

Switching from Other Biologics to ZRC3197 (Adalimumab Biosimilar) in Patients with Spondyloarthropathy: A Prospective Evaluation from Real-Life Clinical Practice

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Abstract

Tumour necrosis factor inhibitors (TNFi) like Infliximab, Etanercept and Adalimumab have been successfully studied in controlled clinical trials and are currently recommended in the treatment of patients with spondyloarthropathy (SPA). Significant proportion of patients in clinical studies have, however, failed to achieve a desired clinical response, or, are discontinued from the therapy due to secondary inefficacy or side effects. Therefore, owing to the different molecular structures and routes of administration, switching from one TNFi to another is considered as an important option in SPA patients eligible to receive TNFi therapy. We report here our experience of switching Indian patients with SPA with inadequate response to other TNFi to ZRC 3197 (Adalimumab Biosimilar) treatment available in India.

Introduction

Tumour necrosis factor inhibitors (TNFi) have significantly transformed the treatment of patients with spondyloarthropathy (SPA).¹ Anti-TNF agents like infliximab (INF), etanercept (ETA) and Adalimumab (ADA) are successfully in clinical use for the treatment of these conditions.^{2,3} These biologics have been effective with a clinical response rate ranging from 43 to 71% by BASDAI50 (Bath Ankylosing spondylitis disease activity index) in patients with ankylosing spondylitis (AS) and from 62 to 87% by PsARC (Psoriatic Arthritis Response Criteria) in subjects with psoriatic arthritis (PsA).⁴ However, a variable percentage of patients in clinical studies still do not achieve adequate clinical response; while a significant proportion of patients discontinue the treatment due to loss of efficacy or poor tolerability.⁵ Hence, for SPA patients who are candidates for

TNF- α inhibitor therapy, switching between molecules is considered an important treatment option, owing to their different molecular structures and routes of administration.³ Physicians do switch treatment from one TNFi to a second and sometimes to a third anti-TNF agent for tackling issues like lack of response, or loss of initial response, or intolerance and adverse events in their patients.^{2,6}

It is difficult to investigate the rate of switching TNFi and its effects through controlled clinical trials owing to ethical reasons. Therefore, there is very limited evidence from controlled trials whether switching between TNFi in patients with AS will improve the clinical outcome or response. Many national registries such as BIOBADASER (Spanish Registry of Adverse Events of Biological Therapies in Rheumatic Diseases),

BSRBR (The British Society for Rheumatology Biologics Registers), DANBIO (a nationwide registry of biological therapies in Denmark), and NOR-DMARD (Norwegian DMARD register) have attempted to provide data on switching of biologics.³ A large regional survey of PsA patients in the north-west of England supported the effectiveness of switching biologics in PsA.¹

In two open-label clinical studies – RHAPSODY and STEREO – the effectiveness and safety of ADA was demonstrated in treating active patients with AS or PsA who were previously treated with IFX or ETA.^{7,8} Recently, a single centre retrospective study from Korea reported drug inefficacy and adverse events as a primary reason for switching TNFi in patients with AS. The study further suggested that complete ankylosis of the sacroiliac joint at the time of TNF- α inhibitor initiation was more likely to lead to switching, and that the use of ADA as the first TNF- α inhibitor was less likely to lead to switching in these patients.³ Another recent retrospective study of real-life data from Italian centres showed that SpA patients who failed with INF or ETA as first-line agents, responded well with ADA as a second-line drug regardless of the reason for switching.⁵

Though Adalimumab (*Humira*®, *Abbott, US*) has been approved globally since 2002 for various autoimmune conditions, the therapy is still not accessible to patients

