

Real-life Efficacy and Safety of Biosimilar Adalimumab (ZRC-3197) in Patients with Plaque Psoriasis: A Tertiary Care Center Experience

Abstract

Background: Adalimumab is proven to be safe and effective in treating plaque psoriasis. A biosimilar adalimumab (ZRC-3197; Exemptia™) - approved by Indian Regulators in 2014 - is a 'fingerprint match' of the reference adalimumab in terms of purity, potency, safety, and clinical efficacy. While reference adalimumab remains unavailable, this biosimilar adalimumab (bADA) serves as an accessible, cost-effective option for Indian patients. This is a first-hand, prospective, real-life data on the clinical use of bADA in Indian patients with plaque psoriasis.

Materials and Methods: Patients with moderate-to-severe plaque psoriasis were prospectively treated with bADA therapy for 16 weeks-80 mg subcutaneously initially, followed by 40 mg every other week from week 1 in real-life setting. Psoriasis Area and Severity Index (PASI) responses, Dermatology Life Quality Index (DLQI) outcomes, and Physician's Global Assessment (PGA) for psoriasis were analyzed. Safety and tolerability evaluations included reported adverse events.

Results: A total of 29 patients (15 males) with median age of 38 (25–56) years were included. After 16 weeks of bADA treatment, 93% patients achieved $\geq 75\%$ reduction in their baseline PASI scores including PASI75, PASI90, and PASI100 responses in 24%, 14%, and 55% patients, respectively. About 52% patients had a DLQI score of 0/1 and 93% patients had a PGA score of 'clear or minimal' at 16 weeks. Treatment was well tolerated with no severe or serious adverse reactions requiring therapy discontinuation. **Conclusions:** This report serves as a real-life evidence for the efficacy and tolerability of biosimilar adalimumab administered for 16 weeks in patients with plaque psoriasis.

Keywords: Adalimumab, biosimilar, DLQI, PASI, plaque psoriasis, safety

Introduction

Psoriasis is a chronic, immune-mediated, inflammatory skin disorder affecting up to 3% population globally and 0.3% of Asians.^[1,2] The underlying pathophysiology involves abnormal interactions between multiple immune cell types including the T-cells, macrophages, and dendritic cells that induce a rapid proliferation and incomplete maturation of the keratinocytes. Most commonly manifested as plaque-type psoriasis; thick, red, scaly lesions are the primary hallmarks of this disease.^[3] Psoriasis not only affects the physical and emotional functioning, but also imposes an increased risk for several comorbidities; thus severely impacting the patient's quality of life.^[4,5]

Traditionally, psoriasis is managed by topical agents, phototherapy, or conventional systemic nonbiologic therapies. Various novel, genetically engineered, targeted

therapies have been introduced owing to the improved understanding of the psoriasis inflammatory cascade. The role of tumor necrosis factor alpha (TNF- α) as a critical cytokine has been explored leading to an array of anti-TNF biologics further revolutionizing the management of these patients.^[6,7] Adalimumab, is one such fully human immunoglobulin G1 (IgG1) anti-TNF monoclonal antibody, first to be approved in the US and Europe for the treatment of moderate-to-severe chronic psoriasis, in addition to other autoimmune conditions.^[3,6,7] The efficacy and safety of adalimumab in plaque psoriasis has been well demonstrated by various randomized trials and open studies.^[6-11]

Of late, the introduction of 'biosimilar' or 'similar biologic' of the reference drug has drastically impacted the management of many critical autoimmune conditions, particularly in growing economies.

How to cite this article: Chopra A, Mitra D, Agarwal R, Saraswat N, Chemburkar P, Sharma L. Real-life efficacy and safety of biosimilar adalimumab (ZRC-3197) in patients with plaque psoriasis: A tertiary care center experience. Indian Dermatol Online J 2020;11:182-6.

Received: March, 2019. **Accepted:** May, 2019.

Published: March, 2020.

