

## In-clinic experience with half dose Etanercept Biosimilar in Indian patients with rheumatic diseases: A single center observational study

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### Abstract

Synovial inflammation in rheumatic diseases leads to cartilage damage, bone erosions and subsequent joint destruction causing significant morbidity. Seronegative spondyloarthropathy or seropositive rheumatoid arthritis and their variants once diagnosed should be treated early to prevent the bony erosion. Delay of up to nine months in initiating Disease-Modifying Anti-rheumatic Drug (DMARD) definitely impacts clinical outcome several years later. During the last decade, introduction of biologics like TNF inhibitors have revolutionized the management of rheumatic diseases leading to early and prompt control over disease activity. One of the TNF inhibitors, Etanercept over the time has proven itself to be a reliable option for treatment of rheumatoid arthritis, spondyloarthropathy, psoriatic arthritis and other rheumatic diseases. Major drawback with biologics like Etanercept is their cost. Indian population differs substantially from western population in terms of height, weight, phenotype as well as genotype. Due to this difference in demographic profile and cost-affordability, many drugs have been used in low dose in Indian population. Etanercept can be a safe and effective option in rheumatic diseases even at half its recommended dose in countries like India where the average weight of people is less as compared to western population. Low dose also improves affordability, reduces risk of infections and may be, minimizes need for vaccination. In the modern era of biologicals, biosimilars have a huge potential to treat rheumatic diseases in India where affordability is a real challenge. This study was over 256 patients.

**Keywords:** Spondyloarthropathy, DMARD, TNF inhibitor, Biologicals, Biosimilars.

### Introduction

Biologic drugs like TNF inhibitors have revolutionized the management of rheumatic diseases leading to early and prompt control over disease activity. One of the TNF inhibitors, Etanercept over the time has proven itself to be a reliable option for treatment of rheumatoid arthritis, spondyloarthropathy, psoriatic arthritis and other rheumatic diseases. Major drawback with biologics like Etanercept is their cost. The evolution of biosimilars has addressed this issue very promptly by providing affordable and quality treatment equivalent to the innovator biologics (reference medicinal products). Not much data is available on the effectiveness and safety of these biosimilars. Moreover, the published data on innovator molecules is predominantly on western population. Indian population differs substantially from western population in terms of height, weight, phenotype as well as genotype. Due to this difference in demographic profile and cost-affordability, many drugs have been used in low dose in Indian population. This study aims to evaluate the in-clinic safety and effectiveness of low dose of Etanercept biosimilar developed by Intas Pharmaceuticals Ltd. (Intacept) in patients with various rheumatic diseases.

### Objective

1. To assess the safety and effectiveness of low dose Etanercept biosimilar in patients of rheumatic diseases.
2. To assess patient related outcome of Etanercept biosimilar in these patients.

### Materials and Methods

This was a retrospective observational study. Data related to safety and patient perceived effectiveness was collected from all patients who received Etanercept biosimilar 25 mg weekly dose (half of full dose 50 mg) in routine clinical practice.

Data maintained at our center was mined and analyzed to assess the safety and patient perceived effectiveness of Etanercept biosimilar 25 mg weekly dose in routine clinical practice. Patient's overall experience with Etanercept biosimilar was also assessed as excellent, good, average and poor (non satisfactory).

The number of patients discontinuing Etanercept was also noted with reason for their discontinuation.

### Results

Total 256 patients, 103 males and 153 females were prescribed Etanercept biosimilar 25 mg weekly as per data analyzed from Aug 2015 to Jul 2018 at our center. The mean age of patients was  $41.75 \pm 18.7$  years (Age range: 8yrs to 65yrs). The study group included patients with spondyloarthropathy (77.3%), rheumatoid arthritis (16.40%), soft tissue rheumatism (5.1%), Sjogren's syndrome (0.8%) and psoriatic arthritis (0.4%). All patients routinely underwent investigations like renal function, liver function, complete blood picture, ESR, rheumatoid factor, uric acid and blood sugar etc.

All patients were prescribed 25 mg of Etanercept biosimilar once in a week through SC route. Co-medications included DMARDS viz. sulfasalazine, methotrexate and hydroxychloroquine in 70.31%, 19.92% and 5.1% patients

respectively. All patients with RA received methotrexate and folic acid along (not on the day of methotrexate dose) with Etanercept. These patients receiving methotrexate were given deflazacort 15 mg to prevent interstitial lung fibrosis. Patients were enquired routinely for co-existing constipation and if present, hydroxychloroquine was preferred in such cases. Most of these patients reported improvement in constipation on follow up visits. All patients received three triamcinolone 40 mg bolus injections at an interval of 3 days after which they were given 6 mg/day deflazacort for 10 days which subsequently was reduced to 6 mg twice weekly for initial 6 weeks. None of the patient received any vaccination.

The dose of anti-diabetic drugs was adjusted in diabetes mellitus patients to compensate for the effect of steroids. Few patients having co-existing anemia were dewormed and given iron preparation with or without erythropoietin depending upon severity of anemia and renal profile.

