A multicenter, randomized, double-blind, placebo-controlled trial evaluating the efficacy and safety of Huang Qi Gui Zhi Wu Wu Tang granules in patients with rheumatoid arthritis

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by swelling, pain, and synovial damage. Effective methods lack in the treatment of RA. A traditional prescription in use for thousands of years in China, Huang Qi Gui Zhi Wu Wu Tang (HQGZWWT) granule is still chosen to relive pain and prevent joint malformation in RA patients. However, no evidence-based medical research has been organized to assess the effectiveness and safety of HQGZWWT granules for RA. Methods/design: We will conduct a multicenter, randomized, double-blind, placebo-controlled clinical trial to determine whether HQGZWWT granules can relieve pain and protect joints. We will randomly divide 120 patients with active arthritis for 3 months. Main measurements include ratio of 50 of ACR (American College of Rheumatology), change of DAS (28) from baseline to 3 months, and SHARP scores of van der Heijde from baseline to 12 months. SecondarymeasurementsincludeACR20, ACR70, Health Assessment Questionnaire-Disability Index (HAQ-DI), arthritis pain score, and Patient Global Assessment of Arthritis. The time points are set as baseline, 2 weeks, 1 month, 2 months, 3 months, 6 months and 12 months. In addition, the rate of change (score) in the ACR50 and DAS28 from the baseline to 2-week, 1-month, 2-month, 6-month, and 12-month follow-up are also the secondary outcome measures. Discussion: The findings of this research will elucidate the efficacy and safety of HQGZWWT granules and provide an alternative treatment for RA. In addition, our data will benefit the clinical decision-making on active RA and possibly be incorporated into future guidelines. Trial registration: ClinicalTrials.gov ID: NCT03593837. Keywords: Traditional Chinese medicine, Huang Qi Gui Zhi wu wu granules, placebo, active rheumatoid arthritis, multicenter, randomized controlled trial.

Background

Rheumatoid arthritis (RA), a chronic systemic inflammatory disease, mainly involves the synovium, leading to joint swelling, pain, bone erosion, and even deformity directly after over-accumulation of synovial fluid and fibrous tissues[1]. Its overall prevalence is lower than 1%, and annual incidence is about 0.05%[2, 3]. Currently, the interventional efforts for RA focus on reducing the degree of disease activity, improving physical function and life quality, and restraining the development of complications[4]. However, their outcomes are still unsatisfactory. So far, safe and effective anti-RA drugs have not yet been invented[5].

As a complementary and alternative medicine (CAM), Chinese herbal medicine may have the potential of remitting RA symptoms or lowering disease activity[6, 7]. HQGZWWT, a traditional Chinese medicinal formula with a history of thousands of years. To safeguard its quality for a longtime, HQGZWWT decoction can be extracted into HQGZWWT granule that has been used in our hospital for decades.

Although HQGZWWT granules have been used clinically for many years, the efficacy and safety of HQGZWWT granules still need evidence-based medical research. So we plan to conduct a randomized, double-blind, placebo-controlled trial to confirm the efficacy and safety of HQGZWWT granules in fighting against RA.

Methods/design

Study design

This study is a multicenter, randomized, double-blind, placebo-controlled clinical trial with 2 parallel arms (Fig. 1). The purpose of this study is to evaluate the efficacy and safety of HQGZWWT granules in the treatment of RA. We will recruit 120 patients from 3 medical institutions in Shanghai, China: Longhua Hospital Affiliated with Shanghai University of Traditional Chinese Medicine, Shanghai Seventh People's Hospital, and Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine. All patients will be randomly assigned to HQGZWWT granule group (experimental group) and placebo (control) group.

Patients in the experimental group will be required to take in WQGZWWT granules: twice a day, one package a time, after breakfast and dinner, for 90 days. Patients in the control group will use HQGZWWT placebo granules in the same manner.

