Study Protocol

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

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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

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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.
2.7.2 Secondary outcome measures

Secondary outcome measures will include the ACR50 and ACR70 responses, side effects of Xinfeng Capsule, DAS28, RA biomarkers, quality of life, and X-rays of the hands and wrists.

The ACR50 and ACR70 responses, DAS28, and the side effects of Xinfeng Capsule will be measured every 4 weeks.

RA biomarkers, life quality assessment, and X-rays will be measured at baseline and after 12-week treatment. RA biomarkers include rheumatoid factor, erythrocyte sedimentation rate, C-reactive protein, anti-cyclic citrullinated peptide antibodies, IgG, IgA, IgM, D-dimers, and coagulation function tests. Life quality assessments will include scores from a Health Assessment Questionnaire\(^\text{[21]}\), the Self-rating Depression Scale\(^\text{[20]}\), the Self-rating Anxiety Scale\(^\text{[21]}\), and a questionnaire on the quality of life with rheumatoid arthritis\(^\text{[21]}\). The anterior and lateral aspects of the hand and wrist are X-rayed.

2.7.3 Safety assessment

Vital signs (including respiration, heart rate, blood pressure and pulse rate) and any adverse events will be closely monitored during the study. Some biological indicators (including urine analysis, stool analysis, and electrocardiogram) will be measured before treatment and after the 12-week treatment period, while other biological indicators (including a complete blood count, ALT, AST, urea nitrogen, and creatinine) will be measured at weeks 0, 4, 8 and 12 during the treatment period.

The participants will have a follow-up assessment 4 weeks after treatment, either by telephone or in person, and will be asked to report clinical symptoms such as joint pain, arthrocele, and early morning stiffness.

The timeline of the participants’ anticipated progression through the trial is shown in Table 1.

2.8 Sample size

According to the literature\(^\text{[22]}\), the ACR20 of patients with RA receiving leflunomide is 62.54%, while our clinical experience puts the ACR20 of patients receiving the Xinfeng Capsule at 79.23%. The \(\alpha\)-value is set at 0.05 and the test

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Timeline of participants’ anticipated progression through the trial</th>
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<tbody>
<tr>
<td>Assessment</td>
<td>Treatment phase</td>
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<tr>
<td></td>
<td>Week 0</td>
</tr>
<tr>
<td>Signed informed consent</td>
<td>✓</td>
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<tr>
<td>Physical examination</td>
<td>✓</td>
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<tr>
<td>Medical history</td>
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<tr>
<td>Safety assessment</td>
<td>Complete blood count</td>
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<td>Urine analysis</td>
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<td>Stool analysis</td>
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<td></td>
<td>Electrocardiogram</td>
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<td></td>
<td>ALT, AST, urea nitrogen, creatinine</td>
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<tr>
<td>Efficacy measures</td>
<td>ESR, RF, CRP, IgA, IgG, IgM, coagulation, anti-CCP function, D-dimer</td>
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<td>X-rays</td>
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<td>Xinfeng Capsule side effects</td>
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<tr>
<td></td>
<td>HAQ, SDS, SAS, quality of life with RA questionnaire</td>
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<tr>
<td></td>
<td>Tender joint count, morning stiffness, swollen joint count, VAS, joint function</td>
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<tr>
<td>Randomization</td>
<td>✓</td>
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<td>Provided with the study drug</td>
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<td>Trial evaluation</td>
<td>Efficacy evaluation</td>
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<td>Patient compliance</td>
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<td>Adverse events</td>
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<td>Safety evaluation</td>
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ALT: alanine aminotransferase; AST: aspartate aminotransferase; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; CRP: C-reactive protein; anti-CCP: anti-cyclic citrullinated peptide; HAQ: Health Assessment Questionnaire; SAS: Self-rating Anxiety Scale; SDS: Self-rating Depression Scale; VAS: Visual Analog Scale.
power is 0.90; therefore $\beta = 1 - 0.90 = 0.10$. The formula for the sample size estimation is as follows:

$$n = \left( Z_a + Z_B \right)^2 \times \left( 1 + \frac{1}{k} \right) \times \left( P(1 - P)/(P_1 - P_2) \right)^2$$

$k$ is the ratio of the two sample sizes, which is 1:1. $P$ is the mean of the ACR20 effective rates of the control group ($P_1$) and the ACR20 effective rates of the Xinfeng Capsule group ($P_2$). The final sample size should be 127 in each group. With an anticipated dropout rate of 20% during the follow-up, the initial sample size for each group should be 152, or 304 in total for two groups.

2.9 Randomization and blinding

The block randomization design was adopted, and a computer-generated list of random numbers was used. SAS randomized program was written in accordance with the randomized parameters and stipulated randomized rules of centers, cases and blocks[24]. The Clinical Evaluation Center at the China Academy of Chinese Medical Sciences in Beijing saves the random number. The allocation sequence is concealed from the researcher who is responsible for enrolling and assessing participants. Participants are randomly assigned by a central randomization system to the experimental group or the control group. The experimental group receives Xinfeng Capsule and a placebo (in place of leflunomide); the control group receives leflunomide and a placebo (in place of Xinfeng Capsule).