Absorption of Etanercept gets initiated at its site of subcutaneous injection.<sup>6</sup> It peaks in concentration around 48-60 hours and starts eliminating from the body slowly with a terminal half life between 70 and 100 hours.

Co-prescription of methotrexate requires dose adjustment of etanercept. Dose should also be adjusted while prescribing in a patient with warfarin or digeoxin.<sup>6</sup> It is for the reason that combining with the above drugs Fc domain of IgG significantly increases its half life. Etanercept is a fusion protein of TNF & Fc.<sup>5</sup>

The mean duration of follow up of the patients was 11.5± 4.2 weeks. 91.8% (n = 235) of the patients remained on Etanercept therapy for a minimum 6 weeks but in majority of case for 12 weeks duration of 12 weeks. (Fig. 1)

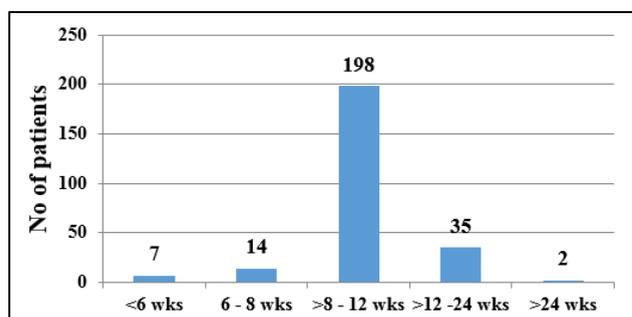


Fig. 1: Duration of therapy wise distribution of cases

**Safety Analysis**

Each patient was enquired for any side effect on all follow up visits. The therapy was well tolerated in most patients with 91.4% of patients not reporting any side effect. None of the patient experienced any opportunistic infection. The side effects reported in the study were injection site local pain during injection, injection site reaction, local redness (Table 1). There was no weight gain in this series.

**Table 1: Adverse events**

S. No.	Adverse event	% of patients (n)
1	Injection site local pain during injection	5.46% (14)
2	Injection site reaction	2.34% (6)
3	Local Redness	1.17% (3)

About 14.45% of patients did not continue with Etanercept biosimilar for even 12 weeks. Common reasons for dropping out were affordability issue due to cost (4.6%), inadequate/no response (2.34%) & side effects (1.17%). (Fig. 2) The cases which did not respond to treatment on first follow up visit at 6 weeks were further analyzed. One such case turned out to be having osteoarticular tuberculosis and another one having degenerative arthritis.

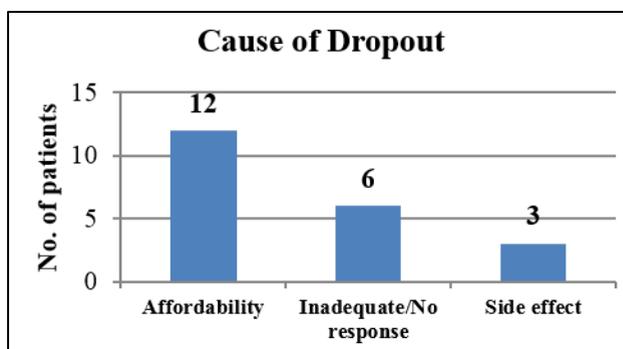


Fig. 2: Cause wise distribution of dropout cases

**Patient Perception of Drug Effectiveness**

Most of the patients reported dramatic improvement by 2<sup>nd</sup> or 3<sup>rd</sup> week and continued to remain in such state. Improvement in global disease activity was noted in visual analogue scale (0 – 100). 51.4% patients observed more than 50% improvement in global disease activity with Etanercept biosimilar, while 10% patients did not get any response with the treatment. (Fig. 3)

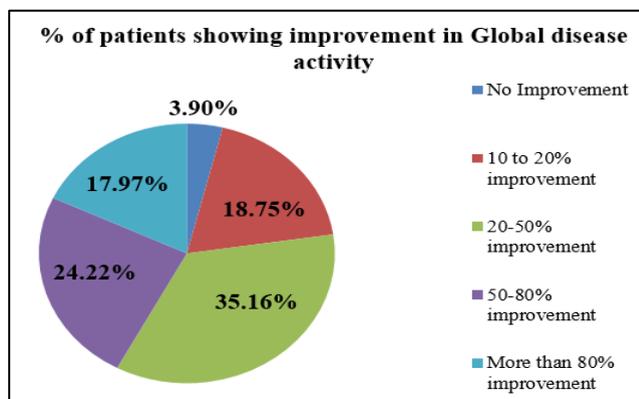
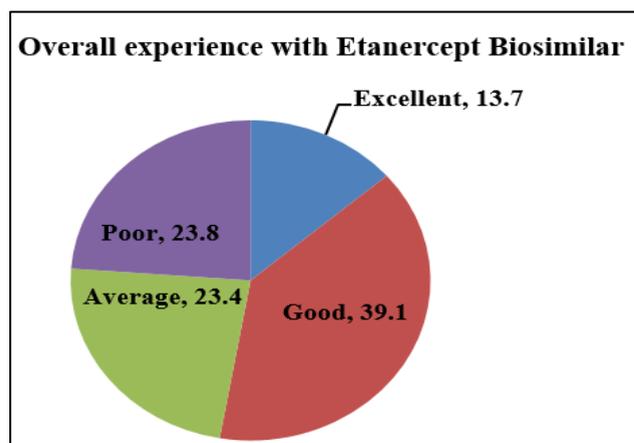