Medication and administration

HQGZWWT granules will be manufactured, packaged and labeled by a factory in Shanghai based on standards for good manufacturing practice. The procedures in the making of HQGZWWT granules are listed in Table1. The crude herbs include: *Astragalus membranaceus* (Huang Qi), 9kg; *Cassia* twig(Gui Zhi), 9kg; *Paeonia lactiflora*pall (Shao Yao), 9 kg; *Radix Glycyrrhizae* (Gan Cao), Ziziphus zizyphus (Da Zao), 18kg (Tab.1). All materials will be supplied in one batch from Long Hua hospital and stored in a cool and dry place. The procedures in the making of HQGZWWT granules are as follows: 1) three rounds of extractions—firstly, put the herbs listed above in a ceramic container, then add 1000 litres of distilled water into the container to macerate the herbs for 1 hour, and then boil the mixture at 100°C for 1 hour for the first extraction; secondly, pour out the liquid extract, and add 1000 litres of distilled water and boil it at 100°C for 1 hour; thirdly, extract after adding 500 litres of distilled water and boiling for half an hour. 2) concentration: concentrate the mixture of 3 extractions at 60°C (660 mm Hg) and spray-dry the mixture into powders. Then the powders are smashed and screened through a mesh size of 80. At last the granules are packaged (4 g a bag) and stored in a clean room at 20°C and 50% humidity. HQGZWWT granule placebo is made up of HQGZWWT extraction (10%) and bitterant (90%). Pigment (such as lemon yellow, caramel pigment and sunset yellow), edible lactose essence, and starch which makes the color, taste/smell, and shape are similar to HQGZWWT granule.

Anti-rheumatic drugs (DMARDs), such as methotrexate and sulfasalazine, may be used during the observation period. Patients' original records are recorded. Non-steroidal anti-inflammatory drugs (NSAIDs) may be used to control patient's pain. The doctor responsible for the project will keep all medication records during the patients' treatment. In addition, other conditions and treatments should be documented in the management manual. Both groups will have a 3-month treatment and a 9-month follow-up. At seven time points (baseline, 2 weeks, 1 month, 2 months, 3 months, 6 months and 12 months after the treatment), visits will be scheduled for each patient. Each patient will be required to visit at least three time points. The plan is shown in Table 2.

Ethical issues

The trial will be conducted in accordance with the Declaration of Helsinki and Ethical Guidelines for Clinical Research, and the trial protocol has been approved by the Research Ethical Committee of Longhua Hospital Affiliated with Shanghai University of Traditional Chinese Medicine, Shanghai, China, (approval Number: 2018LCSY024) and the protocol has been registered on Clinical Trials (ClinicalTrials.gov ID: NCT03593837.).

Participants

Recruitment notice for research participants are publicized on posters and websites at three hospitals (Longhua Hospital Affiliated with Shanghai University of Traditional Chinese Medicine, Shanghai Seventh People's Hospital, Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine). All participants will receive informed consent prior to randomization. The research duration is 12 months.

Criteria:

Inclusion criteria:

Participants meeting the following requirement will be included.

· Diagnosed with rheumatoid arthritis according to the diagnostic criteria developed by the American College of Rheumatology in 1987.

· DAS28 score of 2.6 -5.1.

· Aged 18-70.

· Signing informed consent and ensuring test compliance.

· Women of childbearing age must undergo testing and have no pregnancy plan throughout the trial.

· Having no history of combined disease and active tuberculosis.

Exclusion criteria:

· Having any concurrent rheumatic disease, such as systemic lupus erythematosus, Sjogren’s syndrome, or severe osteoarthritis.

· Having tumor and cancer.

· Having a history of serious allergic reactions.

· Pregnant or lactating women and women of childbearing age who do not have an effective contraceptive method.

· Having cardiac, hematologic, respiratory, neurological, endocrine, renal, hepatic, gastrointestinal, or psychotic disease.

· Having infectious diseases.

· Showing poor compliance, and unwillingness to be followed-up.

· Showing alcoholism or drug dependency.

If the patient cannot complete the trial for severe pain or complications, the investigator will drop this patient out of the study. In addition, when the patient decides to withdraw, the investigator should record the reason. If the patient withdraws due to poor treatment, then the treatment will be considered as having no therapeutic effect.

Interventions

Experimental group (HQGZWWT granule group): Patients are given HQGZWWT granules (orally twice a day for 3 months and instructed to dissolve one package (4 g) with hot water (200 mg). Control group: HQGZWWT placebo will be used.

Supportive therapy of two groups: (1) Anti-rheumatic drugs (DMARDs) can be used during the observation period, such as methotrexate and sulfasalazine (the original dose will be maintained); (2) According to the patient's pain severity, non-steroidal anti-inflammatory drugs (NSAIDs) can be added; (3) Patients should provide a detailed list of drugs used during follow-up and observation period. Researchers must record the name of the drugs, dosage, frequency and duration.

