Open Access

Original Article

Safety and Clinical Response in Ankylosing Spondylitis after Three Months of Etanercept Therapy

Roshaan Tahir, Nadeem Ashraf, Adnan Manzar*, Muhammad Hamza Zaheer, Muhammad Asad Abbass, Ammarah Mehmood**

Department of General Medicine, Pak Emirates Military Hospital/National University of Medical Sciences (NUMS) Rawalpindi Pakistan, *Department of Rheumatology, Combined Military Hospital Lahore/National University of Medical Sciences (NUMS) Pakistan, **Department of Pathology Armed Forces Institute of Pathology/National University of Medical Sciences (NUMS) Rawalpindi Pakistan

ABSTRACT

***Objective*:** To look for safety and clinical response in ankylosing spondylitis after three months of Etanercept therapy and factors associated with response.

Study Design: Prospective longitudinal study.

Place and Duration of Study: Department of Rheumatology and Medicine, Pak Emirates Military Hospital Rawalpindi Pakistan, from Apr 2021 to Jun 2022.

***Methodology*:** Patients with ankylosing spondylitis diagnosed based on Modified New York criteria in the rheumatology department of our hospital were recruited. Bath Ankylosing Spondylitis Disease Activity Index was calculated for all the patients included in the study at baseline and 12 weeks after the treatment. Relevant socio-demographic factors were associated with significant clinical improvement using Etanercept in patients included in our analysis.

Results: Out of 102 patients of ankylosing spondylitis treated with a biological agent (Etanercept), 94(92.2%) had adequate clinical response. In contrast, 8(7.8%) patients did not have adequate clinical response on the Bath Ankylosing Spondylitis Disease Activity Index. The mean age of the study participants was 38.61±7.88 years. The presence of comorbid illnesses and raised levels of erythrocyte sedimentation rate were significantly associated with poor response to treatment with Etanercept in our study participants (p-value<0.05).

***Conclusion*:** More than 90% of the patients had adequate clinical response at the end of three months of treatment with Etanercept. Patients with comorbid medical conditions or raised ESR levels were more at risk of inadequate treatment response with this newer biological agent than other patients.

Keywords: Ankylosing spondylitis; effectiveness; etanercept; safety.

How to Cite This Article: *Tahir R, Ashraf N, Manzar MA, Zaheer MH, Abbass MA, Mehmood A. Safety and Clinical Response in Ankylosing Spondylitis after Three Months of Etanercept Therapy. Pak Armed Forces Med J 2024; 74(4): 1177-1180. DOI: https://doi.org/10.51253/pafmj.v74i4.8893*

INTRODUCTION

Back pain is a common clinical problem which has multiple dimensions from diagnostic and therapeutic points of view.[1] In most cases, the cause is not a serious underlying condition, but still, the patient suffers considerable disability and compromised quality of life.[2] Ankylosing spondylitis is a rheumatological disease which often turns out to be the cause of prolonged unexplained backache in patients across the globe.[3] Adequate understanding of this condition to medical doctors of various specialities may help the patient in timely management.

Diagnosis of ankylosing spondylitis sometimes becomes a challenge for the treating team and usually involves multiple modalities in a tertiary care medical set-up.[4] Treatment of this condition involves symptomatic analgesics, physiotherapy, steroids, and disease-modifying agents.[5] Rapid evolution in rheumatology in the last two decades has enabled clinicians to use new biological agents more commonly in various immune-mediated rheumatoid disorders, including ankylosing-spondylitis.[6]

Etanercept is a newer biological agent gaining popularity as a treatment option for patients with ankylosing spondylitis. Different preparations of this medication are available, and a recent study by Zhao *et al*. revealed that effectiveness is identical in all preparations, whether it is used as 50mg once a week or 25mg twice a week.[7] In 2019, Dong *et al*. went one step ahead. They studied drug levels and anti-drug antibody levels. They tried to figure out a road map for clinicians to monitor drug response and adverse effects during the treatment of this chronic illness.[8] Both radiological and clinical responses can be incorporated into routine practice to look for the effectiveness of this relatively newer agent. Huang *et al*. studied radiological response in their study published in 2019. They advocated the tapering dose for patients with ankylosing spondylitis.[9] Clinical response may be

Correspondence: Dr Roshaan Tahir, Department of General Medicine, Pak Emirates Military Hospital, Rawalpindi Pakistan

Received: 17 Jun 2022; revision received: 23 Nov 2023; accepted: 04 Apr 2024

more beneficial regarding patients' satisfaction and needs.

