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Comparison of efficacy of Infliximab and Etanercept on Rheumatoid Arthritis patients

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This study aimed to compare the efficacy of infliximab and etanercept in rheumatoid arthritis (RA) patients to help clinicians select the most effective treatment options. This was a cross sectional study conducted in Urmia, Iran, from March 21, 2017, to February 20, 2018. Data was collected by checklists from RA patients referred to the Rheumatology Clinic of Urmia Imam Khomeini Hospital who were receiving either infliximab or etanercept. Inclusion criteria were a diagnosis of RA according to the revised 2016 criteria of the American College of Rheumatology (ACR)/European League Against Rheumatism, aged over 18, consent to participate in the study, and poor response to other drugs. Both genders were included. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), tender joint count (TJC), swollen joint count (SJC), and disease activity score (DAS) (28 scores) were analyzed before and after treatment. In a total of 44 eligible patients, 13 patients received infliximab and 31 received etanercept. The mean age was 53.92 ± 10.94 and 52.8 ± 64.13 years in the infliximab and etanercept groups, respectively. No significant differences were reported concerning ESR ($p\ value = 0.97$) or CRP ($p\ value = 0.96$), while a significant decrease in the infliximab group compared to the etanercept group was demonstrated in terms of DAS28 scores ($p\ value = 0.028$), global health (GH)` ($p\ value = 0.005$), SJC ($p\ value = 0.008$), and TJC ($p\ value = 0.01$). This study demonstrated a significant difference between the two groups in the DAS scores 28, SJC, TJC, and GH.

Keywords: C-reactive protein, Erythrocyte sedimentation rates, Rheumatoid arthritis

Introduction_____

Rheumatoid arthritis (RA) is a chronic and progressive inflammatory disease that can cause cartilage damage, bone erosion, chronic pain, loss of function, and disability [1-3]. About 33% of RA patients may be work disabled forever in the first three years of disease, which results in a high economic burden for society [4]. This disease affects women 23 times more than men and can be diagnosed at any age [5]. The prevalence of RA in Iran is estimated to be lower than in western countries at about 0.33-0.37% [6, 7]. Medical management of RA has developed remarkably over the past decade with the introduction of immune-therapies with guaranteed efficacy at alleviating joint inflammation and decelerating or even stopping osteo-cartilaginous destruction [8]. Treatment commonly starts with non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs), preferably methotrexate (MTX). A biological agent such as tumor necrosis factor (TNF) blockers adalimumab or etanercept is added when DMARD therapy is not effective or not tolerated in an adequate dose and has shown its

effectiveness in the treatment of RA [9]. The role of TNF blockers is of great value. Among their diverse pathologic effects, TNF induces the production of proinflammatory cytokines, triggers endothelial cells to express adhesion molecules that attract leukocytes into afflicted joints, increases the rate of synthesis of metalloproteinases via synovial macrophages, fibroblasts, osteoclasts, and chondrocytes, and inhibits the synthesis of proteoglycans in cartilage [10]. Anti-TNFα agents are a commonly used class of biologic agents for the treatment of active rheumatoid arthritis; among them, etanercept and inflixi-mab have dramatically improved symptoms and restricted joint destruction and subsequent disability in patients [11-13]. Adalimumab, etanercept, and infliximab are efficient treatments compared with placebo for RA patients who are not well controlled by DMARDs, improving physical function and slowing radiographic changes in joints [14, 15]. In this study, the efficacy of etanercept and infliximab on patients referred to the Rheumatology Clinic of hospitalized in Urmia Imam Khomeini Hospital was

compared to help clinicians decide which one to choose. In terms of price and expenses, infliximab is more expensive, while biosimilar etanercept is cheaper. Additionally, if one of the drugs has better outcomes in controlling the symptoms of RA, it is reasonable to use that one. The importance of this research is that DAS scores 28, SJC, TJC, GH, ESR and CRP were investigated, while the majority of previous studies investigated only DAS scores 28, SJC, and TJC.

Materials and Methods

Study subjects

In this cross sectional, 44 patients who referred to the Rheumatology Clinic of Urmia Imam Khomeini Hospital from March 21, 2017, to February 20, 2018 and met the inclusion criteria were eligible for inclusion. Thirteen patients received infliximab and 33 patients received etanercept.

