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ORIGINAL ARTICLE

ETANERCEPT IN PATIENTS WITH ANKYLOSING SPONDYLITIS: EFFECTIVENESS AND RATE OF RESPONSE

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Summary

Introduction: "Ankylosing spondylitis (AS)" is an inflammatory disorder that affects the axial skeleton, peripheral joints, as well as entheses, resulting in significant disability. "Tumor necrosis factor-α (TNF-α)" inhibitors are regarded to be a helpful treatment for patients with active "AS". This study aimed to investigate the effectiveness and response rate of "etanercept" in a group of patients with "ankylosing spondylitis" in Mosul, Iraq.

Methods: A prospective, "open-labeled", non-randomized 12 weeks study was undertaken on 43 participants with "ankylosing spondylitis" in the "Rheumatology unit" of "Ibn Sina Teaching Hospital", and the diagnosis was made using the "modified New York criteria". Participants were assessed at the outset of the study, week 4, and week 12 after receiving etanercept 50mg subcutaneously once weekly. The "Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)" was utilized to assess disease activity, while the "Bath Ankylosing Spondylitis Function Index" was utilized to assess functional status (BASFI) at baseline, 4 weeks, and 12 weeks. BASDAI 50 was used to assess the response rate.

Results: Mean patients' age was "36.6±8.47" years; men accounted for "90.7 %" of the cases, with the mean disease length being "9.6±5.90" years. A marked decrease in BASFI and BASDAI was found four and twelve weeks after commencing treatment compared to baseline (p=0.000). "BASDAI 50 %" response was fulfilled by 42.5 % of the participants after 4 weeks and by 65%% after 12 weeks of therapy with "etanercept". There was a marked fall in the mean ESR and CRP after four and twelve weeks of "etanercept" therapy.

Conclusion: In "AS" patients, once weekly "etanercept" 50 mg given subcutaneously for twelve weeks was an effective therapy.

Key words: "ankylosing spondylitis"; etanercept; spondyloarthritis; effectiveness

Introduction

"Ankylosing spondylitis (AS)" is a lifelong inflammatory rheumatic condition that is marked by longstanding backache that is inflammatory in nature, sacroiliac joints and enthesial inflammation, and peripheral arthritis.

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"Acute anterior uveitis" (AAU), psoriasis, and "inflammatory bowel disease" are examples of extraarticular features (1). The disorder generally strikes in the second or third decade of life (2); with men more commonly affected than women in a ratio of "2:1 to 3:1" (3). The prevalence of AS has been estimated to be between 0.1 % and 1.4 % in various parts of the world (4, 5). "Ankylosing spondylitis" is a member of the group of diseases known as "spondyloarthritides" (6). Rather than a single disease with various clinical presentations, this collection of disorders consists of a family of linked but heterogeneous conditions (7). Radiographic sacroiliitis is a defining feature of AS (8). Bony ankylosis can develop as a result of inflammation of the "sacroiliac (SI)" joints and the "spine". Spinal ankylosis is more common in advanced disease and does not develop in many patients with mild disease (9). Spinal fusion, loss of mobility, and functional impairment can all occur as the disease progresses. In turn, patients may face a significant illness burden, including pain and stiffness, declined daily activity, and a significantly lower quality of life (10, 11). "Nonsteroidal anti-inflammatory drugs (NSAIDs)" and physiotherapy used to be the mainstay therapy for AS (12). There is no clear proof that "disease modifying anti-rheumatic drugs (DMARDs)" are beneficial for axial symptoms of ankylosing spondylitis (13, 14). TNF-inhibitors, such as etanercept, have been proven to be a substantial breakthrough in the management of individuals with active AS, and they are capable of treating AS symptoms rapidly in most patients (15). TNF plays a critical regulatory role in host defense, but its dysregulated and accelerated production drives the inflammatory response seen in diseases including RA, "AS, psoriatic arthritis (PsA), Crohn's disease", and other inflammatory diseases (16).

"Etanercept" is a biological drug that combines the "tumor necrosis factor receptor (TNFR)" with the "Fc region of human IgG1" (17). TNF (tumor necrosis factor) is bound by etanercept, which prevents it from interacting with cell surface receptors (18). Etanercept is given as a 50 mg or 25 mg subcutaneous injection once or twice a week (17, 19). In clinical studies of people with AS, etanercept (Enbrel) has been shown to have short-term effectiveness and safety (17, 20-22). Etanercept was generally and well-tolerated in clinical trials. "Injection site reactions, cytopenia, infections, demyelinating disease, heart failure, cutaneous reactions, malignancy, and induction of autoimmunity" are all possible side effects of etanercept (23). This research aimed to investigate the effectiveness as well as the response rate of "etanercept" in a group of patients with "AS" in Mosul, Iraq.