Xinfeng Capsule is composed of Radix Astragali Mongolici, Semen Cociis, Radix et Rhizoma Tripterygi, and Scolopendra. Each capsule contains 0.4 g crude drug extract. Xinfeng Capsule and the placebo are produced by the Preparation Department of the First Affiliated Hospital of Anhui University of Chinese Medicine, Anhui Pharmacist Certification (Approval number: Z20050062).

Leflunomide and the placebo are produced by Fujian Huitian Biological Pharmacy Co., Ltd (Approval Number: H20050175).

The placebos, which are identical in appearance to the testing medicine but without the active ingredient, will be made from cane sugar that contains no medicine.

The subjects, investigators, and outcome assessors will not know the allocation groups of the patients based on the appearance of the given medication.

2.10 Statistical analysis

Statistical analyses will be performed by the Clinical Evaluation Center of China Academy of Chinese Medical Sciences in Beijing, China. The statisticians will be blinded to the allocation of the participants. SAS 9.0 statistical software packages will be used to analyze the data[27].

The intention-to-treat population will include all randomized patients who receive the assigned treatment at least once, and who have an evaluation of outcomes. The per-protocol population will include patients who fully complete the trial with good compliance. The safety population will include all patients who take the treatment at least once[26].

Analysis of the primary endpoint (the ACR20) will be performed by using chi-square test or Fisher’s exact test. Some secondary endpoints (measurement data) will be analyzed by using $t$ test or the rank sum test, and some secondary endpoints (numeration data) will be analyzed by using chi-square test or Fisher’s exact test. Trends over time and time-by-time interaction will be tested by a repeated measures analysis of variance. $P < 0.05$ indicates statistical significance. See Figure 1 for the procedure of this study.

3 Quality control

Quality control must be applied to each stage of the study, and specific measures are as follows: (1) The protocol and its attachments have been discussed and finalized by the principal investigators from each center, and each center is Grade III hospital with high-quality facilities and investigators. (2) At the beginning of the study, investigators involved in the trial attend training meetings, and the investigators clearly understand the proper operational protocols of the trial. (3) Midway through the study, an investigator meeting will be held to reinforce the study standards. (4) The laboratory and clinical evaluation methods used in the trial are standardized in their quality control. (5) The Clinical Evaluation Center at the China Academy of Chinese Medical Sciences, at regular periods, will monitor the trial to assess the progress of the trial.

4 Discussion

RA is an autoimmune disease, characterized by chronic inflammation in synovial joints. Effective treatment for RA is lacking because the clear etiology and pathogenesis of RA have not been fully elucidated[27]. The current pharmacological treatment of RA includes non-steroidal anti-inflammatory drugs, corticosteroids, and DMARDs. Newer biological agents that work by inactivation of pro-inflammatory cytokines are available for treatment of RA[28], but there are limitations in most of the current treatments. First, flare-up symptoms in the disease activity are often quickly controlled, but they tend to relapse after stopping the treatment. Second, long-term use of the pharmaceutical medications causes many side effects, such as gastrointestinal toxicity that may manifest as dyspepsia, ulcers and/or bleeding[29], or abnormal change of transaminase and white blood cells counts. Patients often find long-term treatment difficult to tolerate, due to the multitude of side effects.

According to the clinical manifestations, RA belongs to the category known as Bi Syndrome in CM terminology[30]. CM is a complete medical system with that has been in continuous
practice for over 3,000 years\(^{[31]}\), during which time it has been widely used for RA treatment\(^{[32]}\). But there lacks high-quality, modern scientific evidence that demonstrates efficacy and safety of CM in the treatment of RA.

In this 12-week, randomized, placebo-controlled, double-blind, multicenter clinical trial, we will evaluate the efficacy and safety of Xinfeng Capsule in patients with RA. Our results may suggest that Xinfeng Capsule can control inflammation, joint destruction, and balance the overall immune response. We are hopeful that this trial will provide some much-needed data that Xinfeng Capsule can be an effective and safe treatment option for patients with RA.

This study has a few limitations. It takes place over 16 weeks and does not track the effects of Xinfeng Capsule over a longer time period. Additionally, in real clinical practice, the usage of Xinfeng Capsules is often combined with pharmacological treatment because CM is frequently employed to help reduce the adverse effects of pharmacological treatments\(^{[33]}\). Therefore, future studies that take place over longer time periods and study the combined effects of CM with pharmacological agents may be useful to fully explore the efficacy and safety of Xinfeng Capsule in the treatment of RA.

5 **Fundings and acknowledgements**

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6 **Competing interests**

The authors declare that they have no competing interests.
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Submission Guide

Journal of Integrative Medicine (JIM) is a PubMed-indexed, peer-reviewed, open-access journal, publishing papers on all aspects of integrative medicine, such as acupuncture and traditional Chinese medicine, Ayurvedic medicine, herbal medicine, homeopathy, nutrition, chiropractic, mind-body medicine, Tai Chi, Qigong, meditation, and any other modalities of complementary and alternative medicine (CAM). Article types include reviews, systematic reviews and meta-analyses, randomized controlled and pragmatic trials, translational and patient-centered effectiveness outcome studies, case series and reports, clinical trial protocols, preclinical and basic science studies, papers on methodology and CAM history or education, editorials, global views, commentaries, short communications, book reviews, conference proceedings, and letters to the editor.

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