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Article

Safety and tolerability of a single dose T0001 in Chinese healthy adult volunteers: a first-in-human ascending dose study

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T0001 is the first mutant of etanercept with a higher affinity to tumor necrosis factor α (TNF-α) than etanercept. In order to investigate the safety and tolerability of T0001, a study was carried out in healthy Chinese subjects. A first-in-human, dose escalation study was conducted in healthy Chinese subjects. Fifty-six subjects were divided into six dose cohorts (10 mg, 20 mg, 35 mg, 50 mg, 65 mg and 75 mg) to receive a single subcutaneous injection of T0001. Safety and tolerability assessment were based on the records of vital signs, physical examinations, clinical laboratory tests, 12-lead electrocardiograms and adverse events (AEs). All subjects were in good compliance and none withdraw due to AEs. No serious AEs occurred. A total of twenty-three AEs in sixteen subjects were recorded, and eighteen of these AEs were believed to be related to T0001. The most frequently reported AEs were injection site reactions and white blood cell count increase. All these AEs were of mild to moderate intensity and most of them recovered spontaneously within 14 days. In this study, no dose-limiting toxicity was observed, and the maximum tolerated dose was identified as 75 mg. T0001 was considered safe and generally well tolerated at doses up to 75 mg in healthy Chinese volunteers.

Keywords: T0001. TNF-α. Rheumatoid arthritis. Safety. Tolerability.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory polyarthritis with high morbidity (Sanmartí, Ruiz-Esquide, Hernández, 2013). This disorder affects 0.5% to 1.0% of adults around the world (Josef, Daniel, Iain, 2016). However, the prevalence of RA ranges from 0.2% to 0.37% in mainland China, which is similar to that in most Asian and South American countries (Zeng *et al*., 2008). Research suggests that overproduction of tumor necrosis factor α (TNF-α) can lead to RA (Bazzoni, Beutler, 1996). Therefore, many guidelines recommend TNF-α inhibitors to active RA patients who

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have dissatisfactory responses to conventional disease-modifying anti-rheumatic drugs (Singh *et al*., 2016).

Etanercept, a TNF receptor 2-Fc fusion protein (TNFR2-Fc) acting as a TNF-α inhibitor (Enbrel®, Amgen and Wyeth), has been available for clinical use in the US since late 1998 (Goffe, Cather, 2003). However, 25% to 38% of patients display poor responses to etanercept (Alonso-Ruiz *et al*., 2008), which is partly due to insufficient etanercept affinity to TNF-α. Therefore, enhancing etanercept affinity may contribute to efficacy improvement and dose reduction.

T0001, the first mutant of etanercept, is a recombinant human TNFR-Fc fusion protein mutant (rhTNFR (m): Fc) which has been developed by Shanghai Fudan-zhangjiang Bio-Pharmaceutical Co. Ltd (China). Preclinical studies showed that T0001 had a 1.5-fold higher bioactivity to block TNF-α *in vitro* and a 3.65-fold higher constant value than etanercept. Moreover, it can significantly improve responses in rat arthritis models induced by collagen (Yang *et al*., 2010). In addition, T0001 could induce apoptosis, which had a potential treatment capability in Crohn's disease and ulcerative colitis (Shen *et al*., 2017). T0001 has been registered patent (Liu *et al*., 2009).

The structure of T0001 is similar to etanercept. However, mutation of two amino acid sites may change the safety and tolerability of T0001 in human body. A study has already demonstrated that T0001 was absorbed and eliminated slowly and had a significantly higher C_{max} and $AUC_{0-\infty}$ values compared to etanercept (Wang *et al*., 2017). These results indicated that T0001 had greater exposure and longer retention than etanercept in human body. Nevertheless, whether this high-affinity variant can be used in human safely was still unverified. A first-in-human study was therefore carried out to evaluate the safety and tolerability of T0001.

