Clinical research for curing ankylosing spondylitis through combining etanercept, thalidomide and sulfasalazine

Peng Xiao, Changhe Pang, Xu Zhu and Xuejian Wu*
Department of Orthopedics, the First Affiliated Hospital, Zhengzhou University, Zhengzhou, China

Abstract: This article is to explore the curative effect of treating ankylosing spondylitis (AS) through combining etanercept, thalidomide and sulfasalazine. Sixty-two patients with AS were divided into 3 groups: experimental group A is treated by etanercept + thalidomide + sulfasalazine for 1 year (n=22); control group B was treated with etanercept; control group C was treated with thalidomide + sulfasalazine for 1 year (n=20). In 1st, 3rd, 6th, 12th month after the treatment, ASAS20 and ASAS50 were obtained through Bath ankylosing spondylitis disease activity index (BASDAI), Bath ankylosing spondylitis functional index (BASFI), erythrocyte sedimentation rate (ESR), C react protein (CRP) and then curative effect was analyzed. In 1 and 3 months after the treatment, each indicator had downtrend, and ASAS20 of experimental group and etanercept control group reached 100%; ASAS50 increased compared with the first months' treatment; although ASAS20 and ASAS50 in thalidomide control group was smaller, they increased; in 6 and 12 months after the treatment, ASAS20 improvement ratio in group A still remained on 100%, ASA50 improvement ratio increased; recurrence rate of group B increased; ASA20 and ASA50 had a continuous and significant increase, but its their was less than group A. This study proved that, the effect of curing AS combining etanercept, thalidomide and sulfasalazine is better, therefore, it is a high-feasible treatment approach.

Keywords: Ankylosing spondylitis; Etanercept; Thalidomide; Sulfasalazine Ankylosing spondylitis; Etanercept; Thalidomide; Sulfasalazine.

INTRODUCTION

AS treatment with combination of sulfasalazine, thalidomide and other antirheumatic drugs is relatively traditional treatment method, and accounts for the treatment process of most patients. In recent decades, curing rheumatic diseases with biological agents has been gradually applied in clinical AS treatment with rapid research development in new fields such as cytology, molecular action and so on. (Li and Chunhua, 2014; Yan, 2012).

Etanercept is a kind of dimer fusion protein of recombinant soluble TNFp75 receptor, which can block TNF-α (it is considered to be the important inflammatory factor that causes AS), reduce inflammation factor inducing inflammation, and it has been proved and applied clinically at home and abroad (Jingfeng, 2012; Wenfeng *et al.*, 2010; Hanyou *et al.*, 2011). AS patients need to take this kind of drugs for a long time since AS is easy to reoccur; however, this kind of drugs is expensive and long-time taking will increase the risk of tuberculosis and hepatitis B (Fengju, 2013). Thus, this article adopts prospective, control and opening experimental research method to observe each index of patients with different method of administration, explore the curative effect of curing AS through combing etanercept, thalidomide and sulfasalazine when compared with other methods of administration.

*Corresponding author: e-mail: xpzxwxj@163.com

MATERIALS AND METHODS

Experimental subjects

A total of 62 cases of AS treated by etanercept were recruited from First Affiliated Hospital of Zhengzhou University from February, 2010 to February, 2012, with 49 males and 13 females, ranging in age from 17~38 years (mean 26.12±2.31 years). Condition of AS patients: 1) Patients should be in accordance with AS New York classification standard activity period revised in 1984, Bath (BASDAI) ⩾4, visual simulation test table (VAS) spinal pain score ⩾ 4.2) Exclude following patients: clinical and radiographic inspection validates that spine has complete stiffness, ischemic necrosis; patients ever had a history of active TB, or had close contacts with active TB patients recently; patients with hepatitis B, hepatitis c or HIV/AIDS; patients who are now combined with bacteria, chlamydia, mycoplasma, fungi, treponemal infection, endocrine system disease and illness history; patients who are allergic to any type of experimental drug or have allergic history. Patients and relatives were all informed and signed the inform consent. The treatment plan is approved by Medical Ethics Committee.

Establishing experimental group

AS patients in accordance with requirements are divided into 3 groups (their age, disease course etc are matched to each other). Experimental group A (n=22): etanercept (25mg/ time, 2 times/ week, subcutaneous injection, 3 months' application) + thalidomide (25mg/piece, 50mg/day, taking before bedtime) + sulfasalazine

(0.25g/piece, 3times/day) 1 year's treatment; etanercept control group B (n=20): Etanercept (25mg, 2 times/week, subcutaneous injection) drug withdrawal is applied after 3 months; thalidomide control group C (n=20): thalidomide (50mg/day, before sleep) + sulfasalazine (0.5g, 3 times/day) 1 year's treatment.