Fig. 3: Patient distribution as per improvement in global disease activity (Visual Analogue Scale)

76.2% patients perceived the overall therapy with Etanercept biosimilar as excellent, good or average and while 23.8% patients rated the therapy as poor. (Fig. 4)



**Fig. 4:** Patient's assessment of overall experience with Etanercept biosimilar

## Discussion

Etanercept has been established as an effective and safe TNF inhibitor in spondyloarthropathy. Most of the published data on Etanercept specifically refers to the innovator. In current era, the concept of biosimilars is rapidly being taken up because of their promising effectiveness and safety profile. Unfortunately, the Indian data on biosimilars is scarce and hence, this study was taken up to evaluate the real time in-clinic safety and patient perceived effectiveness of low dose Etanercept biosimilar.

Injection site local pain during injection, injection site reaction, and local redness reported in this study are well established side effects of Etanercept.<sup>1</sup> The pain can be prevented in most of the cases by allowing the medication to come to room temperature and giving the injection by slowly pushing the plunger. Some spontaneous reports of weight gain have also been seen with the innovator Etanercept but none of them had weight gain in our cases. No new safety concerns were observed in the study. Exacerbation of opportunistic infection is one of the reported side effect of TNF inhibitors. Though, there was no infection seen in this study as Etanercept imparts less risk of infection as compared to other TNF inhibitors like infliximab and adalimumab.<sup>1</sup> Moreover, the low dose used in these patients further improved the safety profile of Etanercept.

Discontinuation of treatment is prompted by the production of anti-drug antibodies (ADA) in many cases on biologics after long period of treatment.<sup>7,8</sup> ADA is also responsible for making the treatment ineffective.<sup>9</sup> Etanercept is a molecule with lowest ADA among all other anti-TNF, though its low immunogenicity is still unclear.<sup>7,8,10</sup>

Side effects noted with Etanercept like lymphoproliferative disorders,<sup>11</sup> haematological reactions like thrombocytopenia, pancytopenia and neurological

disorders ranging from headache to more severe demyelinating diseases and congestive heart failure in patients with ankylosing spondylitis.

Acute uveitis, Crohn's disease and sarcoidosis are rare adverse events associated with etanercept therapy in ankylosing spondylitis patients. While some reports have shown that etanercept may prevent acute uveitis in AS, although less effectively than infliximab,<sup>14</sup> in contrast etanercept have also been reported to be responsible for flairs-ups or new occurrences of acute anterior uveitis.<sup>13</sup>

Biologic drugs being expensive necessitates dose tapering, extending intervals of administration and finally drug discontinuation on clinical remission. In 26% of the patients after six injections the interval was increased to 2 weeks for 6 injections and then 4 weeks up to 8-12 injections.<sup>12</sup>

CT guided intra-articular etanercept 25 mg at 0, 4, and 8 weeks have been used in Chinese patients. 2 patients have been treated for involvement of knee joint but have not been included in this series.

Guidelines recommend administering vaccines against pneumococci, influenza, hepatitis B virus and human papilloma virus before prescribing TNF inhibitors in elderly patients or patients at risk of these infections due to chronic underlying condition or the medications.<sup>1,2</sup> No patient in our study was vaccinated and still there was no infection reported. This can again be probably explained by the use of low dose of Etanercept.

When reason for drop out is analyzed, most important reason was affordability issue seen with 4.7% of population. Moreover, this affordability issue was despite the low dose prescribed and the low price of biosimilar compared to innovator. Another cause was non-response or inadequate response. Two such cases turned out to be tuberculosis and one was degenerative osteoarthritis spine. The therapy was stopped after 6 weeks if there was no response. There is a huge list of differential diagnoses when it comes to axial spondylosis. Sometimes, wrong diagnosis can also lead to non-response to Etanercept as seen in this study. Degenerative osteoarthritis can be differentiated from axial spondylosis keeping in mind the fact that in former, osteophytes usually grow transversely while in later, they grow vertically.

One of the important limitations of the study was that no specific established clinical evaluation parameter like ASAS, DAS, BASDAI, BASFI etc were done. The only effectiveness criterion was the patient perceived effectiveness. Still, as the patient's experience is a good indicator of treatment response, the study data will definitely be important in adding to the present understanding of biosimilars presently being used in India.

## Conclusion

The study leads to the conclusion that biosimilar Etanercept can be a safe and effective option in rheumatic diseases even at half its recommended dose in countries like India where the average weight of people is less as compared to western population. Also, low dose improves affordability,

reduces risk of infections and may be, minimizes need for vaccination. More observational and comparative studies are needed to further strengthen the case of low dose Etanercept. In the modern era of biologicals, biosimilars have a huge potential to treat rheumatic diseases in India where affordability is a real challenge.

**Conflict of Interest:** None.

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