MATERIAL AND METHODS

Study drug and administration

The study drug T0001 (batch number: 20130403) was provided by Shanghai Fudan-zhangjiang Bio-Pharmaceutical Co. Ltd (China). The drug was delivered as 0.6 mL prefilled syringes, each containing 30 mg active rhTNFR (m): Fc. All the drug should be stored in a refrigerated unit at 2 °C to 8 °C in the dark. T0001 was administrated by subcutaneous (SC) injection in the abdomen.

Study subjects

Fifty-six healthy Chinese subjects were required in this study. Only subjects who met all the inclusion criteria and not the exclusion criteria were eligible.

Inclusion criteria for this study were Chinese healthy subjects (1) aged from 18 to 45; (2) with a body mass index between 19 and 24 kg m^{-2}; and (3) with normal clinical findings for vital signs (including blood pressure, temperature, heart rate and respiratory rate), physical examination, clinical laboratory tests (hematology, blood biochemistry, urinalysis and stool routine) and 12-lead electrocardiogram (ECG).

Exclusion criteria consisted of subjects who (1) were treated with any biological agents previously; (2) had a history of allergic or hypersensitivity to rhTNFR: Fc components; (3) had history or strong evidences of the respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematologic, neurologic or psychiatric systems abnormalities; (4) had abnormal values of blood biochemistry and hematology test; (5) had evidences of active or latent tuberculosis or infections; (6) participated in other clinical trials within three months; (7) donated blood within three months; (8) had records of drug or alcohol abuse; (9) were positive for anti-drug antibody, anti-nuclear antibody, double-stranded DNA, extractable nuclear antigen, hepatitis B virus surface antigens, hepatitis C virus, HIV or syphilis antibodies. Female subjects who were pregnant or lactating were also excluded.

Study design

The study was conducted at Peking University People's Hospital (Clinical Trials. Gov. Identifier: NCT02291471) in accordance with the principles of the Declaration of Helsinki (World Medical Association, 2003), the Guidance for Good Clinical Practice (State Food and Drug Administration of China, 2003) and other applicable regulatory requirements. The study protocol, protocol amendments, and consent form were approved by the Ethics Committee of Peking University People's Hospital (Approval No. 2014PHA015-01). Informed consents were obtained from all subjects included in the study.

The initial dose of this trail was formulated with the results of preclinical toxicology tests (Tong Y, Zheng W, Fang W, unpublished results). In acute toxicity test, the no observed adverse effect level (NOAEL)

of cynomolgus was greater than 240 mg/kg after SC injection of T0001. In long-term toxicity test, NOAEL of rats and cynomolgus were 120 mg/kg and 60 mg/kg respectively. The minimum human equivalent dose (HED) was calculated to be 21 mg/kg based on the NOAEL value of rat in long-term toxicity tests [HED (mg/kg) = animal NOAEL (mg/kg) × (animal weight in kg/human weight in kg) 0.33]. The safety factor (SF) was selected as 10 to increase assurance, then the maximum recommended starting dose (MRSD) was calculated as 126 mg [MRSD (mg/kg) = HED (mg/kg) ÷ SF, supposing human weight was 60 kg]. However, the pharmacologically active dose (PAD) may be a more sensitive toxicity indicator than NOAEL because toxicity could arise from exaggerated pharmacologic effects in biologics. The PAD of T0001 was calculated as 1 mg/kg in the adjuvant arthritis model of rats and the rheumatoid arthritis model induced by type II collagen. The HED was therefore calculated as 9.8 mg by the PAD [HED (mg/kg) = animal PAD (mg/kg) × (animal weight in kg/human weight in kg) 0.33, supposing human weight was 60 kg] (State Food and Drug Administration of China, 2012). The initial dose was set as 10 mg by combining the results of these two methods and the dosage of similar drugs. The long-term toxicity test of rats indicated that the maximum tolerated dose (MTD) was 120 mg/kg. The MTD of human, which was 1/5 - 1/2 MTD of animal long-term toxicity test, can yield up to 1440 mg (Food and Drug Administration, 2010). Considering the clinical actual needs and the effective dose of similar drugs, the maximum dose was set as 75 mg. The dose increments were in accordance with a modified Fibonacci sequence as following: 2.00, 1.67, 1.50, and 1.30 for the subsequent two dose levels (Penel, Kramar, 2012). Thus the doses were selected as 10 mg, 20 mg, 35 mg, 50 mg, 65 mg and 75 mg. Fifty-six subjects were randomly assigned to these six dose cohorts (six in 10 mg cohort and ten in other cohorts). Doses were administered in a serial manner which proceeded from the lowest to the highest, and safety should be confirmed before each dose increase.