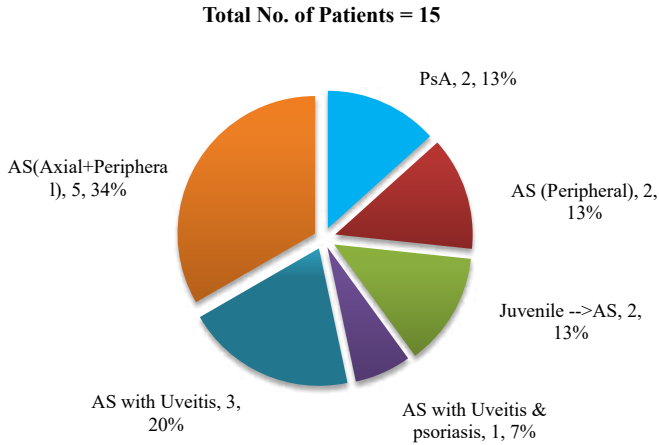


Fig. 1: Indication-wise distribution of patients who were switched to biosimilar Adalimumab

in India. ZRC3197 (*Adalimumab Biosimilar*); Cadila Healthcare Ltd., India) has been approved and introduced in clinical use in India in 2014. Biosimilarity between the biosimilar ADA and the originator ADA for its physicochemical properties was demonstrated using a series of standardized analytical techniques;⁹ and for its clinical efficacy and tolerability properties via a double-blind active controlled study.¹⁰ At present, for patients suffering from immune-mediated inflammatory conditions in India, the biosimilar ZRC3197(*Adalimumab Biosimilar*) serves as an accessible Adalimumab therapy option. We present here our experience and clinical outcomes in real-life SPA patients who were subsequently switched to biosimilar Adalimumab therapy from other TNFi. The primary objective of this analysis was to investigate the possibility of using biosimilar ADA as a second or third choice in these patients.

Methods

Patients with SPA who were treated previously with biologics (INF, ETA), and who met criteria below¹¹ were considered for switching to biosimilar ADA therapy: adults with at least 18 years of age with SPA according to ASAS axial SpA criteria or ASAS peripheral SpA criteria (2011); BASDAI \geq 4 and failure of \geq 2 nonsteroidal anti-inflammatory drugs (NSAIDs);

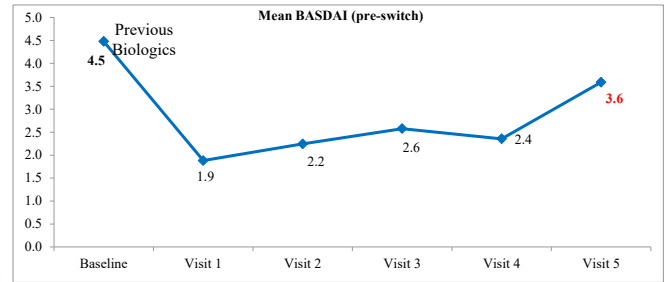
and prior treatment with ETA discontinued \geq 3 weeks and IFX was discontinued \geq 2 months before the first biosimilar ADA injection. Strategy of switching to biosimilar Adalimumab therapy was as per the ASAS consensus recommendations: active disease $>$ 4 weeks; BASDAI on previous TNFi $>$ 4 (0-10). Inadequate response to INF was indicated by a $<$ 50% decline in previous BASDAI.⁸ Biosimilar Adalimumab therapy was initiated at 40 mg subcutaneously (s.c.) every other week; tapering and discontinuation of treatment over 1 year was guided by the disease activity, and was primarily done by increasing the dosing interval rather than decreasing the dose. The aim of the biosimilar ADA treatment was to maintain the BASDAI below 50% of the baseline scores.

Data is presented for two groups of patients: (1) Typical cases group comprising of routine patients with SPA; and (2) atypical cases wherein use of biosimilar Adalimumab and its effectiveness has been discussed with unusual comorbid conditions. Descriptive data are presented. No formal analysis is required.

