Effects of etanercept and infliximab on bone metabolism indexes in patients with ankylosing spondylitis

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Abstract. Effect of etanercept and infliximab on bone metabolism indexes in patients with ankylosing spondylitis (AS) were evaluated. The clinical data of 80 patients with ankylosing spondylitis admitted to Affiliated Hospital of Hebei University of Engineering from June 2015 to March 2016 were selected. There were 39 patients treated with Enbrel as Enbrel group and 41 patients treated with Infliximab as Infliximab group. The general data of the two groups of patients were collected and various indexes before and 12 and 24 weeks after treatment were recorded. Adverse reactions of the two groups of patients after treatment were recorded and the clinical efficacy of the drugs was evaluated. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) levels in both groups decreased significantly before and 12 and 24 weeks after treatment (P<0.05), and 24 weeks after treatment showed a downward trend compared with 12 weeks (P<0.05). The β-collagen special sequence (β-CTX) level in the two groups was significantly lower after treatment than before (P<0.0001). The adverse reaction rate of Infliximab group (21.95%) was higher than that of Enbrel group (5.13%) (P>0.05). The morning stiffness time, BASDAI and BASFI indexes of the two groups of patients after treatment were significantly lower than those before treatment (P<0.0001). Schober test was significantly higher than that before treatment (P<0.0001); BASDAI in Infliximab group was lower than that in etanercept group (P<0.05). Both etanercept and infliximab have good therapeutic effects on AS, which can reduce the bone metabolism level of β-CTX in AS patients and effectively improve the symptoms of affected medullary joints. The short-term efficacy of the two groups of patients is similar, but the incidence of adverse reactions of etanercept is slightly lower than that of infliximab.

Introduction

Ankylosing spondylitis (AS) is a chronic autoimmune disease (1). The morbidity of AS in China is ~0.3%, and the onset age is at 13-31 years, with a peak at 20-30 years (2). AS mainly occurs in spinal column, skeleton, peripheral joints and extra-articular tissues, mainly manifested as backache, and accompanied by peripheral arthritis, attachment point inflammation, and proctitis (3,4). In the early stage of onset, 50-92% patients are accompanied by osteopenia or osteoporosis (5-7), and often accompanied by fractures and neurological complications, which seriously affect the treatment and prognosis of AS patients. Smith (8) considered that the pathogenesis of AS is related to genetic, infection, immunity and physical and chemical factors. At present, there is no cure for AS, but timely treatment can relieve patients’ pain and improve their quality of life (9).

The drugs commonly used in clinic are infliximab and etanercept, which are tumor necrosis factor-α (TNF-α) antagonists. TNF-α is an important inflammatory cytokine in the pathogenesis of AS (10). TNF-α antagonist has significant effect in treating AS patients (11,12), and in 30% of patients symptoms are relieved by 70-80% in short-term treatment (13). Advanced AS patients will be accompanied by severe joint dysfunction, so early diagnosis is very important for AS patients. In the early stage of AS, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) increase rapidly, so ESR and CRP are important evaluation indexes for clinical auxiliary diagnosis (14,15). Recent studies have found that biochemical changes of bone metabolism precede systemic osteoporosis and joint stiffness (16,17), which can also provide basis for early diagnosis of AS (18).

In this study, various indexes were detected before and after treatment, bone metabolism indexes, such as bone-specific alkaline phosphatase (BALP), β-collagen special sequence (β-CTX), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), and adverse reactions and the clinical efficacy of the drugs were evaluated to explore the effect of etanercept and infliximab on AS patients and the effect on bone metabolism index.

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Patients and methods

**General information.** Clinical data of 80 patients with AS admitted to Affiliated Hospital of Hebei University of Engineering (Handan, China) from June 2015 to March 2016 were selected into the study. The average age of the 39 AS patients treated with etanercept was 29.68±7.24 years, with 21 males and 18 females. Further 41 AS patients treated with infliximab were the control group with an average age of 30.48±7.18 years, with 22 males and 19 females.

Inclusion criteria were as follows: The treatment conformed to New York AS Diagnostic Criteria (19) revised in 1984; patients aged 20-50 years; the duration of illness did not exceed 3 years; patients accompanied by family members on admission; patients with complete clinical data and good compliance.

Exclusion criteria were as follows: patients unable to cooperate with the examination due to other factors such as aphasia and dysphoria; patients who had received etanercept and infliximab therapy in the prior 6 months; HIV antibody positive patients; patients participated in other clinical trials; patients with severe organic diseases; patients had previous history of mental illness and family history of mental illness; patients had a history of drug dependence.

