• Study Protocol

Chinese herbal medicine Xinfeng Capsule in treatment of rheumatoid arthritis: study protocol of a multicenter randomized controlled trial

Jian Liu, Chuan-bing Huang, Yuan Wang, Gui-qin Xu, Yuan-yuan Cheng, Yun-xia Feng, Lei Liu, Ya-jun Qi

Department of Rheumatology, the First Affiliated Hospital, Anhui University of Chinese Medicine, Hefei 230031, Anhui Province, China

BACKGROUND: Rheumatoid arthritis (RA), as a common systemic inflammatory autoimmune disease, affects approximately 1 in 100 individuals. Effective treatment for RA is not yet available because current research does not have a clear understanding of the etiology and pathogenesis of RA. Xinfeng Capsule, a patent Chinese herbal medicine, has been used in the treatment of RA in recent years. Despite its reported clinical efficacy, there are no large-sample, multicenter, randomized trials that support the use of Xinfeng Capsule for RA. Therefore, we designed a randomized, double-blind, multicenter, placebo-controlled trial to assess the efficacy and safety of Xinfeng Capsule in the treatment of RA.

METHODS AND DESIGN: This is a 12-week, randomized, placebo-controlled, double-blind, multicenter trial on the treatment of RA. The participants will be randomly assigned to the experimental group and the control group at a ratio of 1:1. Participants in the experimental group will receive Xinfeng Capsule and a pharmaceutical placebo (imitation leflunomide). The control group will receive leflunomide and an herbal placebo (imitation Xinfeng Capsule). The American College of Rheumatology (ACR) Criteria for RA will be used to measure the efficacy of the Xinfeng Capsule. The primary outcome measure will be the percentage of study participants who achieve an ACR 20% response rate (ACR20), which will be measured every 4 weeks after randomization. Secondary outcomes will include the ACR50 and ACR70 responses, the side effects of the medications, the Disease Activity Score 28, RA biomarkers, quality of life, and X-rays of the hands and wrists. The first four of the secondary outcomes will be measured every 4 weeks and the others will be measured at baseline and after 12 weeks of treatment.

DISCUSSION: The result of this trial will help to evaluate whether Xinfeng Capsule is effective and safe in the treatment of RA.

TRIAL REGISTRATION: This trial has been registered in ClinicalTrials.gov. The identifier is NCT01774877.

KEYWORDS: Xinfeng Capsule; rheumatoid arthritis; double-blind method; placebos; ACR criteria; quality of life; randomized controlled trials; clinical protocols

DOI: 10.3736/jintegrmed2013059

Liu J, Huang CB, Wang Y, Xu GQ, Cheng YY, Feng YX, Liu L, Qi YJ. Chinese herbal medicine Xinfeng Capsule in treatment of rheumatoid arthritis: study protocol of a multicenter randomized controlled trial. *J Integr Med*. 2013; 11(6): 428-434.

Received November 1, 2013; accepted November 5, 2013.

Correspondence: Prof. Jian Liu; Tel: 86-551-62838532; E-mail: liujianahzy@126.com

1 Introduction

Rheumatoid arthritis (RA), as a common systemic inflammatory autoimmune disease, affects approximately 1 in 100 individuals[1,2]. Signs and symptoms of RA include pain, swelling, stiffness, and loss of joint function. Disability and diminished health-related quality of

life are commonly experienced by patients with RA[3]. Currently, the causes of RA are not well understood, and the prognosis is often poor[4]. Disease-modifying antirheumatic drugs (DMARDs) are recommended by the American College of Rheumatology (ACR) for the treatment of RA[5]. Leflunomide, an isoxazole derivative, is one such DMARD and has been successfully used for the treatment of RA as a feasible alternative to methotrexate[6]. However, its use has also been associated with significant and serious adverse reactions involving the hematological, hepatic, immune, dermatological and respiratory systems. Patients may also stop leflunomide treatment for RA if they develop severe infections requiring hospitalization[7].