Randomization and allocation

Randomization will be controlled by an independent clinical research coordinator (CRC). Specific operations will be performed by a trusted pharmaceutical company providing us HQGZWWT and placebo. The random number list will be developed by the Shanghai Medical Clinical Research Center using SAS9.1 PROC PLAN. The random number table will be generated in a ratio of 1: 1 using three test centers as a stratification factor, and managed by CRC. When a participant is recruited, the CRC will provide the pharmaceutical factory a number, and the pharmaceutical factory will randomly post the granules to the participants according to the random number list. The provided number and the corresponding number list will be recorded and will be locked in an office cabinet in the pharmaceutical factory.

Blinding

In this trial, all the researchers will not be in contact with the CRC, the clinical pharmacist, or the statistician. The CRC will be isolated from all researchers. The stuff in the pharmaceutical factory do not participant in the trials. Therefore, the investigator, doctors, nurses, statisticians and other participants have no access to the research information until the end of the trial when all statistical work is finished.

Outcome measures

Primary outcome measure

The primary analysis:
1) ACR50 from baseline to 3 months after treatment will be compared. 2) Disease Activity Score (DAS) 28 from baseline to 3 months after treatment will be compared

ACR (American College of Rheumatology) 50 is a standard to describe RA symptoms[8]. ACR 50 is met when the number of tender joints reduces by ≥50%, the number of swollen joints by ≥50%, and at least 3 of the following 5 indexes improves by ≥50%.:

· Patient's assessment on arthritis pain using a visual analogue scale (VAS) of 0-100 mm,

· Patient global assessment on disease activity using VAS scale (0-10),

· Patient's assessment on physical function and disability (Health Assessment Questionnaire - Disability Index (HAQ-DI)),

· Acute phase reactant value, such as erythrocyte sedimentation rate (ESR) or C-reactive Protein (CRP) level.

Similarly ACR20 is met when ≥20% is achieved in the reduction of tender joint number, swollen joint number, and indexes of 3 of the 5 other measurements[9].

Compared to ACR50 and ACR70, ACR20 has been accepted as the efficacy benchmark in RA clinical trials and has greater discriminant capacity to distinguish patients on active treatment from placebo control[8, 10, 11]. However, we chose ACR50 as the primary index for that ACR50 can provide more useful information than ACR70[12, 13] .

The DAS28 is an index calculating the number of painful and swollen joints (28 joints, i.e. shoulders, elbows, wrists, metacarpophalangeal and proximal interphalangeal joints, and knees), erythrocyte sedimentation rate and the score of global assessment[14]. The formula of DAS 28 is $0.56\times\sqrt{(28\text{ painful joint count})} + 0.28\times\sqrt{(28\text{ swollen joint count})} + 0.70\times(\ln \text{ESR}) + 0.014\times\text{GH}$. ESR refers to erythrocyte sedimentation rate. GH is the patient's general health visual analog scale (0–10 mm) [15,16, 17].
The ACR 50 and DAS 28 will be estimated at 5 time points (baseline, 0.5 month, 1 month, 2 months, 3 months after the treatment), and 6 months and 12 months after intervention begins.

Secondary measurements

The secondary outcome will be to compare the rate of change in the ACR20/70, HAQ-DI, Patient Assessment of Arthritis Pain, Patient Global Assessment of Arthritis, and AIS from baseline to 2 weeks, 1 month, 2 months, 3 months, and at the 6 months' and 12 months' follow-up. The rate of change in the ACR50 and DAS28 from the baseline to 2 weeks, 1 month, 2 months, and 6 months' and 12 months' follow-up are also secondary outcome measures, and the change in score on the 36-item Short-Form

Health Survey Questionnaire (SF-36) from baseline to 1 month, 2 months, 6 months, and 12 months is also calculated.

HAQ-DI is a subscale of ACR20 / 50/70 that reports biochemical and physical conditions. It has been widely used in RA clinical trials to assess disease activity and patient disability[18]. The HAQ-DI measure shave eight dimensions of functional activity: pruning, dressing, rising, eating, walking, personal hygiene, reach, grip, and other routine activities. Each item has 4 degrees ranging from 0 to 3. "0" refers to "no functional difficulty", "1" to a bit of functional difficulty, "2" to very much functional difficulty, and "3" to no ability to work. HAQ-DI score 0-1 means mild to moderate functional difficulty; 1-2 means moderate to severe disability; and 2-3 means generally severe disability[19].