Backache and other symptoms related to ankylosing spondylitis are usually too cumbersome for patients to carry on their lives in the same routine as it was before the onset of symptoms. A recent study carried out on the local population stated that ankylosing spondylitis forms a considerable chunk of all the rheumatological disorders diagnosed in Pakistan.[10] Radiological response is sometimes challenging to study due to limited MRI facilities available; therefore, clinicians usually look for clinical response during or after the treatment. Limited local data has been available in this regard, so we planned this analysis to find the effectiveness of Etanercept therapy.

METHODOLOGY

The prospective longitudinal study was conducted at the Department of Rheumatology and Medicine at Pak Military Hospital, Rawalpindi, from April 2021 to June 2022. Ethical approval was taken from the Ethical Committee of the Hospital (letter no A/28). The sample size was calculated using the WHO sample size calculation, using the population prevalence proportion of response in ankylosing spondylitis patients with Etanercept as 52% and the level of significance as 10%.[11] Non-probability consecutive sampling was used to gather the sample.

Inclusion Criteria: All patients who reported to the department during the study period and were diagnosed with Ankylosing spondylitis were included.

Exclusion Criteria: Patients with active Tuberculosis, any malignant condition, or any immunocompromised condition, Patients who were using any other form of biological treatment or systemic steroids at the time of diagnosis, Those with a history of any recent spinal surgical procedure or a history of any severe allergic reaction to Etanercept, women who were pregnant or lactating babies were excluded.

After consent-related formalities, patients who met the criteria set for the study were assessed as per the study protocol at baseline and after three months of treatment with Etanercept. Consultant medical specialist or rheumatologist diagnosed ankylosing spondylitis based on clinical, radiological and laboratory findings.[12] Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was calculated for all the patients included in the study at baseline and 12 weeks after the treatment. It covers multiple clinical parameters. Response to treatment was defined as more than a 50% decrease in score after three months.[13] Etanercept was used in all the study participants at 50mg weekly, a standard adult dose.[14] Adverse effects were monitored by the clinical team on outpatient department visits. Comorbid conditions not part of the exclusion criteria and recorded for study participants included controlled type II diabetes mellitus, hypertension or obesity.

Statistical Package for the Social Sciences (SPSS) version 23.00. Frequency and percentage were calculated for the qualitative variables, whereas mean and standard deviation were calculated for the quantitative variables. Chi-square and Fischer's exact test were used to look for the relationship of age, gender, presence of comorbid illnesses, and erythrocyte sedimentation rate with clinical response at three months of treatment in study participants. The *p*-value less than or equal to 0.05 was considered significant.

RESULTS

The research team recruited one hundred and two patients with ankylosing spondylitis for the study. The mean age of the study participants was 38.61±7.88 years. Out of 102 patients of ankylosing spondylitis treated with a biological agent (Etanercept), 94(92.2%) had an adequate clinical response, while 8(7.8%) patients did not have an adequate clinical response on Bath Ankylosing Spondylitis Disease Activity Index. Table-I summarises the general characteristics of the study participants. Out of the total study participants, 06(5.8%) had infections, 05(4.9%) had injection site reactions, and 04(3.9%) had a rash. Table-II shows the statistical analysis results applied to the data set. It was revealed that the presence of comorbid illnesses (*p*-value-0.003) and raised erythrocyte sedimentation (*p*-value-0.007) rate were statistically significantly associated with poor response to treatment with Etanercept in our study participants. Regarding the age of the patients *P*-value-0.697) and gender (*p*-value-0.873), these socio-demographic variables were found not to be significantly associated with poor response in patients of Ankylosing spondylitis recruited in our study.

DISCUSSION

Biological treatments have gained popularity among clinicians in the last two decades, and their use in various rheumatological and immune-based disorders has increased tremendously. The clinical

Table-I: Characteristics of patients with Ankylosing spondylitis included in the study (n=102)

Parameters	n(%)
Age (years)	
Mean+SD	38.61±7.88 years
Range (min-max)	18 years-54 years
Gender	
Male	91(89.2%)
Female	11(10.8%)
Significant clinical improvement at 12 weeks	
No	08(7.8%)
Yes	94(92.2%)
Comorbid illnesses	
No	74(72.5%)
Yes	28(27.5%)
Adverse events	
Infection	06(5.8%)
Injection site reaction	05(4.9%)
Headache	04(3.9%)
Dizziness	02(1.9%)
Diarrhea	03(2.9%)
Local rash	03(2.9%)

Table-II: Relationship of various factors with Significant Clinical Improvement (N=102)

