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Original Research Article

Efficacy of etanercept in rheumatoid arthritis patients and its effects on interleukin-6 and serum tumor necrosis factor α

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Abstract

Purpose: *To study the effects of etanercept (ETA) on the clinical manifestations and serum levels of TNF-α and IL-6 in rheumatoid arthritis (RA) patients.*
Methods: *A retrospective analysis was performed on the medical files of 138 active RA patients admitted to Guangdong Second Provincial General Hospital, Guangzhou, China for rheumatic diseases from January 2016 to February 2019. Out of the total subjects, 58 patients were administered conventional methotrexate (MTX) as routine treatment (control group), while the remaining 80 patients (classified as study group) received subcutaneous injection of etanercept (ETA). Health Assessment Questionnaire (HAQ) score, and TNF-α and IL-6 serum concentrations of the two groups before and after treatment were assessed.*
Results: *Pre-treatment HAQ score was comparable in both groups ($p > 0.05$). However, at 3, 6, 9 and 12 weeks post-treatment, HAQ scores decreased in the two groups. The mean score was significantly lower in study group than in control group ($p < 0.001$). Pre-treatment serum levels of IL-6 and TNF-α in both groups were comparable. However, after treating for 3, 6, 9 and 12 weeks, serum IL-6 and TNF-α decreased significantly, with lower values in the study group than in control group ($p < 0.001$).*
Conclusion: *ETA has a higher efficacy and safety than MTX for the treatment of joint inflammation and and also achieved greater improvement of joint function. However, further clinical trials are recommended prior to wider application in clinical practice.*

Keywords: *Etanercept, Rheumatoid arthritis, Clinical efficacy, Interleukin-6, Serum TNF-α*

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INTRODUCTION

Rheumatoid arthritis (RA) is a long-term autoimmune illness [1]. Multiple chronic inflammatory cells such as T lymphocytes and macrophages continuously infiltrate into the synovial tissue of the joint in RA patients [2]. The disease causes progressive damage to the synovial tissues of the joint, leading to bone destruction and disability [3]. The incidence of RA in the world is approximately 0.78-1.12 %, while that in China is approximately 0.45-0.52 %.

The middle-aged and elderly women have higher risk of RA, and female RA patients are approximately 2.7 times the population of male RA patients [4]. As at August 2017, China RA cases were as high as 4.378 million [5]. Most RA patients need lifelong treatment, since RA has a long treatment cycle [6]. At present, the common RA treatment drugs are non-steroidal anti-inflammatory drugs, slow-acting anti-rheumatic drugs and steroids, although their effects are not durable, while some result in adverse side effects [7]. Thus, it is important to find active and effective RA treatment drugs with few side effects.

It is known that TNF-α has pro- and anti-inflammatory functions [8]. Interleukin-6 (IL-6) induces the production of TNF-α, thereby enhancing its damaging inflammatory effect and amplifying its biological activity of promoting inflammatory response and degree of joint tissue damage in RA subjects. The TNF-α enhances the expression of IL-6, a cytokine at the downstream of TNF-α [9]. The high expressions of TNF-α and IL-6 are positively correlated with the incidence of RA. Etanercept (ETA) is the earliest marketed TNF-α inhibitor in China. It blocks TNF-α-receptor interaction on cell surface by specifically binding to TNF-α, thereby reducing its biological activity [10].

In this research, the effect of ETA on treatment of RA, and the effects of ETA on the concentrations of TNF-α and IL-6 were studied.

METHODS

Clinical baseline data

A retrospective study was done on the medical records of 138 active RA subjects on admission in our hospital. Their condition was diagnosed as RA via the RA diagnostic criteria of the American College of Rheumatology revised in 1987. A total of 58 patients (control group) comprising 33 females and 25 males with an average age of 55.3 ± 15.1 years, were treated with conventional MTX as routine treatment. The remaining 80 patients were treated with subcutaneous injection of ETA (study group). They comprised 50 females and 30 males, with an average age of 56.1 ± 15.8 years. All procedures were in accordance with the guidelines of Declaration of Helsinki [11]. This study was conducted after receiving approval from the Medical Ethics Committee of Guangdong Second Provincial General Hospital (approval no. GS-JSK-20220238). Patients submitted informed consent forms signed by them or by family members.

