uveitis: Initial dose of 80 mg, followed by 40 mg every other week starting from week one after initial dose. Hidradenitis Suppurativa: 160 mg (Day 1) (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days), followed by 80 mg two weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg every week. Adult Crohn's Disease and Ulcerative Colitis: Initial dose (Day 1): 160 mg s.c. (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days). Second dose two weeks later (Day 15): 80 mg. Two weeks later (Day 29): Begin a maintenance dose of 40 mg s.c. every other week. For patients with Ulcerative Colitis only: Only continue EXEMPTIA™ in patients who have shown evidence of clinical remission by eight weeks (Day 57) of therapy. Pediatric Crohn's Disease: For weight 17 kg (37 lbs) to < 40 kg (88 lbs): Initial dose (Day 1): 80 mg s.c. (two 40 mg injections in one day). Second dose two weeks later (Day 15): 40 mg s.c.. Two weeks later (Day 29): Begin a maintenance dose of 20 mg s.c. every other week. For ≥ 40 kg (88 lbs): Initial dose (Day 1): 160 mg s.c. (four 40 mg injections in one day or two 40 mg injections per day for two consecutive days). Second dose two weeks later (Day 15): 80 mg s.c. (two 40 mg injections in one day).Two weeks later (Day 29): Begin a maintenance dose of 40 mg s.c. every other week. **CONTRAINDICATIONS:** Hypersensitivity to the active substance or to any of the excipients, Moderate to severe heart failure, Active tuberculosis or other severe infections such as sepsis and opportunistic infections. **SPECIAL WARNINGS AND PRECAUTIONS:** Serious and fungal infections: Do not start EXEMPTIA™ during an active infection. If an infection develops, monitor carefully, and stop EXEMPTIATM if infection becomes serious•Anaphylaxis or serious allergic reactions may occur• Hepatitis B virus reactivation: Monitor HBV carriers during and several months after therapy. If reactivation occurs, stop EXEMPTIA™ and begin antiviral therapy• Demyelinating disease: Exacerbation or new onset, may occur• Heart failure: Worsening or new onset, may occur• Lupus-like syndrome: Stop EXEMPTIA™ if syndrome develops **USE IN PREGNANCY AND LACTATION**: Pregnancy Category B: Adequate and well controlled studies with EXEMPTIATM have not been conducted in pregnant women. Adalimumab is an IgG1 monoclonal antibody and IgG1 is actively transferred across the placenta during the third trimester of pregnancy. Lactation: No data is available on the absorption of adalimumab from breast milk in newborn or preterm infants. Caution should be exercised when EXEMPTIATM is administered to a nursing woman. **DRUG INTERACTION** Biological Products- Concomitant administration of EXEMPTIA™ with other biologic DMARDs (e.g., Anakinra and Abatacept) or other TNF blockers is not recommended •Live Vaccines- Avoid the use of live vaccines with EXEMPTIA™. •Cytochrome P450 Substrates- The formation of CYP450 enzymes may be suppressed by increased levels of cytokines (e.g., TNFα, IL-6) during chronic inflammation. Upon initiation or discontinuation of EXEMPTIA™ in patients being treated with CYP450 substrates with a narrow therapeutic index, monitoring of the effect (e.g., Warfarin) or drug concentration (e.g., Cyclosporine or Theophylline) is recommended and the individual dose of the drug product may be adjusted as needed. **UNDESIRED EFFECTS**: The most serious adverse reactions include the following• Serious Infections- Tuberculosis and Opportunistic Infections •Malignancies. The Clinical experience has reported Upper Respiratory Tract Infection (URTI), Increased creatine phosphokinase, Headache, Rash, Sinusitis, Nausea, Urinary Tract Infection (UTI), Abdominal pain, Flulike syndrome, Hyperlipidemia, Back pain, Hypercholesterolemia, Hematuria, Hypertension, Increased alkaline phosphatase as common side effects. STORAGE CONDITION: Store between + 2°C and + 8 °C, in the carton to protect from light. Do not freeze Exemptia™. Do not use Exemptia™ if frozen, even if it has been thawed. Keep out of reach of children. PRESENTATION: a) Injection: 40 mg/0.8 mL in a single-use prefilled syringe b) Injection: 20 mg/0.4 mL in a single-use prefilled syringe.

Please refer to the full Prescribing Information before starting EXEMPTIA™.

Please consult full Prescribing Information before prescribing.

Zydus Cadila does not recommend the use of any product in any different manner than as described in the prescribing information.

Further information is available on request from:

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Thank you

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