Factors	No significant clinical improvement	Significant clinical improvement	p-value
Age			
18-35years	06(75%)	76(80.8%)	0.697
35-60 years	02(25%)	18(19.2%)	
Gender			
Male	07(87.5%)	84(89.3%)	0.873
Female	01(12.5%)	10(10.7)	
Comorbid illnesses			
No	02(25%)	72(76.5)	0.003
Yes	06(75%)	22(23.5%)	
Erythrocyte Sedimentation Rate			
Normal	02(25%)	69(73.4%)	0.007
Raised	06(75%)	25(26.6%)	

team always weighs the risks and benefits of a treatment for an individual patient before starting it, especially if any option has to be continued for a more extended period of time. We selected this relatively newer biological agent to look for effectiveness and safety in the local population so that clinicians no longer need to rely on data from the Western population to tailor the treatment plan for ankylosing spondylitis.

Infliximab and Etanercept originators and their corresponding biosimilar were compared for effectiveness and safety in patients suffering from ankylosing spondylitis. It was concluded that both treatment options were effective in managing clinical symptoms and resolving radiological findings among patients with ankylosing spondylitis.[15] We studied 12 weeks' response to clinical symptoms on a structured scoring system and found that more than 90% of the patients had adequate responses.

Zhang *et al*. studied patients with ankylosing spondylitis with primarily hip joint involvement. They studied the role of TNF inhibitors in clinical and radiological improvement. Both clinical and radiological responses were adequate in their study participants, and they advocated the use of these agents.[16] More than 90% of the patients in our study had an adequate clinical response at the end of three months of treatment with Etanercept. Patients with comorbid medical conditions or raised ESR levels were more at risk of inadequate treatment response with this newer biological agent as compared to other patients.

Huang *et al*. published a meta-analysis on the role of TNF inhibitors in managing ankylosing spondylitis, both from clinical and radiological aspects. It was revealed after an extensive literature search that these agents are effective in managing both aspects of this rheumatological disorder.[17] We studied only one TNF inhibitor, i.e., Etanercept, and concluded that it was a safe and effective drug for these patients. We did not study radiological responses to assess effectivity; we only studied clinical responses. Yang *et al*. assessed the role of dose tapering after quick response in clinical symptoms and bone marrow oedema among patients suffering from ankylosing spondylitis.[18] They reported excellent and quick responses within twelve weeks of treatment. Our study results supported the findings generated by Yang *et al*.[18]

LIMITATIONS OF STUDY

The main limitation is that clinical response assessment only includes biochemical and radiological parameters. MRI changes in bone marrow oedema are usually important in determining treatment response. Long-term safety was not established as patients were not followed up beyond twelve weeks of treatment.

CONCLUSION

More than 90% of the patients had adequate clinical response at the end of three months of treatment with Etanercept. Patients with comorbid medical conditions or raised ESR levels were more at risk of inadequate treatment response with this newer biological agent than other patients.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