Inclusion and exclusion criteria

Inclusion criteria

Patients diagnosed in line with the RA diagnostic criteria of the American College of Rheumatology, revised in 1987 [12]. Patients ≥ 40 years old, those who had no joint surgery, and patients with no other hereditary disease, were included in this study.

Exclusion criteria

Patients in the following categories were excluded: patients aged ≥ 75 years, patients with severe joint deformity at the advanced stage, those with cardiovascular and cerebrovascular diseases, patients with a previous history of cancer, and patients who took antibiotics three months before the study.

Main reagents and equipment

The RA drug, MTX was purchased from Shanghai Shangyao Xinyi Pharmaceutical Co. Ltd. (SFDA approval no. H31020644), while RA drug ETA was product of Shanghai Sansheng Guojian Pharmaceutical Co. Ltd (SFDA approval no. S20050059). Centrifuge was purchased from Zhongke Zhongjia Scientific Instrument Co. Ltd, Model: SC-3616. Automatic chemiluminescence analyzer was bought from American Siemens, model IMMULITE1000; TNF-α and IL-6 chemiluminescence kits were purchased from American Siemens, Model: 100T, Item No. LKNF1, LK6P1.

Treatments

Control group

MTX was orally administered (10 mg) once a day, once a week.

Study group

ETA was injected subcutaneously (50 mg), once a week. In addition, 10 mg of Prednisone acetate tablets (Zhejiang Xianju Pharmaceutical Co., Ltd., SFDA approval no. H33021207) was administered to the two groups of patients during the treatment, once a day, 5 times a week. Both groups of patients were treated for 12 weeks.

Specimen collection

All patients fasted overnight, after which venous blood (5 mL) was sampled from the elbow region, and the whole blood sample was placed in a refrigerator for 12 h. Thereafter, the whole

blood sample was kept at 30 °C for about 30 min, followed by approximately 20-min centrifugation at 1000 rpm to obtain serum. Thereafter, it was allowed to stand for 10 min before the supernatant was carefully collected. Prior to use, the serum samples were refrigerated at -20 °C.

Determination of levels of IL-6 and TNF-α

Chemiluminescence analysis was used to determine levels of these factors in blood of patients. Specimen to be tested and the kit were mixed well at a room temperature of 30 °C to avoid generating bubbles. The blank well contained standard and sample diluent (100 µL), while the other wells contained 100 µL of sample to be tested or standard sample, which were also added slowly to avoid generating bubbles. The sample was carefully added to the bottom of the ELISA plate when loading, without touching the well wall, and mixed lightly, followed by coating of the plate and incubation for 1½ h at 37 °C. The standard sample solution was used only once. After the incubation, the incubation medium in each well was removed and replaced with 100 µL of newly prepared biotinylated antibody working solution, and the wells were coated again. After incubation for 1 h at 37 °C, and the medium was discarded, and the ELISA plate rinsed thrice. The water was patted after each soaking for 2 min. Then, an aliquot (100) µL of luminescent substrate solution was pipetted into each well, followed by coating and incubation at 37 °C for 5 min a second time.

Evaluation of RA

The evaluation was performed based on the Health Assessment Questionnaire [13] (HAQ) of RA patients, with the HAQ evaluation criteria shown in Table 1.

Statistical analysis

Statistical analysis was carried out using the SPSS 17.0 software. Measurement data are presented as mean ± SD. Two-group comparison was done with *t*-test, while count data were compared with χ^2 test. Values of $p < 0.05$ were considered statistically significant.

RESULTS

Patient baseline information

Table 2 shows that there were no statistically significant difference between study and control groups with regard to age, gender, body mass index, disease course, tender joint count, swollen joint count, ESR and C-RP concentration ($p > 0.05$).