Data was collected by checklists from the Rheumatology Clinic of Urmia Imam Khomeini Hospital that surveyed patient's demographic and disease information. Treatment effectiveness was compared among a sample of patients with RA who were treated with anti-TNF agents (etanercept or infliximab). Demographic data of the patients, including age, gender, disease period, and disease activity, was obtained and recorded from all patients. Inclusion criteria were diagnosis of RA according to revised 2016 criteria of American College of Rheumatology (ACR)/European League Against Rheumatism (2016 ACR/EULAR) [16], consent to take part in the study, adults of both genders over the age of 18, and patients who did not respond appropriately to other treatments. Exclusion criteria comprised any active infection, SLE, CHF, positive serology for Hepatitis B or C, pregnancy or breastfeeding, tuberculosis, cancer, or history of IBD.

Altebrel™, a biosimilar product with the generic name of etanercept, manufactured by AryoGen Pharmed Company in Iran, was used, and the brand of infliximab was Remicade which is manufactured by Johnson and Johnson, USA. It has been reported that biosimilar etanercept has equivalent efficacy as the reference product, while there may be an increased incidence in terms of hepatobiliary adverse effects [17]. Etanercept dosage was 50 milligrams subcutaneous weekly, and infliximab was given intravenously as 3 mg per kilogram of body weight at weeks 0, 2, 6, and then every eight weeks. ESR and CRP were checked for all patients, and DAS28 scores were measured three months after the first dose of the drug was given (Figure 1).

Clinical measurements

Disease severity was assessed using DAS28 scores before patients received either infliximab or etanercept by counting the number of tender and swollen joints of the shoulders, elbows, wrists, MCP, PIP, and bilateral knees, assessing ESR, and putting the data along with GH declared by the patient in the following formula:

$$DAS28 = 0.56 * sqrt (tender28) + 0.28 * sqrt (swollen28) + 0.70 * ln (ESR) + 0.014 * GH$$

Finally, the scores were categorized as:

silent (DAS < 2.6), low activity (2.6 < DAS < 3.2), intermediate (3.2 < DAS < 5.1) and severe (5.1 < DAS < 28).

Statistical Analysis

Quantitative variables were presented as mean ± standard deviation [18], and qualitative variables were reported as percentages. The normality of data distribution was checked by the Kolmogorov-Smirnov test. Between-group comparisons were performed using an independent sample t-test (if not normal, its nonparametric Mann-Whitney test was used). The chi-square test was used to compare qualitative data, and mean amounts before and after drug injection were compared by paired T-test. Statistical analysis of data was performed using SPSS 20, and a *p value* < 0.05 was considered significant.
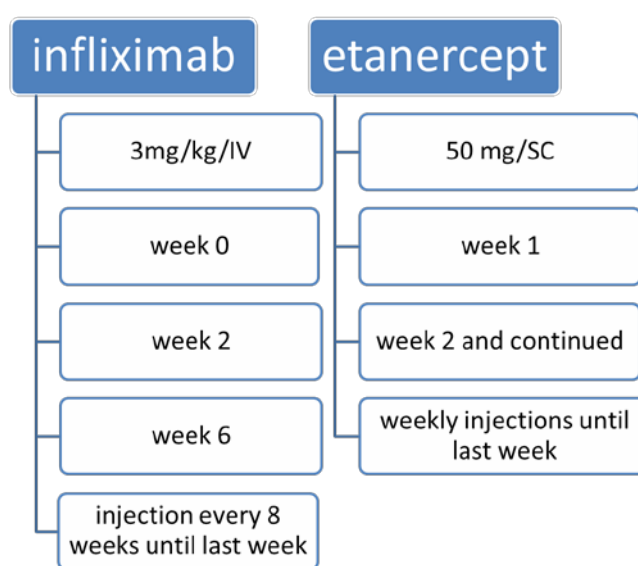

Figure 1. given drugs and timing process (*at week 12, ESR and CRP were checked and the DAS scores 28 were measured*)

Study variables between groups were compared before and after receiving treatment.

Results

Forty-four patients (13 (29.5%) in the infliximab group and 31 (70.5%) in the etanercept group) were included in this study. Overall, 72.72% of the patients were female. Five men and eight women received infliximab, and seven men and twenty-four women received etanercept. No significant statistical difference was observed between the groups (*p*-value = 0.28). Mean age was 53.92 ± 10.94 and 52.8 ± 64.13 in the infliximab and etanercept groups, respectively, which was not statistically significant (*p value* = 0.84). The disease period was not statistically significant between groups. Disease severity before treatment in the two groups had no statistically significant difference. Disease severity in the infliximab group was intermediate in four patients (30.8%) and severe in nine patients (69.2%). In the etanercept group, it was intermediate in 16 (51.6%) and severe in 15 (48.4%) patients (Table 1).