This study was approved by the Ethics Committee of Affiliated Hospital of Hebei University of Engineering. All the patients and their families were informed in advance and signed a complete informed consent form.

**Method**

**Treatment methods.** Thirty-nine patients in the etanercept group received intermittent administration for 24 weeks (etanercept; Shenzhen Phys Biotechnology Co., Ltd., item no. 152). Subcutaneous injection was carried out twice a week for the first eight weeks (20 mg), once a week for the ninth to sixteenth weeks (15 mg), and once every two weeks for the last eight weeks (10 mg). Further 41 patients in infliximab group received intermittent administration for 24 weeks (infliximab; Shanghai Teramabs Biotechnology Co., Ltd. item no. TM-Infl-00002_1), 100 mg in the first week, the second week and the sixth week, and the same dose every six weeks. Patient’s rest and diet were adjusted, appropriate rehabilitation exercise and adequate sleep were maintained.

**Blood collection.** A total of 4 ml of fasting peripheral blood was collected early in the morning before treatment, 12 weeks after treatment and at 24 weeks. Sample was put into anticoagulant tubes, and sent to clinical laboratory to examine CRP and ESR.

**Evaluation indicators**

Efficacy evaluation (19): Cure: no morning stiffness, limited activity, pain in trunk joints, ESR and CRP returned to normal. Markedly effective: morning stiffness, movement restriction, trunk joint pain, ESR and CRP decreased significantly. Effective: morning stiffness, movement restriction, trunk joint pain, ESR and CRP decreased. Ineffective: morning stiffness, movement restriction, trunk joint pain, ESR and CRP did not decrease.

**Results**

Comparison of general data between the two groups. There was no difference in general clinical data between the two groups in terms of age, sex, body mass index, smoking and drinking history, education level and complications (P>0.05) (Table I).

**CRP and ESR levels before and after treatment in the two groups of patients.** The CRP and ESR levels between the two groups before and after treatment were compared (Figs. 1 and 2). There was no significant difference in CRP levels between the two groups before treatment (37.58±19.89 and 38.62±20.41 mg/l), 12 weeks after treatment (9.65±3.94 and 8.94±3.81 mg/l) or 24 weeks after treatment (6.78±2.72 and 6.21±2.25 mg/l) (P>0.05). CRP levels in both groups decreased significantly before treatment, and 24 weeks after treatment (P<0.05), and there was a downward trend from 12 to 24 weeks after treatment (P<0.05). There was no significant difference in ESR level between the two groups before treatment (53.67±18.75 and 55.71±19.87 mm/h), 12 weeks after treatment (9.43±6.74 and 17.68±7.12 mm/h) or 24 weeks after treatment (9.74±2.65 and 10.81±3.10 mm/h) (P>0.05). CRP levels in both groups decreased significantly before treatment, and 24 weeks after treatment (P<0.05).
Comparison of bone metabolism levels before and after treatment between the two groups. The bone metabolism levels between the two groups before and after treatment were compared (Figs. 3 and 4). There was no significant difference in BALP level between Enbrel group and Infliximab group before treatment (18.72±8.62 and 18.98±8.51 µg/l) and after treatment (17.59±7.71 and 17.84±7.64 µg/l) (P>0.05), and there was no significant difference between the two groups before and after treatment (P>0.05). After treatment, β-CTX levels in Enbrel group and Infliximab group (362.58±211.45 and 354.74±231.52 ng/ml) were significantly lower than those before treatment (638.52±268.74 and 642.75±271.66 ng/ml) (P<0.0001), but there was no significant difference between the two groups before and after treatment (P>0.05).

Table I. Comparison of clinical general data (mean ± SD), n[%].

|                     | Enbrel group (n=39) | Infliximab group (n=41) | \(\chi^2/t\) value | P-value |
|---------------------|---------------------|------------------------|-------------------|---------|
| Average age (years) | 29.68±7.24          | 30.48±7.18             | 0.50              | 0.62    |
| Sex                 |                     |                        | 0.00              | 0.99    |
| Male                | 21 (53.85)          | 22 (53.66)             |                   |         |
| Female              | 18 (46.15)          | 19 (46.34)             |                   |         |
| Body mass index (kg/m\(^2\)) | 21.51±3.42     | 20.89±3.58             | 0.79              | 0.43    |
| Smoking             |                     |                        | 0.01              | 0.92    |
| Yes                 | 11 (28.21)          | 12 (29.27)             |                   |         |
| No                  | 28 (71.79)          | 29 (70.73)             |                   |         |
| Drinking            |                     |                        | 0.28              | 0.59    |
| Yes                 | 5 (12.82)           | 7 (17.07)              |                   |         |
| No                  | 34 (87.18)          | 34 (82.93)             |                   |         |
| Educational level   |                     |                        | 0.03              | 0.86    |
| Junior high school  | 7 (17.95)           | 8 (19.51)              |                   |         |
| College degree or above | 32 (82.05)       | 33 (80.49)             |                   |         |
| Complication        | Hypertension        | 6 (15.38)              | 0.24              | 0.63    |
| High blood lipid    | 4 (10.26)           | 3 (7.32)               | 0.22              | 0.64    |
Table II. Comparison of clinical efficacy n[%].