Experience with Switching to Biosimilar Adalimumab

Typical Cases

Data of 15 patients with SPA, who were switched to biosimilar Adalimumab from other TNF- α inhibitors previously are discussed here. This group included 13 patients



IR: Insufficient response defined as $<$ 50% improvement in BASDAI post infusion of previous biologics

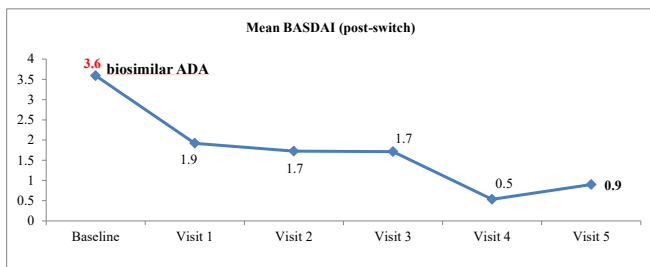
Fig. 2a: Mean BASDAI score [Pre-Switch]

Table 1: Baseline demographic and clinical characteristics of patients

Parameters	N = 15
Age (in years)	40.5 \pm 9.26
Male/Female	13/2
Average Disease duration	11 years
HLA – B27 Positive	80% (12/15)
Extra Articular Manifestation	
<i>Enthesitis</i>	7/15 (47%)
<i>Uveitis</i>	4/15 (26%)
<i>Psoriasis</i>	3/15 (20%)
Mean BASDAI	4.2
Mean ESR (mm/hr)	54
Mean CRP (mg/l)	50.4
Mean Hb (g/dl)	12.6
Concomitant Therapy	
DMARDs	13/15 (86.6%)
Steroids (Intra-articular)	4/15 (26.6%)
NSAIDs	6/15 (40%)
Infliximab mean duration	4.9 years

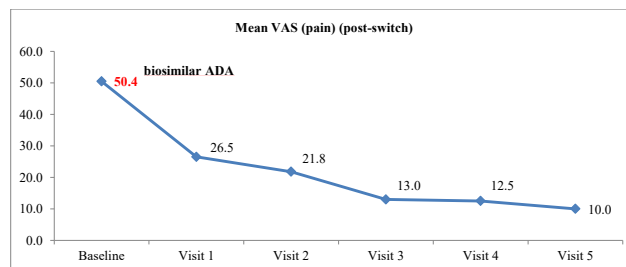
Data presented as: mean; mean \pm standard deviation; number of patients(n)/total number of patients (N); n/N (percentage of patients); unless specified otherwise.

(86%) who previously received INF; 1 patient (7%) who initially received INF followed by ETA; and 1 patient (7%) on ETA; who were switched to biosimilar ADA therapy. Indication-wise distribution of patients who switched to biosimilar ADA is presented in Figure 1. Five out of 15 patients (34%) presented with both, axial and peripheral symptoms. The baseline demographic and clinical characteristics of the patients are presented in Table 1. Most of the patients (13) were males; the average disease duration for the group was 11 years. Reasons for switching to biosimilar ADA in this patient group included: secondary inefficiency in 10 patients (66.6%); uveitis flare-up with IFX in 3 patients (20%); and no



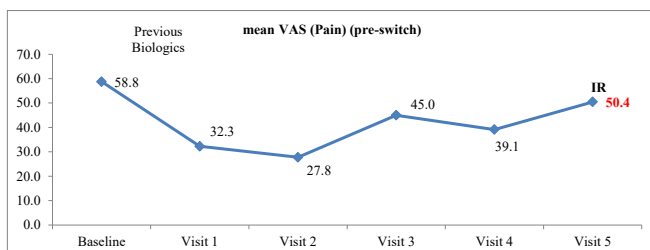
ADA: Adalimumab.
BASDAI score reduced significantly in patients who had insufficient response to previous biologics and were switched to biosimilar Adalimumab.