Table 1. Comparison of demographic characteristics of RA patients who received infliximab or etanercept

Demographic variable	Infliximab group	Etanercept group	P value
Age	53.92 ± 10.94	52.8±64.13	0.84*
Disease period	12.7 ±19.1	7.7±3.44	0.16*
Gender(male)	5(38.5%)	7(22.6%)	0.28**
Gender(female)	8(61.5%)	24(77.4%)	0.28**
Intermediate disease activity(DAS score)	4(30.8%)	16(51.6%)	0.21**
Severe disease activity(DAS score)	9(69.2%)	15(48.4%)	

*p value: Independent T-test analysis, ** p value: Chie-square test analysis*

Within-group comparisons showed that ESR, TJC, SJC, DAS28 scores, and GH had a statistically significant decrease after intervention in the infliximab and etanercept groups (*p value* < 0.05). However, CRP showed a statistically significant change only in the etanercept group (*p value* < 0.05); in the infliximab group, the change was not significant (*p value* > 0.05) (Table 2).

Table 2. Comparison of mean amounts of variables before and after treatment with infliximab or Etanercept

variables	Infliximab group (Mean± SD)			Etanercept group (Mean± SD)		
	Before treatment	After treatment	p-value	Before treatment	After treatment	p value
ESR	33.69 ± 27.46	19.69±15.43	0.04	39.35±18.05	25.51±13.59	<0.001
TJC	12.53±7.10	6.84±4.93	0.05	7.64±3.61	6.13±3.27	0.01
SJC	11.07±6.04	3.38±3.40	<0.001	6.67±3.75	3.35±2.76	<0.001
DAS28 scores	5.94±1.36	4.36±1.56	<0.001	5.74±0.83	4.84±1.07	<0.001
CRP	1.46 ± 0.77	1.23±0.6	0.08	1.45±0.61	1.19±0.40	<0.001
GH	67.07±26.16	26.69±15.17	< 0.001	48.51±15.60	31.12±12.56	<0.001

p value: Paired t-test analysis

Mean changes of ESR and CRP were not statistically significant between the two groups (*p value* > 0.05), whereas TJC, SJC, DAS score, and GH experienced more remarkable decreases in the infliximab group compared to the etanercept group (*p value* < 0.05). The mean changes of TJC, SJC, GH, and DAS scores between the two groups were statistically significant (*p value* < 0.05) (Table 3).

Table 3. differences in mean amounts of variables in infliximab and Etanercept group

variables	Infliximab group	Etanercept group	p value¶	Adjusted *P values* *
ESR	-14±23	-13.83±12	0.97	0.250
CRP	0.0±23.43	-0.52±0.68	0.96	0.208
TJC	-5.69±9.54	-1.15±3.07	0.01	0.125
SJC	-7.67±5.15	-3.23±3.49	0.008	0.083
GH	-28.40±28.54	-17.83±16.25	0.005	0.042
DAS score	-1.85±1.13	-0.09±0.78	0.028	0.167

p value: Independent t-test analysis

* Benjamini and Hochberg False Discovery Rate multiple testing correction

Disease severity after treatment between the two groups did not change significantly (*p value* > 0.05). The silent disease was reported in two cases (15.4%) of the infliximab group and one patient (3.2%) of the etanercept group. Low disease activity was reported in one patient (7.7%) of the infliximab group and three cases (9.7%) of the etanercept group. Intermediate disease activity was reported in seven patients (53.8%) of the infliximab group and 22 cases (71%) of the etanercept group. Severe disease was reported in three patients (23.1%) of the infliximab group and five patients (16.1%) of the etanercept group (Table 4).

Table 4. Comparison of disease activity after treatment in infliximab and Etanercept groups