Ajay Chopra,
Debdeep Mitra,
Reetu Agarwal,
Neerja Saraswat,
Pooja Chemburkar,
Loknandini Sharma

Department of Dermatology,
Base Hospital Delhi Cantt,
New Delhi, India

Address for correspondence:

Dr. Debdeep Mitra,
Department of Dermatology,
Base Hospital Delhi Cantt,
New Delhi - 110 010, India.
E-mail: debdeep7@gmail.com

Access this article online

Website: www.idoj.in

DOI: 10.4103/idoj.IDOJ_120_19

Quick Response Code:



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Once reference biologic is approved, biosimilar's approval primarily rely on bioequivalence data from head-to-head randomized comparisons with the reference molecule.^[12] One such indigenously developed biosimilar adalimumab (ZRC-3197, Exemptia™; Cadila Healthcare Ltd., India) is approved for use in India since 2014.^[13] This biosimilar adalimumab (bADA) is a 'fingerprint match' of the reference adalimumab in terms of its physicochemical and functional attributes.^[14] Biosimilarity to the reference adalimumab for clinical efficacy and safety was demonstrated via a prospective, randomized, double-blind, active controlled trial in rheumatoid arthritis.^[15] As with biosimilars, the use of this bADA therapy is currently extrapolated to all autoimmune conditions including plaque psoriasis, in line with the approved indications for the reference adalimumab.

Despite its global presence, reference adalimumab is yet to be available in Indian market. Hence, biosimilar versions offer an accessible and cost-effective treatment option for eligible patients. While this bADA therapy is already in clinical use in Indian population, there is a scarcity of data on its clinical efficacy and tolerability, especially with patients with chronic plaque psoriasis. Hence, the current report aims to provide the real-life efficacy and tolerability data for the bADA therapy in biologic naïve Indian patients with chronic plaque psoriasis.

Materials and Methods

This was a prospective evaluation conducted at our center from September 2016 to September 2017. Men and women of >18 years of age with moderate-to-severe psoriasis, as defined by >10% body surface area involvement and a Psoriasis Area and Severity Index (PASI) of >12, were included in this study. Patients had plaque psoriasis for at least 1 year and stable disease for at least 2 months. All the patients had inadequate response to prior systemic or biologic therapy or phototherapy and had active psoriasis despite treatment with topical agents. The washout period for prior psoriasis therapies consisted of at least 2 weeks for topical and ultraviolet (UV) B phototherapy, 4 weeks for UVA phototherapy, and nonbiologic systemic therapies, and 12 weeks for all other biological therapies.

Patients consented to receive biologic therapy with biosimilar adalimumab (Exemptia™). Treatment was administered at an initial dose of 80 mg subcutaneously, followed by 40 mg every other week starting from week 1 after the initial dose, for up to 16 weeks. The PASI and Dermatology Life Quality Index (DLQI)^[16-18] were evaluated for all patients at each treatment visit. Scores for PASI ranged from 0 (no disease) to 42 (severe disease). The reduction in mean PASI scores, proportion of patients achieving PASI75, PASI90 and PASI100 responses, and improvements in the DLQI score were evaluated as efficacy outcomes. Physician's global assessment (PGA) for psoriasis was also done after 16 weeks of treatment.

Safety and tolerability assessments included reported adverse events or adverse drug reactions throughout the treatment period. Ethics committee approval was sought for data collection and analysis.

Statistical analysis

Continuous variables were summarized using mean and standard deviation, and median with range. Categorical values were estimated using frequencies and percentages. Statistical analyses were performed using SPSS version 10.0. The mean PASI score were compared using Wilcoxon's Sign rank test and DLQI using Student's t-test. All values were reported based on two-sided distribution and all tests were interpreted at a significance level of 5%.