|                | Cure       | Markedly effect | Effective | Ineffective | Total efficiency |
|----------------|------------|-----------------|-----------|-------------|-----------------|
| Enbrel group (n=39) | 11 (28.20) | 12 (30.77)      | 12 (30.77)| 4 (10.26)   | 35 (89.74)      |
| Infliximab group (n=41) | 12 (29.27) | 13 (31.70)      | 12 (29.27)| 4 (9.76)    | 37 (90.24)      |

$\chi^2$ value: -
P-value: 0.01

Table III. Comparison of postoperative adverse reactions n[%].

|                          | Skin allergy | Hot flashes | Infection | Respiratory tract reaction | Gastrointestinal tract reaction | Skin reaction at injection site | Incidence of adverse reactions |
|--------------------------|--------------|------------|-----------|----------------------------|--------------------------------|--------------------------------|-------------------------------|
| Enbrel group (n=39)      | 0 (0.00)     | 0 (0.00)   | 0 (0.00)  | 0 (0.00)                   | 1 (2.56)                       | 1 (2.56)                       | 2 (5.13)                      |
| Infliximab group (n=41)  | 2 (4.88)     | 0 (0.00)   | 2 (4.88)  | 2 (4.88)                   | 3 (7.32)                       | 0 (0.00)                       | 9 (21.95)                     |

$\chi^2$ value: -
P-value: 0.03

Figure 3. Comparison of bone metabolism level-BALP between two groups before and after treatment. BALP level of patients in Enbrel group and Infliximab group had no significant difference before and after treatment, and there was no significant difference in the same group before and after treatment. BALP, bone-specific alkaline phosphatase.

Figure 4. Comparison of bone metabolism level of $\beta$-CTX between two groups before and after treatment. The $\beta$-CTX level in Enbrel group and Infliximab group decreased significantly after treatment, but there was no significant difference between the two groups before and after treatment. *P<0.05 compared with the same group before and after treatment. $\beta$-CTX, $\beta$-collagen special sequence.

effective rate of Enbrel group (89.74%) and Infliximab group (90.24%) had no significant difference (P>0.05).

Comparison of adverse reactions between the two groups of patients. The adverse reactions of the two groups of patients after treatment were compared (Table III). The adverse reactions of the two groups of patients were relieved after symptomatic treatment. The adverse reaction rate of Infliximab group (21.95%) was higher than that of Enbrel group (5.13%) (P>0.05).

Comparison of various indexes between the two groups before and after treatment. The various indexes between the two groups before and after treatment were compared (Table IV). The morning stiffness time, BASDAI, BASFI and Schober tests of the two groups were basically the same before treatment, and there was no difference between the two groups (P>0.05). After treatment, the morning stiffness time, BASDAI and BASFI indexes of the two groups were significantly lower than before treatment (P<0.0001). Schober test significantly increased (P<0.0001). BASDAI in Infliximab group was lower than that in etanercept group (P<0.05).

Discussion

The monoclonal antibody infliximab formed by chimeric mouse and human, is a combined soluble TNF-α and transmembrane TNF-α receptor, thus blocking the pathological effect and signal conduction by TNF-α (22,23). Etanercept with receptor-immunoglobulin fusion technology is composed of the extracellular ligand binding site of human tumor necrosis factor receptor 2 (TNF-2/p75) and Fc fragment of human IgG1. The fusion protein is expressed in vitro. Soluble TNF-α in plasma and on the surface of cell membrane is highly compatible with
this fusion protein, which is neutralized by etanercept, resulting in loss of biological activity of TNF-α and achieving inhibition of abnormal immune response and inflammatory process mediated by receptor (24), thus effectively treating AS.