Patients and methods

Study design

Between October 2020 and March 2021, an open-labeled study that has a prospective design was done in the Rheumatology unit of "Ibn Sina Teaching Hospital". The research was carried out in agreement with the "Helsinki Declaration's" principles and was endorsed by the" medical research ethics committee", "College of Medicine, University of Mosul (Ref. no. : UOM/COM/MREC/20-21 (24), in 7/4/2021)". A written informed consent form was obtained from the participants. All of the patients were administered "etanercept" via subcutaneous injection at a dose of 50 mg once weekly, and their effectiveness was assessed at the start of the study, week four, and week twelve.

Sample selection

This study included forty participants who have been classified as AS using the "modified New York classification criteria" for "AS" (24). Eligible patients were ≥ 18 years old, had a BASDAI score of 4 or greater (active disease) in spite of NSAID treatment and they had been given etanercept or adalimumab for not less than 3 months, with treatment discontinuation for 3–5 months due to drug shortages. If the patient experienced relapse, a BASDAI ≥ 4, etanercept treatment was restarted. Patients were allowed to take NSAIDs as needed.

Patients who refuse to participate in the trial, leave therapy, or have serious complications were removed from the study.

Clinical evaluation

Data will be collected using a questionnaire form. The effectiveness of the treatment will be evaluated through evaluation of the activity of disease as well as functional status at the start of the study (week 0), as well as after 4

and 12 weeks, using "Bath ankylosing spondylitis disease activity index (BASDAI) and Bath ankylosing spondylitis functional index (BASFI)", respectively.

The "BASDAI" (25) is a patient-based survey that uses a "0–10 numeric rating scale" (NRS) to assess the intensity of tiredness, spine or hip ache, peripheral joint pain, regional tenderness, amount and length of time of morning stiffness. A final score of 4 or more is usually used to describe the active disease, necessitating a change in the therapeutic plan.

The "BASFI" (26) is the most commonly used index for measuring function, which is based on a questionnaire filled out by the patient. The BASFI is made up of ten questions that are answered using NRS. The activities are graded on a scale of 0 to 10, with 0 pointing to lack of impairment and 10 means severe impairment. The final result is the average score for all the questions, which range from 0 (no restriction) to ten (maximum restriction of function). Although no cut-off point has been established, the higher the score, the more functional limitation caused by ankylosing spondylitis.

After four and twelve weeks of commencing "etanercept" therapy, a significant "clinical response" was considered as a 50% reduction or greater in the baseline "BASDAI" (BASDAI 50). Laboratory tests for estimating 'inflammatory markers", like "erythrocyte sedimentation rate (ESR)" as well as "C reactive protein (CRP)", were carried out at the outset of the study, after 4 as well as 12 weeks.

Statistical analysis

The information was gathered and structured in "Microsoft Excel 2007", before being analyzed using the "Statistics Package for Social Sciences (SPSS 26.0 for Windows)". Regarding continuous variables, the data were reported as means and standard deviations. Numbers and percentages were used to represent categorical variables. To analyze the means of the "BASDAI", "BASFI", and lab results, as well as to determine the significance of alterations in these parameters over time, the "analysis of variances (ANOVA)" was utilized. To determine the real statistical differences, a "post hoc test" was used. A "p-value" of less than 0.05 was regarded to be statistically significant.

Results

This study enrolled 43 AS patients, and 40 of them finished it. Uveitis developed in one patient, and covid-19 infection in two others. The baseline features of the patients are seen in Table 1. The patients' mean age was "36.6±8.57" years, and their mean "disease duration" was "9.6±5.9" years. Thirty-nine participants (90.7 percent) were men. About 90 percent were taking NSAIDs, and approximately two-thirds and one-third of the participants respectively had formerly used "adalimumab and etanercept".

Table 1. Baseline features of the "ankylosing spondylitis" patients.

Variable		value
Age (mean± SD)		36.55±8.47
Gender n (%)	Males	39(90.7%)
	Females	4 (9.3%)
Duration (mean± SD)		9.6±5.90
Smoking n (%)	Ex-smoker	2 (4.7%)
	never	16 (37.2%)
	current	25(58.1%)
NSAID users', n (%)	39 (90.7%)	
MTX users', n (%)	6(14 %)	
Steroid users', n (%)	5 (11.6%)	
Previous "TNF- α inhbitors", n (%)	Adalimumab	29 (67.4%)
	Etanercept	14(32.6%)

The patients' mean baseline BASDAI was 5.70±1.29, which fell to 4.01 ±1.00 after 4 weeks of weekly treatment with etanercept medicine, and to 3.39±1.04 after 12 weeks. The "BASDAI" for the investigated "AS" participants decreased significantly for their follow-up period after therapy with etanercept medicine (p-value=0.000). The change in "BASDAI" was statistically significant (p-value= 0.001), implying that etanercept has a positive effect (table 2).