All eligible subjects checked into the Phase I Clinical Research Unit of Peking University People's Hospital with unified accommodation and standard food. At 8:00 am on day 1, all the subjects were administered a single SC injection of T0001. Consumption of food within four hours or water intake within two hours was avoided after drug administration. All subjects were continuously observed for 96 hours in the ward and 35 days after discharge. To assess drug safety and tolerability, all subjects were closely monitored for clinically significant findings. Vital signs and physical examination were checked 1 h before dosing and 2 h, 12 h, 24 h after injection. Hematology, C-reactive protein (CRP) and ECG were measured 12 h, 24 h after injection. Further follow-ups were conducted on days 3, 14, 21 for the aforementioned tests and other clinical laboratory tests (blood biochemistry, urinalysis, stool routine and erythrocyte sedimentation rate). Adverse events (AEs) and serious AEs were monitored and recorded throughout the study.

The study would be terminated if any serious AEs occur, or over half of the subjects experience AEs of grade II or greater according to the Common Terminology Criteria for Adverse Events Version 4.0 (US Department of Health and Human Services, 2009). The records on AEs described the intensity, duration, outcome, seriousness and the relationship with the study drug.

Safety and tolerability assessment

The study diary of each subject was reviewed to ascertain compliance and help with AEs discussion after the study. Indicators for the safety assessment were based on physical examinations, vital signs, laboratory tests, 12-lead ECGs and local tolerability evaluations. Special attention was paid to the possibility of infectious diseases. The MTD was defined as the highest T0001 dose with acceptable side effects or dose-limiting toxicities (DLTs). DLTs were connected with the events related to the study drug, which were deemed grade II, grade III, or grade I persisting longer than two weeks.

Statistical analyses

The demographic characteristic comparisons among the six treatment groups were performed using analysis of variance (ANOVA) with SAS version 9.3 (SAS Institute Inc., Cary, USA). Statistical analyses of safety and tolerability for each cohort were performed using repeated measures of ANOVA; the level of significance was set at $P < 0.05$. Safety parameters were summarized with descriptive statistics, graphs and numerical tables as appropriate.

RESULTS

Demographics and baseline characteristics

A total of fifty-six healthy volunteers were enrolled in the T0001 dose-escalation trial. The demographics and baseline characteristics of each group are listed in Table I. All subjects received their designated doses. No dose interruption, dose adjustment, dropout or discontinuation took place during the trial.

Safety and tolerability results

All subjects were compliant. No serious AEs or unexpected AEs occurred and no subject withdrew due to AEs during the trial. Twenty-three AEs in sixteen subjects were observed. The incidences of AEs in 10 mg, 20 mg, 35 mg, 50 mg, 65 mg and 75 mg cohorts were 1.8%, 8.9%, 3.6%, 5.4%, 5.4% and 3.6%, respectively. The differences were not statistically significant ($P = 0.24$, $P > 0.05$). Eighteen AEs were considered to be drug-related. The most frequently reported drug-related AEs were injection site reactions (4 cases; 7.1%) and white blood cell (WBC) count increase (3 cases; 5.4%) (Table II). The mean values of infection indicators, including WBC count, neutrophils count and CRP, were compared at each scheduled visit time (Figure 1). No statistically significant differences were found in these indicators among six dose groups over the study ($P > 0.05$). However, significant statistical differences occurred in WBC count ($P = 0.007$, $P < 0.05$) and neutrophils count ($P = 0.000$, $P < 0.05$) during different follow-ups within two days after T0001 administration. Nevertheless, no obvious trend were found. CRP during different follow-ups did not show any statistical differences ($P > 0.05$).