Bone metabolism markers are divided into bone formation markers, bone turnover markers, bone absorption markers and osteoporosis-related hormone markers. β-CTX is an index of bone resorption, and some researches have shown that it is a valuable and reliable index for evaluating bone resorption (25,26). However, in this study, there was no significant difference in the level of BALP before and after treatment between Enbrel group and Infliximab group (P>0.05), and there was no significant difference in the same group before and after treatment. Consistent with the results of a previous study (27), it was presumed that bone metabolism index BALP has little effect on AS. In this study, the morning stiffness time, BASDAI and BASFI indexes of the two groups of patients after treatment were significantly lower than before treatment (P<0.0001), and Schober test was significantly higher (P<0.0001). Consistent with the reduction of morning stiffness time in the clinical efficacy of etanercept in the treatment of AS by Liu et al (28).

According to the observation of the therapeutic effect of infliximab on AS (29), the indexes of BASDAI and BASFI of the two groups of patients after treatment were significantly lower than before treatment (P<0.0001), and Schober test was significantly higher (P<0.0001). Consistent with the reduction of morning stiffness time in the clinical efficacy of etanercept in the treatment of AS by Liu et al (28).

The present study evaluated the effect of etanercept and infliximab on bone metabolism indexes of AS patients by detecting bone metabolism index (BALP, β-CTX) levels, CRP and ESR before and after treatment, recording adverse reactions of the two groups of patients after treatment and evaluating the clinical efficacy of the two groups of drugs. Collectively, etanercept and infliximab improved the therapeutic effect on AS patients. All indexes are decreased, effectively reducing bone metabolism indexes, which is worthy of clinical promotion.

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Availability of data and materials

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

CW wrote the manuscript. CW and WL conceived and designed the study. CW was responsible for the collection and analysis of the experimental data. WL interpreted the data and drafted the manuscript. CW and WL revised the manuscript critically for important intellectual content. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Affiliated Hospital of Hebei University of Engineering (Handan, China). Patients who participated in this research had complete clinical data. Signed informed consents were obtained from the patients and/or guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Braun J and Sieper J: Ankylosing spondylitis. Lancet 369: 1379-1390, 2007.
2. Biasi D, Carletto A, Caramaschi P, Pacor ML, Maleknia T and Bambara LM: Efficacy of methotrexate in the treatment of ankylosing spondylitis: a three-year open study. Clin Rheumatol 19: 114-117, 2000.
3. Quan DH, De Winter LM and Somers V: Detection of novel diagnostic antibodies in ankylosing spondylitis: An overview. Autoimmun Rev 15: 820-832, 2016.
4. Stolwijk C, Essers I, van Tubergen A, Boonen A, Bazelier MT, De Bruin ML and de Vries F: The epidemiology of extra-articular manifestations in ankylosing spondylitis: A population-based matched cohort study. Ann Rheum Dis 74: 1373-1378, 2015.
5. Davey-Ransasinghe N and Deodhar A: Osteoporosis and vertebral fracture in ankylosing spondylitis. Curr Opin Rheumatol 25: 509-516, 2013.
6. van der Weijden MA, Claussius TA, Nazari T, Lems WF, Dijkmans BA and van der Horst-Bruinsma IE: High prevalence of low bone mineral density in patients within 10 years of onset of ankylosing spondylitis: A systematic review. Clin Rheumatol 31: 1529-1535, 2012.
7. Singh HJ, NimarpREET K, Ashima, Das S, Kumar A and Prakash S: Study of bone mineral density in patients with ankylosing spondylitis. J Clin Diagn Res 7: 2832-2835, 2013.
8. Smith JA: Update on ankylosing spondylitis: Current concepts in pathogenesis. Curr Allergy Asthma Rep 15: 489, 2015.
9. Machado MA, Moura CS, Ferre P, Bernatsky S, Rahim E and Acucro Fde A: The epidemiology of extra-articular manifestations in ankylosing spondylitis: A population-based matched cohort study. Ann Rheum Dis 74: 1373-1378, 2015.
10. Maxwell LJ, Zochling J, Boonen A, Singh JA, Veras MM, Tanjong Ghogomu E, Benkhalti Jandu M, Tugwell P and Wells GA: TNF-alpha inhibitors for ankylosing spondylitis. Cochrane Database Syst Rev: Apr 18, 2015 [Epub ahead of print]. doi: 10.1002/14651858.CD005468.pub2.
11. Prince DS, McCuinian LE and McGirr EE: Working life and physical activity in ankylosing spondylitis is pre and post antitumor necrosis factor-alpha therapy. Int J Rheum Dis 17: 165-172, 2014.
12. Podlubný DA, Song IH and Sieper J: The safety of celecoxib in ankylosing spondylitis treatment. Expert Opin Drug Saf 7: 401-409, 2008.