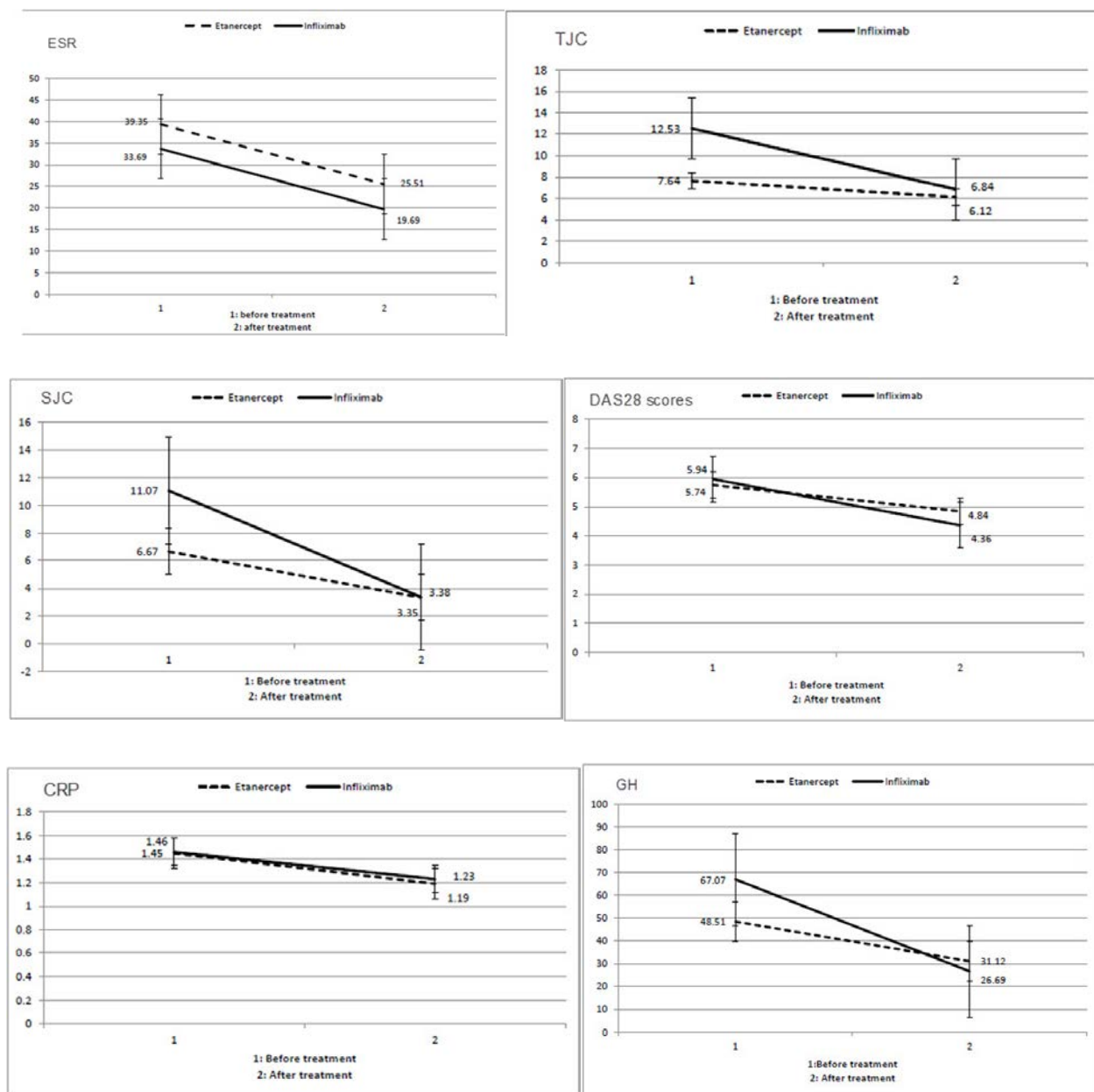| Disease activity	infliximab	Etanercept	*P value*
silent	2(15.4%)	1(3.2%)	
Low-activity	1(7.7%)	3(9.7%)	
High-activity	7(53.8%)	22(71.0%)	0.41
severe	3(23.1%)	5(16.1%)	

p value: Fisher`s Exact test analysis

Figure 2. Changes in mean amounts of TJC, SJC, GH, DAS28 scores, ESR and CRP before and after treatment

Discussion_____

The results of this study demonstrated that infliximab was significantly more effective than etanercept in terms of SJC, TJC, GH, and DAS28 scores, while ESR and CRP did not have significant between-group differences. Rheumatoid arthritis is a chronic, systemic, and inflammatory disease that results from a systemic autoimmune response attributed to B-cells, IL-1, IL6, and TNF; it can vary from a mild to a severe form [19-21]. The introduction of anti-TNF therapy is a valuable addition to the materials of RA treatment to control the symptoms and reduce the progression of the erosive disease by suppressing the inflammatory effects of TNF alpha [22, 23].