Table 1: Health Assessment Questionnaire (HAQ)

Activity	Not difficult	Difficult	Very difficult	Impossible
Dress yourself, tie your shoes and do your buttons	0	1	2	3
Wash hair on your own	0	1	2	3
Stand up from the chair without help of hands	0	1	2	3
Get in and get out of bed	0	1	2	3
Drink from a cup	0	1	2	3
Cut vegetables	0	1	2	3
Unscrew caps	0	1	2	3
Walk down the road outdoors	0	1	2	3
Go up five steps	0	1	2	3
Take a bath and dry body on your own	0	1	2	3
Use a toilet on your own	0	1	2	3
Kneel and pick up clothes on the floor	0	1	2	3
Reach the clothes on the hanger	0	1	2	3
Open and close the faucet	0	1	2	3
Get in and off the car	0	1	2	3
Visit the supermarket	0	1	2	3
Do housework	0	1	2	3
Walk one kilometer	0	1	2	3
Participate in favorite activities	0	1	2	3
Sleep well at night	0	1	2	3

Usually**,** HAQ mainly evaluates the patient's physical condition in the previous week, and the patient is scored based on each question (0-3 points). Score 0 means not difficult, 1 point means difficult, 2 points means very difficult, and 3 points means impossible. The scores are added to give the total score which is divided by 20 to get the average score. The smaller the HAQ score, the better the health of the RA patient.

Table 2: Baseline information [n (%)]

Category/group		Study (n=80)	Control (n=58)	χ^2	*P*-value
(Age (years)				0.512	0.489
	<55	31(38.75)	26(44.83)		
	≥55	49(61.25)	32(55.17)		
Gender				0.440	0.598
	Male	30(37.50)	25(43.10)		
	Female	50(62.50)	33(56.90)		
				0.381	0.645
	<24	68(85.00)	47(81.03)		
	≥24	12(15.00)	11(18.97)		
Disease course (months)				0.278	0.609
	<24	35(43.75)	28(48.28)		
	≥24	45(56.25)	30(51.72)		
Tender joint (counts)				0.049	0.863
	<12	44(55.00)	33(56.90)		
	≥12	36(45.00)	25(43.10)		
Swollen joint (counts)				0.107	0.862
	<8	45(56.25)	31(53.45)		
	≥8	35(43.75)	27(46.55)		
ESR (mm/h)				0.141	0.847
	<20	23(28.75)	15(25.86)		
	≥20	57(71.25)	43(74.14)		
C-RP (mg/L)				0.575	0.523
	<10	18(22.50)	10(17.24)		
	≥10	62(77.50)	48(82.76)		

Table 3: HAQ scores in both groups during treatment

Group	HAQ score				
	Before treatment	Treatment for 3 weeks	Treatment for 6 weeks	Treatment for 9 weeks	Treatment for 12 weeks
Study (n=80)	2.68±0.27	2.23±0.22	1.78±0.17	1.23±0.14	0.87±0.11
Control (n=58)	2.71±0.25	2.45±0.23	2.14±0.15	1.97±0.21	1.58±0.16
t	0.665	5.689	12.890	24.830	30.890
P	0.508	<0.001	<0.001	<0.001	<0.001

Clinical efficacy

Before treatment, HAQ score was 2.68 ± 0.27 in study group and 2.71 ± 0.25 in control group, with no statistically significant difference between the two groups ($p > 0.05$). After 3 weeks of treatment, the HAQ scores of the two groups decreased, with values of 2.23 ± 0.22 and 2.45 ± 0.23 in the study and control groups, respectively ($p < 0.001$). The decreases in HAQ scores continued up to six weeks: it was 1.78 ± 0.17 in study group and 2.14 ± 0.15 in control group ($p < 0.001$). After 9 weeks of treatment, the HAQ scores of the two groups also decreased, with values of 1.23 ± 0.14 and 1.97 ± 0.21 in study and control groups, respectively ($p < 0.001$). After 12 weeks of treatment, there were further decreases in HAQ scores of the two groups, with study and control group values of 0.87 ± 0.11 and 1.58 ± 0.16, respectively ($p < 0.001$).