Table 2. Comparison of BASDAI and BASFI scores before and after 4 and 12 weeks of treatment.

Outcome measure	Baseline	Week 4	Week 12	P-value*
BASDAI	5.70±1.29	4.01±1.00	3.39±1.04	0.001
BASFI	6.97±1.33	5.33±1.05	4.15 ±1.15	0.001

"BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Function"

The mean BASFI of AS participants at the start of the study were 6.97 ± 1.33, which decreased to 5.33 ± 1.05 after 4 weeks and 4.15 ± 1.15 after 12 weeks. This difference is likewise highly statistically significant (p-value=0.000). These results show that etanercept is beneficial in terms of disease activity reduction as well as in improving the functional status.

BASDAI 50 percent response was attained by 42.5 percent of participants after four weeks and 65 percent after twelve weeks of commencing etanercept therapy in the present research, as shown in Figure 1.

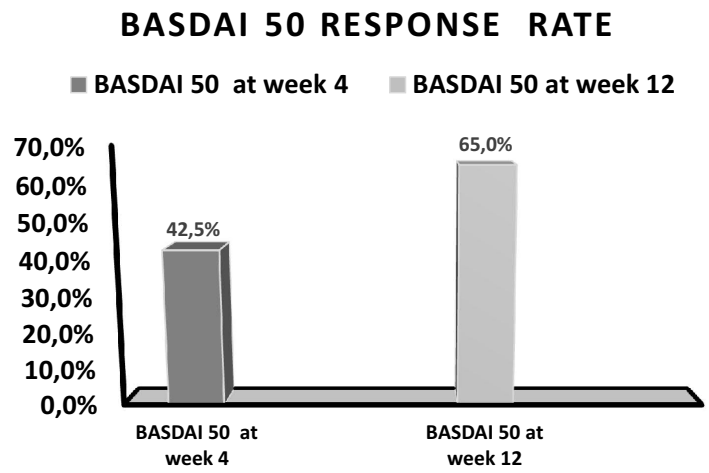

Figure 1. "BASDAI 50" response rate among patients with "AS" treated with etanercept after 4 and 12 weeks of treatment.

The mean ESR at baseline was 38.59±18.80, changed after 4 weeks to 31.79 ±14.60, and after 12 weeks to 25.44±10.30 as shown in Table 3. The mean CRP at baseline was 3.2±0.5, changed after 4 weeks to 2.4±0.3, and after 12 weeks to 0.9±0.1 as shown in Table 3.

Table 3. Acute-phase reactant among patients with AS treated with etanercept before and after 4 and 12 weeks of treatment.

Acute-phase reactant	Baseline	Week 4	Week 12	P-value*
ESR	38.59±18.80	31.79 ±14.60	25.44±10.30	0.001
CRP	3.2±0.5	2.4±0.30	0.9±0.1	0.001

ESR= "erythrocyte sedimentation rate"; CRP= "C-reactive protein"

Discussion

During the three-month follow-up period of this study, once weekly fifty mg injections of "etanercept" given subcutaneously generated a significant, immediate, and persistent improvement in disease activity score and functional ability of "AS" participants. In a study carried out by Gorman, *et al*. (2002), patients have been assigned randomly to get two times weekly "subcutaneous injections" of "etanercept (25 mg)" or "placebo" for nearly 4 months. Cases under the treatment of etanercept showed a substantially higher decrease in the disease activity measures and BASFI than did patients receiving placebo (21). In their 24-week multicenter controlled trial, Davis, *et al.* (2003) randomized "277" participants to have either "placebo" or "etanercept 25" mg subcutaneously two times weekly. They reported that those who received "etanercept" had considerably better improvements in "BASDAI" as well as "BASFI" after 12 and 24 weeks (17). "Calin, *et al*. (2004)" performed a 12-week multicenter randomised "placebo-controlled clinical trial", wherein 45 participants were allocated to have either "etanercept 25 mg" or "placebo" 2 times weekly. The BASDAI composite index scores of etanercept patients improved by 44 % (p=0.01 versus placebo), according to the researchers. Furthermore, according to a "post hoc analysis" of "BASDAI responses", the frequency of "etanercept" patients having "BASDAI scores" lower than 40 jumped from about 10 % at the start of the study to 71 % 12 weeks after commencing "etanercept" therapy (27).