Fig. 2b: Mean BASDAI score with biosimilar Adalimumab [Post-Switch]



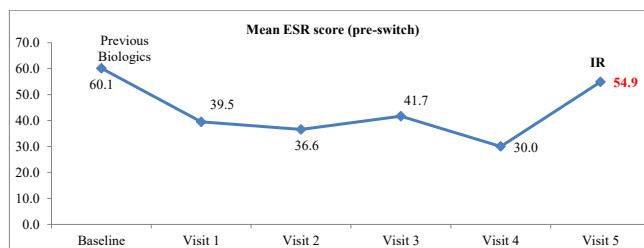
ADA: Adalimumab
VAS score showed pain reduced significantly in patients who had insufficient response to previous biologics and were switched to biosimilar Adalimumab.

Fig. 3b: Mean VAS (Pain) score with biosimilar Adalimumab [Post-Switch]



IR: Patients with Inadequate response to previous biologics had increased Pain reported in follow-up visits

Fig. 3a: Mean VAS (Pain) score [Pre-Switch]



IR: Patients with Inadequate response to previous biologics had increased Inflammatory markers (ESR) reported in follow-up visits

Fig. 4a: Mean ESR score [Pre-Switch]

improvement in psoriasis in 2 patients (13.3%). Patient follow-up was done every 15 days for initial 3 months and every month thereafter. Figures 2-4 show the mean BASDAI, mean VAS (pain) and mean ESR scores for the group, pre- and post-switching to biosimilar ADA. All the patients showed insufficient responses for all these parameters while on treatment with previous other biologics, prior to switching. There was a substantial drop in all these scores when the patients were switched to biosimilar ADA, suggestive of efficacy of the treatment.

At the time of concluding this analysis i.e. post 1 year of treatment with biosimilar ADA; all the patients were continuing on the biosimilar Adalimumab therapy. There was no inefficacy or serious adverse events noted in these patients.

Atypical Cases

We discuss here our atypical experience with biosimilar ADA therapy in 5 patients with AS.

Cases # 1 and 2: AS with Achilles Tendonitis

Two patients were diagnosed of AS with enthesitis. Both the patients had persisting *Achilles Tendonitis*. Patients had received IFX, and were

switched to biosimilar ADA 40mg s.c. after persistence of Heel enthesitis. The patients received 3 doses of biosimilar ADA and responded completely for Achilles Tendonitis.

Case # 3: AS with hip involvement

A 38 years old male patient was diagnosed of AS and was receiving IFX for 5 years. Patient had undergone a left hip replacement. After 2 months, patient developed severe right hip pain, and increased disease activity on IFX. Patient was switched to biosimilar ADA therapy, and his hip pain was relieved post 3 doses of the treatment.

Case # 4: AS with Uveitis Flare

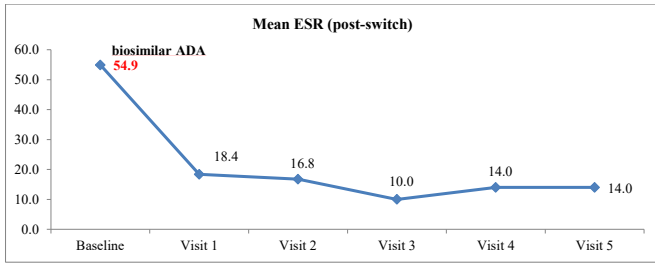
A 31 years old male patient was diagnosed of AS (peripheral) with Uveitis flare in spite being treated with IFX. The duration of the disease was 15 years and HLA B27 tested negative. The patient had received IFX. After inadequate response to Uveitis, the patient was switched to biosimilar ADA. Figure 5 shown the improvement in clinical parameters post switching to biosimilar ADA.

Case # 5: AS with chest enthesitis resistant to IFX

A male patient was diagnosed on

AS involving axial and peripheral symptoms, with chest enthesitis. The patient was also hypertensive. The patient developed a flare in chest enthesitis leading to difficulty in breathing, while on IFX treatment for 5 months. Treatment was switched to biosimilar ADA and there was an immediate improvement in the overall condition of the patient. The changes in the clinical parameters are shown in Figure 6. Biosimilar ADA therapy was tapered to slow withdrawal.