TABLE I - Demographic and baseline characteristics of enrolled subjects of all cohorts

Parameter	Treatment cohort						
	10 mg (n = 6)	**20 mg (n = 10)**	**35 mg (n = 10)**	**50 mg (n = 10)**	**65 mg (n = 10)**	**75 mg (n = 10)**	**P**
Male	3	5	5	5	5	5	--
Female	3	5	5	5	5	5	--
Age (year)	24.5 ± 2.6	25.4 ± 3.2	24.3 ± 3.3	24.4 ± 2.8	26.7 ± 3.1	24.4 ± 2.6	0.433
Height (cm)	167.6 ± 4.8	165.0 ± 7.3	165.3 ± 6.6	165.6 ± 10.7	170.7 ± 9.6	168.9 ± 11.2	0.662
Weight (kg)	60.4 ± 4.9	59.0 ± 7.7	58.5 ± 6.5	60.9 ± 9.5	63.6 ± 8.2	60.0 ± 7.4	0.562
BMI (kg/m^2)	21.5 ± 1.3	21.6 ± 1.4	21.4 ± 1.6	22.1 ± 1.5	21.7 ± 1.2	21.0 ± 1.4	0.634

Values of age, height, weight and BMI are presented as the mean ± standard deviation (SD);
The number of male and female participants for each cohort is indicated;
BMI, body mass index.