Results

Patient characteristics

A total of 29 patients with plaque-type psoriasis - 15 males and 14 females - were included in this analysis. Baseline demographic and clinical characteristics of these patients are presented in Table 1. The mean age for the entire patient group was 37.10 ± 06.90 [median (range): 38 (25–56) years]; median body mass index (BMI) was 24.6 (19–30), median duration of psoriasis was 6 (1–20) years, mean PASI score was 35.03 ± 11.83 , and DLQI ranged from 7–22 at baseline. A total of 11 patients had psoriatic arthritis and 18 patients presented with nail changes. All patients received emollients and topical steroids during their prior episodes of exacerbation. Topical steroids were tapered and discontinued at least 1 month before starting adalimumab therapy. Other prior treatments received included methotrexate in 25 patients, infliximab in 2 patients, and narrow band phototherapy in 14 patients. Concomitant medications included oral hypoglycemic agents in eight patients, injective insulin in one patient, antihypertensive in four patients, and three patients were receiving atorvastatin for dyslipidemia. Therapy with methotrexate was not feasible in four patients due to intolerance; cyclosporine was not indicated in seven patients with renal impairment due to coexisting diabetes or hypertension, and retinoids were contraindicated in dyslipidemic patients. All patients completed 16 weeks of treatment with biosimilar adalimumab. After 16 weeks, patients continued to receive bADA therapy at the dose of 40 mg every other week.

Efficacy outcomes

Efficacy outcomes - PASI, DLQI, and PGA - were evaluated for all the patients throughout the treatment period till 16 weeks of therapy. The mean PASI score significantly improved within first 4 weeks of the bADA therapy (35.03 pretreatment vs. 20.83 at week 4) and continued to improve consistently and significantly till week 8. At the end of 16 weeks, the mean PASI score improved to 5.24 corresponding to a significant overall

Table 1: Baseline demographic and clinical characteristics of patients with plaque psoriasis

Characteristics	n=29
Age (years)	37.10±06.90 38 (25.00-56.00)
Gender	
Male	15 (52%)
Female	14 (48%)
Race (Asian)	100%
Height (cms)	166.03±10.22 168 (158-184)
Weight (kg)	67.85±10.42 68 (50-88)
BMI (kg/m ²)	24-84±2.26
BMI (kg/m ²)	24.6 (19-30)
>25	14 (48%)
Duration of disease (years)	7.78±5.44 06 (01.00-20.00)
Patient with psoriatic arthritis	11 (38%)
Prior psoriasis treatment	
Methotrexate	25 (86%)
Infliximab	2 (6%) ^a
Narrow band phototherapy	14 (48%)
Topical therapy	29 (100%)
Steroids	29 (100%)
Mean PASI score	35.03±11.83 22-42
Mean DLQI score	12.03±3.95 11 (7-22)
PGA score	
Moderate psoriasis	12 (41%)
Severe psoriasis	11 (38%)
Very severe psoriasis	6 (21%)

Data presented as: mean±standard deviation; median (minimum-maximum); number of patients (percentage).

BMI: Body Mass Index; PASI: Psoriasis Area and Severity Index; DLQI: Dermatology Life Quality Index; PGA: Physician's Global Assessment (for Psoriasis). ^aInfliximab was administered according to standard protocol for psoriasis (infliximab at 5 mg/kg at time 0 and at 2, 6, and every 8 weeks, before the patients were switched to adalimumab biosimilar due to lack of response

fall of 85.0% in the baseline PASI scores. Efficacy results are presented in Table 2. At 16 weeks of therapy, about 93% patients achieved a cumulative ≥75% reduction in their baseline PASI scores. This includes 24% patients with PASI75, 14% patients with PASI90 and 55% patients with PASI100 response. The change in mean PASI score over 16 weeks of treatment is diagrammatically represented in Figure 1.

The pretreatment DLQI scores ranging from 7 to 22 showed immediate improvement after the first dose of therapy in all except 3.4% patients. Over 16 weeks of