In a "double-blind, placebo-controlled multi-center" trial on 356 AS participants, Braun, *et al*. (2007) studied the impact of "etanercept 50 mg" once-weekly, "etanercept 25 mg" 2 times weekly, and "placebo" for 12 weeks on patient-reported measures. They found that treatment with etanercept (both groups) led to a considerable decline in BASDAI and significant improvement in BASFI compared with placebo (28).

Alosami, *et al*. (2013) studied 74 individuals with ankylosing spondylitis in a single-center open-labeled prospective research. Patients were tested at baseline, month 1, 3, and 6 after receiving etanercept 25mg twice weekly. When compared to baseline, BASFI and BASDAI decreased significantly after one, three, and six months (29).

A meta-analysis of 14 randomised, "placebo-controlled clinical trials" with 1,570 participants was performed by Li, *et al*. to investigate the effectiveness and safety of "etanercept" in Caucasians compared to Chinese patients and found that etanercept is advantageous in both controlling disease activity and relieving of symptoms. Furthermore, the frequency of serious adverse effects was not greater (30).

Multiple randomized studies and meta-analyses of randomized trials have established the effectiveness of TNF inhibitors to diminish disease activity in patients with AS (31-32). Each of the five commercially marketed TNF inhibitors have been tested in clinical trials. In a 2007 meta-analysis, all three TNF inhibitors ("adalimumab, etanercept, and infliximab") were found to be equally effective in individuals with AS. Although these drugs have not been directly compared, indirect comparisons were unable to show differences between them (33).

In a 2015 "systematic review and meta-analysis" of randomized trials encompassing over 2400 patients, the effectiveness of TNF inhibitors (including "etanercept, adalimumab, infliximab, certolizumab, and golimumab") in the treatment of axial SpA was established. Patients who received these drugs were considerably more likely than those who received placebo to improve by at least 40 % from baseline, as judged by the "Assessment of SpondyloArthritis International Society (ASAS) 40 percent" (ASAS40) composite response measure (31).

In the current study, "BASDAI 50 % response" was attained by about 42 % of the participants after four weeks and by 65 % after 12 weeks of commencing "etanercept". After 4 weeks of therapy with etanercept, a BASDAI 50 response has been observed in 65 % of the cases who got BASDAI 50 at week 12. In their study, Rudwaleit, *et al*. (2004) found that 56 % of patients attained a "BASDAI 50 response" after twelve weeks of commencing "etanercept" or infliximab therapy. In cases that got BASDAI 50, the reaction to treatment has been observed early throughout treatment. A "BASDAI 50" response was noticed in 82 % of the cases who got "BASDAI 50" at week 12 following 6 weeks of treatment with TNF-α inhibitors (34).

In their multicenter study, Navarro-Sarabia, *et al*. (2011) reported that 43 % of patients received "etanercept 50 mg" once weekly attained a fifty percent reduction in the "BASDAI score" at Week 2. This proportion increased to 63 % at Week 12 (35). Liu, *et al*. (2016) performed a "network meta-analysis" to analyze the clinical results of active "AS"

cases got treatment with "TNF-α inhibitors". Etanercept showed a substantial improvement compared to placebo for both "ASAS20" and "BASDAI 50 %" (36). In the present study, there was a substantial decline in ESR and CRP of AS patients "4" and "12" weeks after commencing etanercept therapy. This study's findings are in accordance with former studies which showed significant improvement in ESR and CRP in AS after etanercept treatment (17, 20, 29, 30, 34).

The present study's primary limitations are the short duration of follow up and small sample size. Long-term studies along with higher numbers of cases are vital to deal with the issue of effectiveness further and to define the impacts of "etanercept" on the progression of ankylosing spondylitis.

Conclusion

"Etanercept" 50 mg once weekly for 12 weeks was an effective treatment in patients with AS, as evident by the significant reduction of disease activity and the marked improvement in functional status. The improvement was rapid and significant. In addition, etanercept was well tolerated and relatively safe drug. So etanercept is a good choice in AS patients who failed NSAIDs, and even in those patients who had been treated previously with TNF inhibitors.

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Author Contribution

The authors contributed equally to this study.

Conflict of interests

The authors declare no potential conflict of interests.

Adherence to Ethical Standards

The study was approved by the "Ethical committee at the University of Mosul, College of Medicine" (Ref. no. : UOM/COM/MREC/20-21 (24), in 7/4/2021).

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