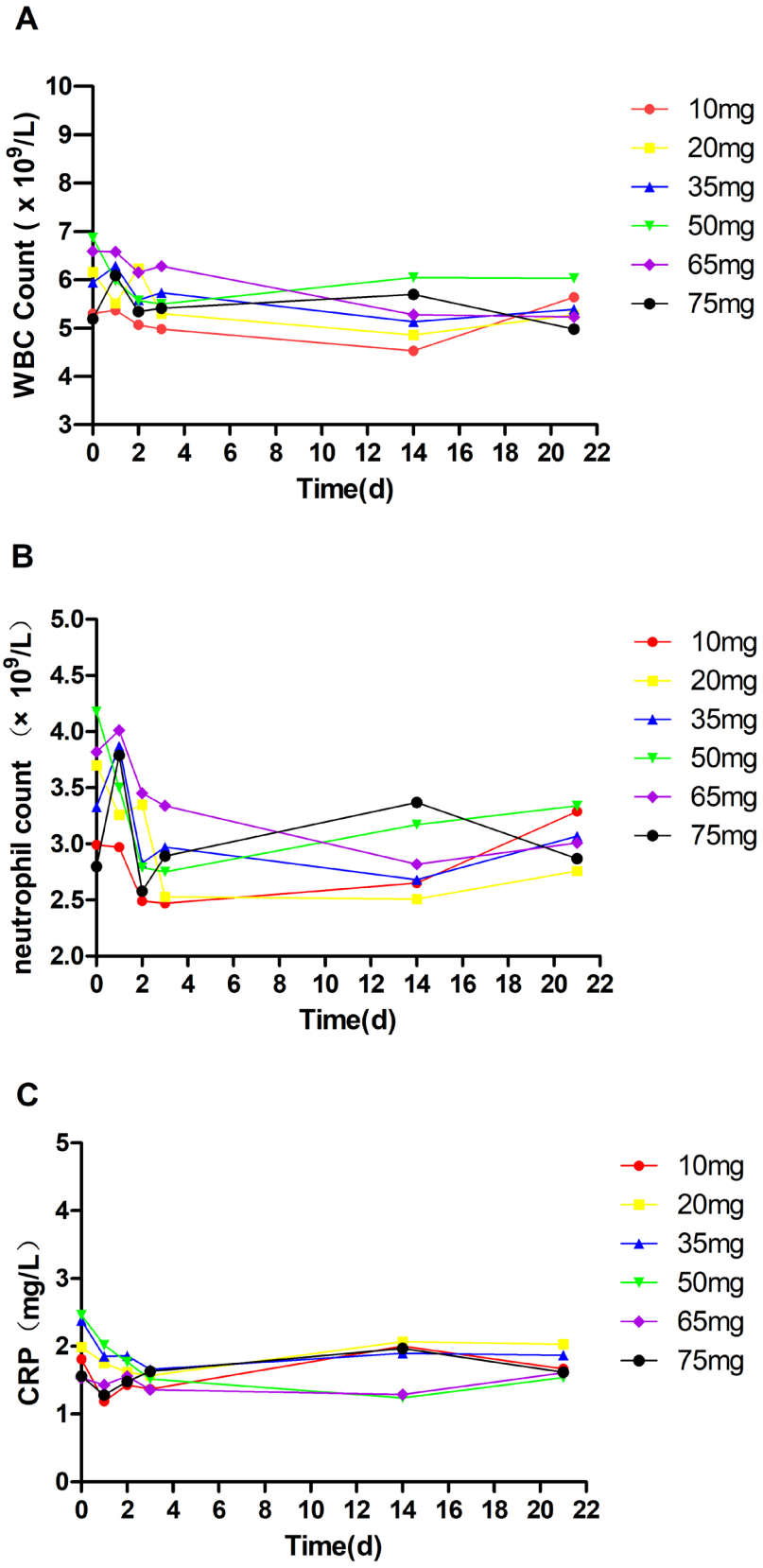

FIGURE 1 - Changes detection in the value of laboratory parameters after single dose subcutaneous administration of T0001 in healthy subjects in each of the follow-up period (day 0, day 1, day 2, day 3, day 14 and day 21). (A). WBC count; (B.) Neutrophil count; (C). CRP; WBC = white blood cell, CRP = C-reactive protein.

TABLE II - List of adverse events recorded after a single subcutaneous administration of T0001

Adverse events (AEs)	Dose group						
	10 mg (n = 6)	20 mg (n = 10)	35 mg (n = 10)	50 mg (n = 10)	65 mg (n = 10)	75 mg (n = 10)	Total (N = 56)
AEs (%)	1 (1.8)	5 (8.9)	2 (3.6)	3 (5.4)	3 (5.4)	2 (3.6)	16 (28.7)
Drug-related AEs (%)	1 (1.8)	5 (8.9)	1 (1.8)	2 (3.6)	3 (5.4)	2 (3.6)	14 (25.0)
Injection site reaction	0	3	0	1	0	0	4
White Blood cell count increased	0	0	1	0	2	0	3
Oral infection	0	0	0	0	0	1	1
Upper respiratory tract infection	1	0	0	0	0	0	1
White Blood cell count decreased	0	1	0	0	0	1	2
Erythrocyte sedimentation rate increased	0	2	0	0	0	0	2
Plasma uric acid increased	0	1	0	0	1	0	2
Conjugated bilirubin increased	0	1	0	0	0	0	1
Human chorionic gonadotrophin increased	0	0	0	1	0	0	1
Neutrophilic granulocye count increased	0	0	1	0	0	0	1
Hemobilirubin increased	0	1	0	0	0	0	1
Epigastric discomfort	0	0	0	1	0	0	1

Data are presented as the number of AEs; N is the total number of subjects studied and n is the number of subjects in each cohort.

The severity of all reported AEs was mild, with the exception of three moderate AEs in the 10 mg, 20 mg and 75 mg groups. Two of these three AEs, upper respiratory tract infection (in 10 mg cohort) and oral infection (in 75 mg cohort), were reckoned as infection which were related to T0001. Both subjects recovered from infection after receiving 0.4 mg levofloxacin mesylate tablets for three days. The other moderately severe AE was WBC count decreased to 2.89×10^9 L^{-1} in 20 mg cohort on day 21 after T0001 administration. The decrease returned to normal 7 days later (normal range: 3.5–9.5 $\times$ 10^9 L^{-1}, details are showed in supplementary information). The relationship between this AE and T0001 treatment was hard to ascertain yet. All other drug-related AEs resolved spontaneously within 14 days. None of these events required additional medical treatments or had any impacts in the study. No DLT was observed even in the highest dose cohort. Therefore, the MTD was identified as 75 mg in this trial.