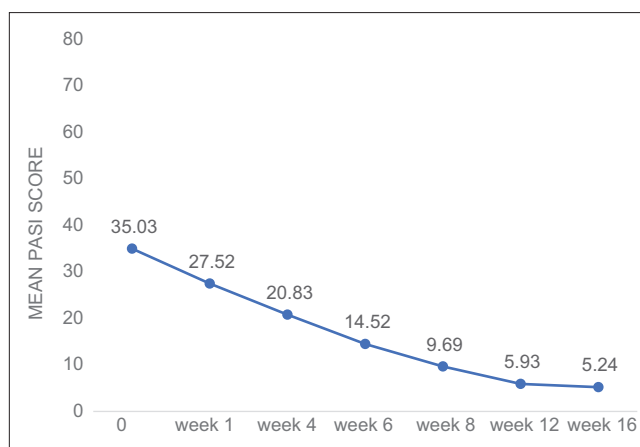


Figure 1: Change in mean PASI score over 16 weeks of biosimilar adalimumab therapy

bADA therapy, patients showed consistent improvement in their DLQI score; with 52% patients improving their DLQI score to 0–1 at 16 weeks, reflecting a marked improvement in the patient's quality of life [Table 2]. The PGA of 'clear' or 'minimal' was observed in most of the patients (93%) at the end of 16 weeks of treatment; which include 69% patients with a 'clear' score.

Tolerability and side effects

Overall, bADA therapy was well tolerated by all our patients with minor side effects. Generalized itching was reported by all the patients, injection-site pain was noted in four patients and injection-site hematoma in one patient. Four patients developed acneiform eruption over face that lasted over the entire duration of therapy and seven patients reported headache. Seven patients developed episodes of common cold, fever, and sore throat; requiring oral antibiotics for pharyngitis in two patients. All the adverse events reported were self-limiting and did not require treatment discontinuation. No other severe or serious adverse drug reactions, like reactivation or fresh incidences of tuberculosis, sinus pain, deep fungal infection or candidiasis, were noted in any of these patients.

Discussion

With reference biologics approaching patent expiry, biosimilar versions are gaining momentum by offering accessible and cost-effective treatment alternatives for various autoimmune disorders like plaque psoriasis.^[19] This is particularly important in growing economies like India where reference biologics are either not accessible or not affordable by most patients as they bear their own healthcare expenditure. Considering the way in which biosimilars are manufactured, they are 'similar' but not identical to the approved 'reference' biologic, and hence extrapolating the therapeutic indications and interchangeability with the originators remains a practical concern.^[19] It is therefore crucial to ensure effectiveness and safety of biosimilars in

Table 2: Efficacy outcomes in patients with plaque psoriasis after treatment with biosimilar adalimumab for 16 weeks

Efficacy assessments	16 weeks post biosimilar adalimumab treatments (n=29)
PASI response	
Mean PASI score	05.24±07.43* [<i>P</i> <0.0001]
PASI 75	7 (24%)
PASI 90	4 (14%)
PASI 100	16 (55%)
Cumulative PASI ≥75	27 (93%)
Improvement in DLQI score	
Mean DLQI	1.72±1.62; 1 (0-7)
Mean DLQI change [absolute]	10.31±3.52 * [<i>P</i> <0.0001]
Mean DLQI change [percentage]	86±10 (%)
Patients with DLQI of 0/1	15 (52%)
PGA at 16 weeks	
PGA, clear, or minimal	27 (93%)
PGA, clear	20 (69%)

Data presented as: Mean±standard deviation; median

(minimum-maximum); number of patients (percentage).

BMI: Body Mass Index; PASI: Psoriasis Area and Severity Index; DLQI: Dermatology Life Quality Index; PGA: Physician's Global Assessment (for psoriasis). **P*<0.0001 significant reduction as compared to baseline (values in Table 1) by Paired Student's *t*-test (DLQI)/Wilcoxon Sign Rank Test (PASI)

clinical practice, thus putting much emphasis on the need of real-world data from their clinical use in patients at large. The biosimilar adalimumab under discussion (Exemptia™) demonstrated similarity in terms of physicochemical, functional^[14] as well as clinical efficacy and safety,^[15] to the reference adalimumab (Humira®), based on which it was approved for clinical use by the Indian authorities. The current report provides a first-hand 'real-life' data on the clinical use of this biosimilar adalimumab in patients with plaque psoriasis, an indication extrapolated for use from the approved reference product.