Examination of observation index

Examination evaluation was performed on BASDAI, BASFI, ESR, CRP of patients on baseline and in 1, 3, 6 and 12 months after the treatment, respectively. Reexamination was performed on patients for every 1-2 months, and then the record was analyzed.

Evaluation for curative effect

For the proportion of patients who reaches 20%, 50% (ASAS20, ASAS50) of AS curative effect standard, it defines that at least 3 aspects of following 4 indicators achieve 20%, 50%, and absolute number of VAS evaluation value at least has the progress of 1 point (0~10 points); if it could not reach 20%, 50%, there is no deterioration compared with baseline: 1) Evaluation for patients' overall VAS score; 2) VAS score evaluation for back pain at night and general back pain; 3) BASFI; 4) inflammation of the spine: VAS average score of the last two items of BASDAI that is related to morning stiffness.

STATISTICAL ANALYSIS

Data was processed using SPSS11.5 software. The measurement data in each observation indicator was expressed by $\overline{X} \pm s$. t-test or rank sum test was adopted for comparison. Counting data comparison adopted p test. All statistical test adopted two-sided test. $p<0.05$ was considered to have statistical significance.

The experimental results

The general clinical data of AS patients

A total of 62 patients were divided into 3 groups according to its disease course age and other corresponding condition and its basic indicators were detected. It is shown in table 1.

Clinical curative effect of AS patients in 1, 3,6,12 months after the treatment

in one month after the treatment, numerical value of each indicator had downward to different degrees, and ASAS20 in experimental group and etanercept control group reached 100%, while ASAS50 reached 76% and 77.7%, respectively; when comparing etanercept control group with the other two groups, ASAS20 and ASAS50 were relatively small, only reaching 32.7% and 8.2% and there was statistical signficance when compared with group A and B ($p<0.05$). It is shown as table 2.

In 3 months after the treatment, each indicator continued to decline, ASAS20 of experimental group and etanercept control group still maintains at 100%, and the effect of ASAS50 improved compared with the condition in one month after the treatment. In addition, although the numerical value of ASAS20 and ASAS50 in thalidomide control group C were smaller than that of experimental group and etanercept control group, its numerical value has increased significantly when compared with the curative effect of the first month. There was statistical significance when compared with group A and B ($p<0.05$). It is shown as table 3.

in 6 months after the treatment, numerical value of each indicator still declined except for individual value, ASAS20 improvement standard rate of experimental group continued to maintain at 100%; ASAS50 improvement rate had slight increase, reaching 86.4%; etanercept control group B stopped taking drugs in 3 months, and its recurrence rate was 30% (6/20) when rechecked. ASAS20 and ASAS50 in thalidomide control group were 61.3% and 36.8%, respectively, with a slight increase, as shown in table 4

in 12 months after the treatment, numerical value of each indicator had slight rise except for individual value; improvement standard rate of ASAS20 and ASAS50 in experimental group was the same with the condition in 6 months after the treatment, 100% and 86.4%, respectively; etanercept control group B stopped taking drugs after 3 months, and its recurrence rate was 80% (16/20) when rechecked0; ASAS20 and ASAS50 of etanercept control group were 61.3% and 36.8%, respectively, with a slight increase. It is shown in table 5.

Evaluation for drug safety

Of the 62 cases of AS, 8 cases appeared untoward effect, 3 patients had dry mouth, 3 patients felt tired, but the symptom improved along with the administration time. There were 2 else cases occurring mildly abnormal liver function, but improved after using liver protection medicine.

DISCUSSION

Various researches at home and abroad have validated that biological agent has gradually taken the place the DMARDs drugs to be the center drug for treating AS for its good curative effect and rapid working. However, high price and disease relapsing after drug withdrawal make patients daunting (Wenfeng *et al.*, 2010; Hanyou *et al.*, 2011). In this research, each indicator of AS patients in group A and B was significantly improved, and pain and morning stiffness were relieved, proving that etanercept works fast and has impressive effect (Hanyou *et al.*, 2011). Different from previous researches with long curing course, etanercept was stopped after 3 months, and its recurrence rate turned to be 30%; after drug withdrawal for 6 months, its recurrence rate was as high as 80%,

Table 1 Comparison for clinical features of 3 groups at baseline ($\overline{X} \pm s$, p>0.05)