Moreover, safety comparison between genders was conducted since gender ratio of subjects in the study was 1: 1. However, no gender difference was found in

that the AE incidences were similar in male and female subjects (male AE % = 43.75%).

DISCUSSION

This was the first study to investigate the safety and tolerability of T0001 in human body. All the six dose escalation cohorts displayed good safety and tolerability after SC injection of T0001. No significant difference occurred in different groups and genders.

Nevertheless, the two AEs of WBC count decrease were unexpected in this study, one of which occurred in 20 mg cohort on day 21 and the other in 75 mg cohort on day 14. Both AEs were spontaneously stabilized to normal within 7 days. A previous study demonstrated that the half-life of T0001 was 42.1–58.2 h and single use of T0001 almost completely metabolized after five half-lives (Wang *et al*., 2017). Therefore, the AE occurred 21 days after T0001 administration may be unrelated to the study drug. However, the AE reported on day 14 was considered to be T0001-related. Significant hematological disorders with serious complications, in particular leukopenia and neutropenia, have been reported in patients treated with etanercept or other TNF-α inhibitors for many times (Wenham, Gadsby, Deighton, 2008; Azevedo *et al*., 2012; Haroon, Daly, Harney, 2012). A post-marketing study showed that 3.2% of patients developed a hematological AE after receiving etanercept (Feltelius *et al*., 2005). The British Society for Rheumatology has updated their guidelines to monitor complete blood cell count regularly in patients on anti-TNF therapies in 2010 (Ding *et al*., 2010). Nevertheless, as far as we know, other guidelines have not yet been implemented. TNF-α is part of a complex network of cytokines that controls hematopoiesis, but the pathogenesis of the observed blood abnormalities is still unknown (Bessissow *et al*., 2012). On the one hand, TNF-α can elicit either a stimulatory or an inhibitory effect on the *in vitro* growth of hematopoietic progenitors (Jacobsen *et al*., 1994). On the other hand, TNF-α regulates the granulocyte macrophage colony-stimulating factor and several pro-inflammatory cytokines, such as IL-1, IL-6 and IL-8. It is, therefore, speculated that anti-TNF-therapy can induce bone marrow failure by blocking stem cell differentiation theoretically (Keystone, 2001).

The clinical safety results of etanercept, which supported the initial RA indication approvals, were involved to compare safety results with T0001 (European Medicines Agency, 2004). The most frequently reported AEs in etanercept-treated patients were injection site reactions (42%) and infections (58%). Other AEs included headache (17%), rhinitis (13%), rash (13%), nausea (12%), abdominal pain (9%), asthenia (7%), pharyngitis (7%) and back pain (5%). No complaints of headache, rhinitis and pharyngitis were recorded in T0001, implying that mutations of the two amino acid sites may reduce the likelihood of these AEs. However, differences in study design and subject status should be taken into account. Further clinical trials of T0001 with more subjects and longer follow-up periods are definitely needed in the future.

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REFERENCES

Alonso-Ruiz A, Pijoan JI, Ansuategui E, Urkaregi, A, Calabozo M, Quintana A. Tumor necrosis factor alpha drugs in rheumatoid arthritis: systematic review and metaanalysis of efficacy and safety. BMC Musculoskel Dis. 2008;9(1):52.

Azevedo VF, Silva MB, Marinello DK, Santos FD, Silva GB. Leukopenia and thrombocytopenia induced by etanercept: two case reports and literature review. Rev Bras Reumatol. 2012;52(1):110-2.

Bazzoni F, Beutler B. The tumor necrosis factor ligand and receptor families. New Engl J Med. 1996;334(26):1717-25.

Bessissow T, Renard M, Hoffman I, Vermeire S, Rutgeerts P, Assche G. non-malignant haematological complications of anti-tumour necrosis factor alpha therapy. Aliment Pharm Therap. 2012;36(4): 312-23.

Ding T, Ledingham J, Luqmani R, Westlake S, Hyrich K, Lunt M, et al. BSR and BHPR rheumatoid arthritis guidelines on safety of anti-TNF therapies. Rheumatology. 2010;49(11):2217-19.