Pivotal controlled clinical studies, their pooled *post hoc* analysis as well as small open trials have demonstrated the efficacy and safety of reference adalimumab in patients with plaque psoriasis.^[6-11,20] In the preliminary phase II dose-finding study,^[8] 53% and 25% of patients had achieved PASI75 and PASI90, respectively, at the end of 12 weeks of adalimumab given every other week. About 49% of these patients reported PGA of 'clear' or 'almost clear'. In the phase III CHAMPION study,^[6] 80% of patients had achieved PASI75 after 16 weeks of adalimumab treatment, while 16.7% had achieved complete clearance, i.e., PASI100 and 51% achieved PASI90. About 67% of these patients had reported a PGA score of 'clear' or 'minimal'. In another phase III trial, 71% of adalimumab-treated patients had achieved ≥75% improvement in PASI score at 16 weeks; PASI 90 and 100 scores were reported in 45% and 20% of patients.^[7] *Post hoc* analysis of the pooled data from these

three controlled trials^[6-8] also reported a PASI75 response in 72.1% of overall patients at the end of 16 weeks; 45.8% patients had achieved PASI90 and 19.7% patients had achieved PASI100 response.^[10] In a small, open-label study of 30 patients, the mean PASI score had improved from 19.2 to 2.5, corresponding to 87% of PASI75 and 70% of PASI90 responders at 12 weeks of weekly adalimumab treatment. The DLQI scores had also improved from 12.3 to 3.2 indicating considerable enhancement in the patient's quality of life.^[9] A retrospective study of 100 patients receiving 16 weeks adalimumab treatment had reported PASI75 response in 94%, PASI90 in 76%, and complete remission (PASI 100) in 39% of the patients.^[11] In a 16-week, open-label, phase IIIb trial, switching psoriasis patients with suboptimal response to etanercept, methotrexate, or phototherapy to adalimumab was associated with a PGA of 'clear' or 'minimal' in 52% of patients.^[20]

Our analysis reports a significant improvement in PASI score post 16 weeks of biosimilar adalimumab treatment. About 93% of our patients achieved ≥75% of improvement in their baseline PASI scores; and 55% reported complete remission, i.e., PASI100. About 14% of our patients were PASI90 and 24% were PASI75 responders. Most of our patients (93%) had a PGA score of 'clear' or 'minimal' at the end of 16 weeks of bADA therapy. These results from our patients concur with the published efficacy data of reference adalimumab discussed above and are thus suggestive of a comparable efficacy. At 16 weeks in our study, a drastic improvement in the quality of life of patients was also evident with 52% patients having a DLQI score of 0–1. Overall, efficacy outcomes from our study are reflective of bADA's efficacy in line with the reported literature for the reference adalimumab.

The safety and tolerability profile of adalimumab, as well-reported in the literature, is favorable and similar to that expected from anti-TNF- α agents. Injection-site reactions remain the most common side effects, followed by increased risk of infections, with these agents.^[6-11] In our patients too, bADA was generally well tolerated and the reported adverse events are in line with the overall expected tolerability profile of adalimumab and anti-TNF agents. There were no reports of severe or serious infections requiring hospitalization or deterioration of the underlying disease.

The authors acknowledge the limitations of these analyses in terms of its observational real-time prospective nature, small, and nonrandomized patient pool and the impact of missing data or underreporting of side effects, that might have contributed to the findings. Nevertheless, these data provide useful insights into the real-life clinical efficacy and tolerability of this biosimilar adalimumab in patients with plaque psoriasis. This report shall strengthen the future programs for vigilant monitoring of such biosimilar treatments in patients and guide future studies.

Conclusion

This report serves as a first-hand, real-life evidence of the efficacy and tolerability of the biosimilar adalimumab (Exemptia™) therapy in patients with plaque psoriasis. Ongoing real-life safety monitoring is crucial in the clinical use of biosimilars. Reports like these shall further strengthen and guide the treatment choices for clinicians in day-to-day clinical practice.

Acknowledgements

The authors acknowledge the contribution of Dr Hetal Shah, Principal Consultant, MeWriT™ from Ahmedabad, India, for her medical writing and editing support in the development and revision of this manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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