The current results are not consistent with those of Gavrila et al., in terms of DAS 28 scores for infliximab and etanercept. They investigated infliximab, adalimumab, rituximab, and etanercept on rheumatoid arthritis patients before and after treatment and demonstrated that ESR did not change in months six and 12, but DAS28 scores decreased in months six and 12 after using these drugs. In the present study, the decrease in ESR after treatment with these drugs was significant without significant between-group differences [1]. Greenberg et al. indicated that no significant difference was observed in terms of DAS28 score, ESR, or TJC in patients who received infliximab, etanercept, or adalibomab, while in terms of SJC, etanercept had a better effect, which is not consistent with the results of the present study [24]. In another study conducted by Irini Flouri et al., the efficacy of infliximab, etanercept, and adalimumab was compared. Patients were assessed every six months for three years. After 12 months, TJC, SJC, GH, DAS scores, and ESR had no significant differences among the three groups, whereas in the current study, TJC, SJC, GH, DAS scores had a more remarkable decrease in the infliximab group. The decrease in CRP was not statistically significant in the two groups in the current study, which was consistent with the mentioned study. One possible reason for this difference is the longer investigation period in Irini's study, which assessed the patients in months sixth and twelve, while patients in the current study were assessed only three months after treatment [12]. Canhao et al. showed that there was no significant difference between the patients who received infliximab and those who received etanercept in terms of DAS score 28 at three, six, and twelve months in the follow-up period. This differed from the present results, which showed remarkable improvement in DAS 28 scores for patients who received infliximab [25].

In a related retrospective study by Grant W. Cannon et al., clinical outcomes and treatment costs with infliximab, etanercept, and adalimumab were compared; no statistically significant difference was reported in study variables. DAS scores 28 were significantly lower in all groups after initiating TNF inhibitor therapy, which is similar to the results of the present study [26]. In another study by Anna D'Souza et al., the medicinal effects of infliximab, adalimumab, and etanercept were assessed. According to the VAS system, treatment outcomes were investigated as improvement in the number of tender joints, swollen joints, joint stiffness, and fatigue. The mean age of participants was similar to the current study, and only patients who received infliximab showed improvement in swollen, tender, and stiff joints; in the current study, however, these criteria were improved in both groups after treatment, and the improvement was significant in the infliximab group [27]. In a study conducted by Y. Shinizu et al., DAS28 scores were assessed before and after treatment with etanercept, infliximab, adalimumab, and tocilizumab. Similar to the present study, they showed that DAS 28 scores decreased significantly [28].

It is worth noting that the current study used intravenous infliximab, and according to the results of the meta-analysis conducted by Caporali et al. [29], subcutaneous biosimilar infliximab (CT-P13) was superior compared with IV infliximab and etanercept in almost every efficacy outcome such as DAS score 28, CRP, ESR, ACR responses, and safety outcomes. This necessitates the need for other studies which consider all kinds of treatments with their different routes of administration. Changes in mean amounts of TJC, SJC, GH, DAS28 scores, ESR, and CRP before and after treatment are shown in Figure 2.

The risk of severe infection in RA patients who receive TNF blockers is another important point for consideration. Dartel et al. [30] reported that this risk was much lower in patients who received etanercept compared with those who received infliximab.

Although treatment with tumor necrosis factor inhibitors has revolutionized the management of RA patients, high numbers of patients did not respond to these medicines as expected, and remission frequency is still less than 50% in RA patients. Because of this and the disparities among the mentioned studies, it is recommended that other studies be conducted with larger sample sizes, longer follow-up periods, and assessments of other treatments such as rituximab [31].

Limitations_____

The most important limitation of this study was the small sample size, especially in the infliximab group, which can affect the accuracy of the results. This can be attributed somewhat to the type of sampling which was done during a specified time. Additionally, other medications which were used by the patients of this study could not be considered, and this is a confounding factor for the results of the study. The authors believe that there is a need for other studies in the future with larger sample sizes in which all factors such as other drugs used by the participants are considered. Finally, future studies must consider adverse events and investigate them as a part of the study.

Conclusion_____

This study indicated that both infliximab and etanercept are effective drugs, although a statistically significant difference was observed in efficacy variables including SJC, TJC, GH, and DAS28 scores in patients who

underwent infliximab treatment. However, ESR and CRP had no remarkable differences between the two groups.

Ethical considerations_____

This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Urmia University of Medical Sciences (IR. umsu.ret.1396.336). No additional costs were imposed on the patients, and their identities were not disclosed. Written informed consent was obtained from patients before participation in the study.

Conflict of interest_____

The authors have no conflicts of interest to declare.

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