RT & NA: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

AM & MHZ: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

MAA & AM: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Wu A, March L, Zheng X, Huang J, Wang X, Zhao J, et al. Global low back pain prevalence and years lived with disability from 1990 to 2017: estimates from the Global Burden of Disease Study 2017. Ann Transl Med 2020; 8(6): 299. https://doi.org/10.21037/atm.2020.02.175
2. Wu A, Dong W, Liu S, Cheung JPY, Kwan KYH. The prevalence and years lived with disability caused by low back pain in China, 1990 to 2016: findings from the global burden of disease study 2016. Pain. 2019; 160(1): 237-245. https://doi.org/10.1097/j.pain.0000000000001396
3. Maguire S, Fitzgerald G, Gallagher P, O'Shea F. Advances in treatment of axial spondyloarthritis are associated with improved patient outcomes: data from the Ankylosing Spondylitis Registry of Ireland (ASRI). Rheumatol Int 2022; 42(5): 831-838. https://doi.org/10.1007/s00296-021-05067-z
4. Louis-Sidney F, Kahn V, Suzon B, Bandt MD, Deligny C, Arfi S, et al. Epidemiology and Characteristics of Spondyloarthritis in the Predominantly Afro-Descendant Population of Martinique, a French Caribbean Island. J Clin Med 2022; 11(5): 1299. https://doi.org/10.3390/jcm11051299
5. Zhu W, He X, Cheng K, Zhang L, Chen D, Wang X et al. Ankylosing spondylitis: etiology, pathogenesis, and treatments. Bone Res 2019; 7(3): 22. https://doi.org/10.1038/s41413-019-0057-8
6. Lindström U, Olofsson T, Wedrén S, Qirjazo I, Askling J. Biological treatment of ankylosing spondylitis: a nationwide study of treatment trajectories on a patient level in clinical practice. Arthritis Res Ther 2019; 21(1): 128. https://doi.org/10.1186/s13075-019-1908-9
7. Zhao D, He D, Bi L, Wu H, Liu Y, Wu Z et al. Safety and Efficacy of Prefilled Liquid Etanercept-Biosimilar Yisaipu for Active Ankylosing Spondylitis: A Multi-Center Phase III Trial. Rheumatol Ther 2021; 8(1): 361-374. https://doi.org/10.1007/s40744-021-00276-1
8. Dong Y, Li P, Xu T, Bi L. Effective serum level of etanercept biosimilar and effect of antidrug antibodies on drug levels and clinical efficacy in Chinese patients with ankylosing spondylitis. Clin Rheumatol 2019; 38(6): 1587-1594. https://doi.org/10.1007/s10067-018-04424-x
9. Huang ZX, Deng WM, Guo X, Huang ZP, Huang YK, Lin CL, et al. Clinical and MRI response to dose reduction of an etanercept-biosimilar for hip arthritis in patients with ankylosing spondylitis: an observational, retrospective cohort study. Clin Rheumatol 2019; 38(6): 1595-1604. https://doi.org/10.1007/s10067-019-04466-9
10. Ahsan T, Erum U, Jabeen R, Khowaja D. Ankylosing Spondylitis: A rheumatology clinic experience. Pak J Med Sci. 2016; 32(2): 365-368. https://doi.org/10.12669/pjms.322.9366
11. Lord PA, Farragher TM, Lunt M, Watson KD, Symmons DPM, Hyrich KL, et al. Predictors of response to anti-TNF therapy in ankylosing spondylitis: results from the British Society for Rheumatology Biologics Register. Rheumatology 2010; 49(3): 563-570. https://doi.org/10.1093/rheumatology/kep422
12. Korotaeva T, Dina O, Holdsworth E, Fallon L, Milligan G, Meakin S, et al. Correction to: Investigating diagnosis, treatment, and burden of disease in patients with ankylosing spondylitis in Central Eastern Europe and the United States: a real-world study. Clin Rheumatol 2022; 41(4): 1269. https://doi.org/10.1007/s10067-022-06069-3
13. Lubrano E, Parsons WJ, Perrotta FM. Assessment of Response to Treatment, Remission, and Minimal Disease Activity in Axial Psoriatic Arthritis Treated with Tumor Necrosis Factor Inhibitors. J Rheumatol 2016; 43(5): 918-923. https://doi.org/10.3899/jrheum.151404
14. van der Heijde D, Da Silva JC, Dougados M, Geher P, van der Horst-Bruinsma I, Juanola X, et al. Etanercept 50 mg once weekly is as effective as 25 mg twice weekly in patients with ankylosing spondylitis. Ann Rheum Dis 2006; 65(12): 1572-1577. https://doi.org/10.1136/ard.2006.056747
15. Lindström U, Glintborg B, Di Giuseppe D, Nordstrom D, Proven SA, Gudbjornsson B, et al. Treatment retention of infliximab and etanercept originators versus their corresponding biosimilars: Nordic collaborative observational study of 2334 biologics naïve patients with spondyloarthritis. RMD Open 2019; 5(2): e001079. https://doi.org/10.1136/rmdopen-2019-001079
16. Zhang K, Zheng Y, Han Q, Liu Y, Wang W, Ding J, et al. The Clinical and MRI Effect of TNF-α Inhibitors in Spondyloarthritis Patients With Hip Involvement: A Real-World Observational Clinical Study. Front Immunol 2021; 12: 740980. https://doi.org/10.3389/fimmu.2021.740980
17. Huang Y, Chen Y, Liu T, Lin S, Yin G, Xie Q. Impact of tumor necrosis factor α inhibitors on MRI inflammation in axial spondyloarthritis assessed by Spondyloarthritis Research Consortium Canada score: A meta-analysis. PLoS One 2020;15(12): e0244788. https://doi.org/10.1371/journal.pone.0244788
18. Yang R, Liu H, Fan M. A quick decrease of bone marrow edema in sacroiliac joint could be served as a novel marker for dose tapering of etanercept in ankylosing spondylitis patients. Medicine 2019; 98(11): e14620. https://doi.org/10.1097/MD.0000000000014620