European Medicines Agency. Enbrel, INN-etanercept. [citad 2004 Oct 1]. Available from: http://www.ema.europa.

eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000262/WC500027358.pdf.

Feltelius N, Fored CM, Blomqvist P, Bertilsson L, Geborek P, Jacobsson L, et al. Results from a nationwide post-marketing cohort study of patients in Sweden treated with etanercept. Ann Rheum Dis. 2005;64(2):246-52.

Food and Drug Administration. International Conference on Harmonisation; Guidance on M3 (R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals; availability. Notice [J]. Federal register, 2010;75(13):3471.

Goffe B, Cather JC. Etanercept: an overview. J Am Acad Dermetol. 2003;49(2):105-11.

Haroon M, Daly M, Harney S. Re-challenge with etanercept in patients with etanercept-induced neutropenia. Clin Rheumatol. 2012;31:151-5.

Jacobsen SE, Jacobsen FW, Fahlman C, Rusten LS, et al. TNF-alpha, the great imitator: role of p55 and p75 TNF receptors in hematopoiesis. Stem Cells. 1994;12(Suppl 1):111-28.

Josef SS, Daniel A, Iain BM. Rheumatic arthritis. Lancet. 2016;388(10055):2023-38.

Keystone EC. Tumor necrosis factor-α blockade in the treatment of rheumatoid arthritis. Rheum Dis Clin N Am. 2001;27(2):427-43.

Liu YJ, Yang T, Shen YJ, Wu JS, Wu F. Recombinant human TNFR-Fc fusion protein mutant. Patent No. PCT/CN2009/000037. Shanghai Fudan-zhangjiang Bio-Pharmaceutical Co. Ltd.; 2009.

Penel N, Kramar A. What does a modified-Fibonacci dose-escalation actually correspond to? BMC Med Res Methodol. 2012;12(1):103.

Sanmartí R, Ruiz-Esquide V, Hernández MV. Rheumatoid arthritis: a clinical overview of new diagnostic and treatment approaches. Curr Top Med Chem. 2013;13(6):698-704.

Shen Y, Li G, Gu C, Chen B, Chen A, Li H, et al. T0001, a variant of TNFR2-Fc fusion protein, exhibits improved Fc effector functions through increased binding to membrane-bound TNF-α. Plos One. 2017;12(5):e0177891.

Singh JA, Saag KG, Bridges SL, Bridges SL, Akl EA, Bannuru RR, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis & Rheumatology. 2016;68(1):1-26.

State Food and Drug Administration of China. Guideline for good clinical principles. [citad 2003 Aug 6]. Available from: http://samr.cfda.gov.cn/WS01/CL0053/24473.html

State Food and Drug Administration of China. Guidance for industry: estimating the maximum safe starting dose in initial clinical trials in healthy adult volunteers. [citad 2012 May 15]. Available from: http://samr.cfda.gov.cn/WS01/CL1616/90954.html.

US Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE) version 4.0. National Institutes of Health, National Cancer Institute. 2009;4(03).

Wang Y, Liu C, Chen S, Wang W, Dong L, Wang Q, et al. Pharmacokinetics and immunogenicity of T0001, a newly developed anti-TNFα fusion protein, in healthy volunteers. Eur J Clin Pharmacol. 2017;73(9):1095-1101.

Wenham C, Gadsby K, Deighton C. Three significant cases of neutropenia with etanercept. Rheumatology. 2008;47(3):376-7.

World Medical Association. Declaration of Helsinki. Ethical principles for medical research involving human subjects. [citad 2003 Jul 2]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2566407/pdf/11357217.pdf.

Yang T, Wang Z, Wu F, Tan J, Shen Y, Li E, et al. A variant of TNFR2-Fc fusion protein exhibits improved efficacy in treating experimental rheumatoid arthritis. Plos Comput Biol. 2010;6(2):e1000669.

Zeng QY, Chen R, Darmawan J, Xiao ZY, Chen SB, Wigley R, et al. Rheumatic diseases in China. Arthritis Res Ther. 2008;10(1):R17.

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