Literature suggest inefficacy or loss of efficacy over time as a major reason for discontinuation of the initial biologic and switching to another agent. A study in patients with PsA reported an adequate response to second or third line biologic in majority of the patient group.¹ Patients with PsA showed the best response rate to the second anti-TNF agent in another observational study.² Switching between the three most commonly used TNFi in patients with AS had revealed that use of Adalimumab as the first TNFi was less likely to lead to switching in a recent study.³ A retrospective study, similar to



Inflammatory marker (ESR) showed significant reduction in patients who had insufficient response to previous biologics and were switched to biosimilar Adalimumab.

Fig. 4b: Mean ESR score with biosimilar Adalimumab [Post-Switch]

our analysis, had evaluated the switching from INF or ETA to ADA in resistant or intolerant patients with SPA. In these patients who failed the first TNFi for whatever reasons, survival curves for ADA as a second or a third TNFi were significantly better than those for the first TNFi.⁵ Our experience concurs with these published findings and supports the use of biosimilar ADA for switching Indian patients from other TNFi in case of inadequate response or secondary inefficacy. The tapering and discontinuation strategy applied in our study concurs with recently published literature for Adalimumab discontinuation/tapering strategies.¹² Tapering by increasing dose intervals may indirectly support cost reduction, rather than completely discontinuing the TNFi therapy.

To conclude, biological therapy is one amongst the few options available for the treatment of patients

with SPA. Decreasing efficacy with time is usually seen in clinical practice with TNFi, which can be overcome by switching to other agents. In our experience, biosimilar ADA served as an effective option with an acceptable tolerability, for switching Indian patients with SPA not responding to other TNFi.

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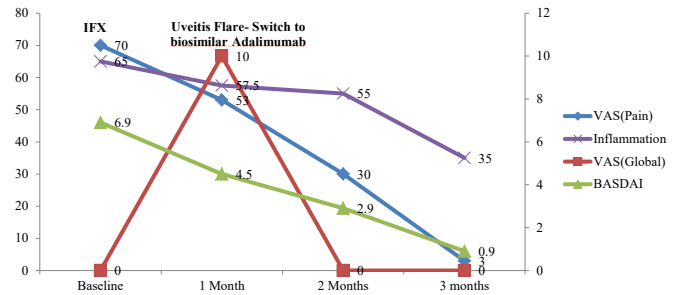


Fig. 5: Atypical case # 4: AS with uveitis flare

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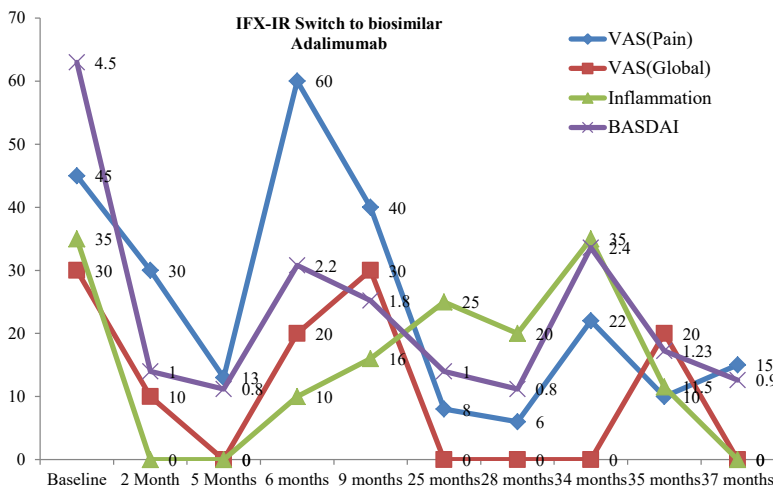


Fig. 6: Atypical Case # 5: AS with inadequate response to IFX