In China, Chinese medicine (CM) has long been utilized for the treatment of diseases such as RA[8]. Xinfeng Capsule, a patent Chinese herbal medicine, has been used in the treatment of RA in recent years[9,10], and studies involving animal subjects have helped shed light on the mechanism of action of Xinfeng Capsule[11-16]. However, presently, there are not any large-sample, multicenter, randomized controlled trials to evaluate the effects of Xinfeng Capsule. Therefore, we aimed to design a randomized, placebo-controlled, double-blind, multicenter trial to assess the efficacy and safety of Xinfeng Capsule in the treatment of RA.

2 Methods and design

2.1 Trial design

This is a randomized, placebo-controlled, double-blind, multicenter study. The sample ratio of the experimental group and the control group will be 1:1. This study began in May 2013 and will be finished in December 2014. The first participant was recruited on 26th July 2013. There have been no changes to the study methods after the trial commenced.

2.2 Participants

2.2.1 Inclusion criteria

Participants are enrolled in this trial if they meet the following criteria: (1) meet the ACR 2010 revised criteria[17] for RA and be classified into three functional classes: I, II or III; (2) between 18 to 65 years of age; (3) receive a stable non-steroidal anti-inflammatory drug (NSAID) dose during the 4 weeks prior to screening, or not take NSAIDs for at least 1 week prior to screening; (4) not take DMARDs during the 4 weeks prior to screening; (5) participants taking corticosteroids have a dose of ≤ 10 mg prednisone or equivalent and will have done so for more than 4 weeks before the trial; (6) agree to participate in the study, and sign an informed consent form.

2.2.2 Exclusion criteria

Participants will be excluded if they meet one of the following criteria: (1) patients have received intra-articular or systemic corticosteroid injections within 4 weeks of screening; (2) patients with a high disease activity (disease activity score (DAS) 3 variables (DAS 28-3) score > 5.1); (3) patients are diagnosed with any other chronic inflammatory diseases or connective tissue diseases, such as Sjögren's syndrome (also known as sicca syndrome) or systemic lupus erythematosus; (4) patients with severe cardiovascular, brain, lung, liver, kidney, or hematopoietic diseases; (5) pregnant women or breastfeeding mothers or those with known psychiatric disorders; (6) white blood cell count < 3.5×10^9/L, platelet < 90×10^9/L, hemoglobin < 85 g/L; (7) alanine aminotransferase (ALT) > 66 U/L, or aspartate aminotransferase (AST) > 57 U/L, or serum creatinine > 84 μmol/L; (8) patients with an active gastroduodenal ulcer or gastritis caused by the long-term use of NSAIDs; (9) patients that are found to be hypersensitive to the trial medication; (10) patients that have participated in other clinical trials within 4 weeks of screening.

2.3 Ethical considerations

The study will adhere to the ethical guidelines of the *Declaration of Helsinki*, and the study protocol was approved by the Medical Ethics Committee of the First Affiliated Hospital of Anhui University of Chinese Medicine in September 2012 with an approval number 2012AH-038-01. Written informed consent will be obtained from each participant prior to enrollment.

2.4 Participants recruitment

Patients with RA are recruited from the outpatient clinics or the inpatient departments of the following four hospitals: (1) the First Affiliated Hospital of Anhui University of Chinese Medicine; (2) the First Affiliated Hospital of Bengbu Medical College; (3) the First Affiliated Hospital of Anhui Medical University; (4) Yijishan Hospital of Wannan Medical College (the First Affiliated Hospital of Wannan Medical College).

2.5 Trial registration

This trial has been registered in ClinicalTrials.gov. The trial registration number is NCT01774877.

2.6 Interventions

In the experimental group, Xinfeng Capsule at a dose of three capsules is administered orally after meals, three times daily for 12 weeks; the placebo, an imitation leflunomide pill, will be taken orally once daily after a meal, for 12 weeks. In the control group, the leflunomide will be taken orally at a dose of 10 mg, once daily after a meal, for 12 weeks; the placebo, imitation herbal capsules, is administered three times daily after meals for 12 weeks. Participants taking stable doses of glucocorticoids and NSAIDs will continue with those medications as they did prior to their entry into the study.

2.7 Outcome measures

2.7.1 Primary outcome measure

The primary outcome measure will be the ACR 20% response rate (ACR20)[18], which will be measured every 4 weeks after randomization.