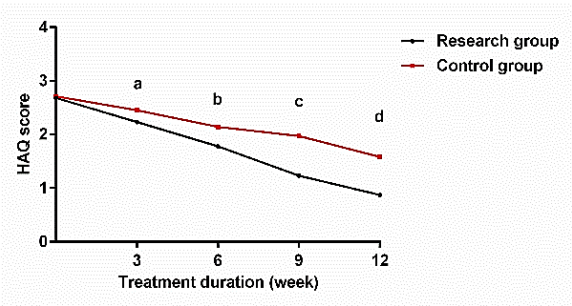

Figure 1: Health Assessment Questionnaire (HAQ) scores as a function of treatment time. Pre-treatment HAQ score was comparable in both groups. At 3, 6, 9 and 12 weeks of treatment, the HAQ scores of the two groups decreased, but the score was lower in the study group than in the control group ($p < 0.001$). The letter *a* indicates significant difference ($t = 5.689$, $p < 0.001$). Letter *b* indicates significant difference ($t = 12.890$, $p < 0.001$). Letter *c* indicates significant difference ($t = 24.830$, $p < 0.001$). Letter *d* indicates that the difference between the study group and control group was significant ($t = 30.890$, $p < 0.001$)

Serum TNF-α and IL-6 levels

Before treatment, the concentrations of TNF-α and IL-6 in blood were 51.85 ± 8.23 and 28.49 ± 7.37 in study group. In the control group, the concentrations of TNF-α and IL-6 in blood were 52.14 ± 9.12 and 29.92 ± 6.99, respectively. The levels of each parameter were comparable in both groups. After treating for 3 weeks, TNF-α concentration decreased: the values were 44.23 ± 7.34 in study group and 48.37 ± 8.37 in control group. After 6 weeks of treatment, there were yet further reductions in TNF-α concentration, with values of 36.52 ± 6.45 and 43.47 ± 7.95 in study group and control group, respectively. After 9 weeks of treatment, there were further reductions in TNF-α concentration: the values were 29.36 ± 6.11 in study group and 38.54 ± 7.09 in control group. After 12 weeks of treatment, the TNF-α concentration decreased, with values of 20.34 ± 5.31 in study group and 31.43 ± 4.72 in control group, with statistically marked difference in TNF-α level between both groups (p < 0.05; Table 4).

The IL-6 concentration decreased throughout the study period. Pre-treatment values were 24.73 ± 6.74 in study group and 27.77 ± 6.27 in control group. After 6 weeks of treatment, the IL-6 concentration decreased to 19.59 ± 6.04 in study group and to 23.89 ± 6.05 in control group, and after 9 weeks of treatment, it also decreased to 15.32 ± 5.41 in study group and to 20.14 ± 5.49 in control group. After 12 weeks of treatment, the IL-6 concentration decreased further to 10.24 ± 4.62 in study group and to 16.52 ± 4.58 in control group. There was marked difference in IL-6 level between the 2 groups (p < 0.05; Table 5).

DISCUSSION

The pathogenesis of RA is very complicated. The disease is mainly characterized by joint erosion and destruction. Its prevalence in China is as high as 0.53 %, and it is more common in women than in men. A prominent feature of RA is strong recurrence, which may lead to death or disablement of some patients [14]. Since RA is teratogenic, joint deformity often occurs in about 2 - 3 years, and RA may be accompanied by extra-articular manifestations such as subcutaneous nodule, neuritis, iritis, pericarditis and vasculitis [15]. The disease seriously affects human life. With advances in medical research, the treatment of RA patients has improved to some extent, but some patients still have poorly improved conditions. A traditional drug for RA treatment such as MTX, often causes severe gastrointestinal adverse reactions such as nausea and vomiting. In addition, the side effects of such drugs are serious: they cause liver and kidney damage in patients, and long-term application of small doses causes hepatic cirrhosis [16]. Therefore, it is very important to develop newer RA treatment drugs with minimal side effects, good efficacy and high safety.