Group	Number of cases	age/years old	Disease course/ month	BASDAI	BASFI	ESR/mm·h-1	CRP/mg·L-1
Group A	22	28.5±7.1	14±6	5.3±0.9	7.3±1.3	46±12	23±14
Group B	20	29.2±6.9	12±4	4.8±1.3	6.8±1.6	49±13	25±15
Group C	20	28.9±6.8	14±4	4.9±1.1	7.1±1.4	49±10	24±13

Table 2 Comparison of observation indicators of 3 groups in one month after the treatment

Group	No. of cases	BASDAI	BASFI	ESR/mm·h-1	CRP/mg·L-1	ASAS20	ASAS50
Group A	22	3.0±1.1	6.6±1.5	28±8	14±8	100%	76%
Group B	20	3.2±1.0	6.5±1.4	30±7	13±7	100%	77.7%
Group C	20	5.3±1.4*	6.6±1.4	44±11*	23±15*	32.7%	8.2%

Table 3 Comparison of observation indicators of 3 groups in 3 months after the treatment

Group	No. of cases	BASDAI	BASFI	ESR/mm·h-1	CRP/mg·L-1	ASAS20	ASAS50
Group A	22	2.6±0.7	2.8±1.1	23±6	10±5	100%	82.8%
Group B	20	3.0±1.0	3.2±1.1	26±9	10±6	100%	86%
Group C	20	3.1±1.2	5.8±1.4Δ	43±10Δ	12±14	53.2%	32.7%

Note: comparison with experimental group and etanercept control group, ΔP<0.05.

Table4 Comparison of observation indicators of 3 groups in 6 months after the treatment

Group	Number of cases	BASDAI	BASFI	ESR/mm·h-1	CRP/mg·L-1	ASAS20	ASAS50
Group A	22	2.4±0.8	2.7±0.8	21±7	11±6	100%	86.4%
Group B	20	4.4±1.4☆	5.3±1.3☆	43±11☆	23±16☆	—	—
Group C	20	2.8±1.1	3.7±1.1	30±10	15±10	61.3%	36.8%

Table 5 Comparison of observation indicators of 3 groups in 12 months after the treatment

Group	No. of cases	BASDAI	BASFI	ESR/mm·h-1	CRP/mg·L-1	ASAS20	ASAS50
Group A	22	2.9±1.3	3.0±1.2	22±9	8±5	100%	86.4%
Group B	20	5.0±1.3☆	5.1±1.4☆	52±14☆	28±16☆	—	—
Group C	20	3.0±1.2	3.9±1.2	24±7	12±6	77.7%	61.3%

Note: comparison between experimental group and thalidomide control group, ☆P<0.05.

which was similar but still different from reoccurring of more than 2/3 in 12 weeks after stopping drugs, and reoccurring of all cases in 24 weeks after stopping drugs recorded in foreign literature (Brandt *et al.*, 2005). It maybe related with sample size and gene difference at home and abroad. But it indicated that treating AS patients through combing etanercept, thalidomide and sulfasalazine could benefit a lot of patients from biological agent.

Professor Feng Huang et al had performed systematic research on treating AS with thalidomide in 1999 and 2010, and thought that thalidomide is a kind of relatively weak TNF-α antagonist, and can inhibit monocyte generating TNF-α, while thalidomide maybe show curative effect within 3~6 months, and reach the maximum curative effect in 6 to 12 months (Jian *et al.*, 2010; Shulin *et al.*, 2011). In this experiment, it is visible that, in the first and third month after the treatment in thalidomide control group, there is not significant change in each index, and numerical value of ASAS20 and ASAS50 is obviously smaller than remaining two groups, while in the six and twelfth month after the treatment, each indicator declines relatively significantly, and numerical value of ASAS20 and ASAS50 has increased significantly. Curative effect trend is consistent with research.

Sulfasalazine, the classically recommended drugs for curing AS, can inhibit folic acid absorption and metabolism, prostaglandin synthesis, decrease serum IgA level and other activity indicators in laboratory through cell immunity, and improve joint function; it is confirmed as the only effective drug for curing AS with low price and slow working (Hanyou *et al.*, 2011; Dongping and Liyun, 2012; Daniel *et al.*, 1996; Dougados *et al.*, 1995; Baohua, 2013). Curative effect of Etanercept is good, but its price is high. In this experiment, patients have

extremely low adverse reaction after accepting AS treatment with etanercept for 3months and then combing thalidomide and sulfasalazine for treatment. They have light adverse symptoms and good tolerance. Therefore, this method deserves to be promoted in area with limited economy.

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