Interleukin-6 (IL-6), an important cytokine involved in immune regulation and response in human body, is very important in the inflammatory processes. Moreover, TNF-α releases a 'cytokine storm' during inflammation process in RA. It promotes inflammatory response in RA, and it enhances apoptosis and abnormal proliferation of synovial cells and the progression of RA inflammatory response by interacting with various tissue factors and matrix

Table 4: TNF-α and IL-6 serum levels before treatment (mean ± SD)

Parameter	Study group (n=80)	Control group (n=58)	t	*P*-value
TNF-α	51.85±8.23	52.14±9.12	0.195	0.846
IL-6	28.49±7.37	29.92±6.99	1.150	0.252
TNF-α	44.23±7.34	48.37±8.37	3.082	0.003
	36.52±6.45	43.47±7.95	5.662	<0.001
	29.36±6.11	38.54±7.09	8.141	<0.001
	20.34±5.31	31.43±4.72	12.680	<0.001

Table 5: Post-treatment IL-6 serum levels (mean ± SD)

IL-6	Study (n=80)	Control (n=58)	*t*	*P*-value
Treatment for 3 weeks	24.73±6.74	27.77±6.27	2.692	0.008
Treatment for 6 weeks	19.59±6.04	23.89±6.05	4.125	<0.001
Treatment for 9 weeks	15.32±5.41	20.14±5.49	5.134	<0.001
Treatment for 12 weeks	10.24±4.62	16.52±4.58	7.911	<0.001

proteins [17]. An increase in the level of TNF-α is an important cause of inflammatory activity and soft tissue destruction in RA patients, and it increases blood level of IL-6. Increased concentrations of TNF-α and IL-6 were reported in serum of synovial membrane of peripheral joints of patients with ankylosing spondylitis and osteoarthritis [18].

With advancements in science and technology, the use of targeted treatment drugs is now more frequently discussed. As a TNF-α inhibitor that affects the pathogenesis of RA through targeted treatment, ETA exerted obvious treatment effects by significantly relieving the symptoms of RA patients and improving their quality of life.

Pre-treatment HAQ score was similar in both groups. However, after 3, 6, 9 and 12 weeks of treatment, the HAQ scores of the two groups decreased, but the study group scores were markedly lower. There were no marked variations in blood levels of IL-6 and TNF-α between the study and control groups before treatment. After 3, 6, 9 and 12 weeks of treatment, blood IL-6 and TNF-α levels were markedly decreased, with lower concentrations in study group ($p < 0.05$). There were no marked differences between study group and control group in age, gender, body mass index, disease course, tender joint and swollen joint counts, ERS, and C-reactive protein concentration.

In a study by Bathon *et al*. [19], it was demonstrated that ETA was safe and effective in the treatment of RA, and it achieved significant outcomes in long-term treatment of RA. According to a study by Semerano *et al* [20], IL-6 is a key cytokine in the pathogenesis of RA, and its concentration is positively correlated with the incidence of RA. Studies by Jia *et al* [21] have shown that TNF-α is closely related to the inflammatory response and tissue destruction in RA, and RA may be effectively treated using TNF-α inhibitor. This indicates that TNF-α and IL-6 have certain beneficial values in monitoring RA disease during treatment.

Limitations of the study

This study is a retrospective case investigation. The collection of patients' basic information, the clinical examination, the special examination and other information were not flawless. Besides, there was limited amounts of specimens. Thus, the data were not enough for statistical comparison. Therefore, in future, the sample size will be expanded, the experimental research and statistical methods will be improved, and more clinical data will be collected for conduction of research. More accurate experimental results will be obtained to ensure their reliability and credibility.

CONCLUSION

Serum IL-6 and TNF-α levels may be used as disease-monitoring indicators during the treatment of RA patients. Furthermore, ETA therapy rapidly and efficaciously reduces the levels of IL-6 and TNF-α in RA patients, and also safely and effectively relieves joint inflammation and improves joint function. However, further clinical trials are required to validate this therapeutic strategy.

DECLARATIONS

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Ethical approval
None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article, and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Suihua Li and Qinghua Mei conceived and designed the study. Suihua Li, Dan Qian, Xianghong Huang, Cuimiao Fan and Jia Quan collected and analyzed the data. Qinghua Mei wrote the manuscript. All authors read and approved the manuscript for publication.

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