A comprehensive assessment of patients with joint pain and arthritis has been performed using 2 criteria (ACR 50/70) and visual analogue scale (VAS) 0-100 mm.[9]

People with RA often have sleep disorders that worsen as RA deteriorates[9, 20]. The Athens Insomnia Scale (AIS) can help patients quantitatively self-evaluate sleep disorders with a psychometric instrument that includes eight indicators for sleep induction, awakenings during the night, final awakening, total sleep duration, sleep quality during the night, wellbeing during the night, functioning capacity during the day time, and sleepiness during the day time. The score for each indicator ranges from 0 to 3, and the total score is 24 points. The higher the score, the worse the sleep quality, and vise versa[21].

The SF-36 measures eight dimensions, including vitality, body function, body aches, general health perceptions, body functions, emotional function, social function and mental health. SF-36 is widely used in the evaluation of quality of life in patients with rheumatoid arthritis[9, 22].

In addition, concomitant medications are also recorded as secondary outcomes.

Safety assessments

The HQGZWWT granule has been used for hundreds of years in China, and the herbs in the HQGZWWT granule are safe according to the recommended amount in Pharmacopoeia of the People's Republic of China (2015 version). The incidence and severity of adverse reactions are observed in each testing. Clinical and laboratory tests on joint swelling, tenderness, morning stiffness, and average grip strength in both hands are based on DAS28, visual analogue scale (VAS) of 100 mm, HAQ - disability Index. The assessment time will be baseline to 2 weeks, 1 month, 2 months, 3 months, and at the 6-month and 12-month after intervention. Standard blood and biochemical tests, as well as urine analysis, are also performed at the beginning and ending of this trial.

In the case of serious adverse events, we will provide emergency services and report the incident to the Institutional Review Committee within 24 hours. We will break the blind method, provide the participants with an entire medical history, and record it in due course.

Participant timeline

The participants will be researched for 24 months, from 1st November 2018 to 1st November 2020. The final visit of all participants is scheduled on 31st December, 2020.

Statistical analysis

According to the intention-to-treat principle for effectiveness and safety analysis, the method of last observation carried forward will be applied in analysis of missing values. All statistical analysis will be conducted using SPSS (version 21). P<0.05 is statistically significant. The mean and standard deviation will be used for the description of continuous variables on clinical outcomes, demographics and others. The percentage is used to categorize the variable's description. Continuous variables subject to normal distribution will be compared by *t* test or non-parametric test to illustrate the differences between groups.

Sample size calculation

Formula of sample size calculation is n1=n2=. In this formula, N1 and N2 are the number of HQGZWWT granules and placebo group. =1.96 when type 1 error is 0.05;=1.282 when type II error is 0.1 in two-sided tests. is the mean of and [25]. It was estimated that approximately 50 participants per group were needed to achieve 90% power and a (two-sided) 5% significance level in detecting treatment differences. We estimate that 120 patients (60 in each group) will be enrolled to ensure that the results are statistically significant, considering a reduction rate of 20%.

Data collection and monitoring

This is a 12-month clinical trial in which participants will receive 3 months of medication and 9 months of follow-up. Disease activity will be assessed at seven time points (baseline, 2 weeks, 1 month, 3 months, 2 months, 6 months and 12 months), and the safety at six time points (baseline, 1 month, 2 months, 3 months, 6 months and 12 months). Longhua Hospital affiliated with Shanghai University of Traditional Chinese Medicine is responsible for quality control.

Discussion

RA may lead to complications such as severe infection and malignant tumor[28,29,30]. Inappropriately treating rheumatoid arthritis brings back with irreversible joint deformity and disability, which seriously affects the patients' working ability and life quality of life. Doctors used DMARDs and MTX to treat RA patients with a good improvement. However, in MTX-resistant patients, the effective rate is only 25-40% [24,25,26,27]. Therefore, it is urgent to develop new effective therapies. Chinese traditional medicine has accumulated rich clinical experience in the treatment of RA. HQGZWWT granule has been used as a classic prescription of RA for thousands of years. Its effectiveness has already been experienced, but still needs to be scientifically confirmed with solid evidence[31,32]. Therefore, we plan to carry out this multicenter randomized controlled clinical research. We evaluated the lesion condition with ACR 50, DAS28 and van der Heijde modified Sharp score, and the life quality with secondary HAQ-DI, AIS and SF-36.

To the best of our knowledge, this is a well-designed, randomized, controlled trial investigating the efficacy of the HQGZWWT pill for the treatment of active RA. This study is built on our preliminary open experiment with a small sample, as well as hundreds of years' use of the HQGZWWT decoction in China for the treatment of RA. The findings of this research will elucidate the efficacy and safety of HQGZWWT granules and provide an alternative treatment for RA. In addition, our data will benefit the clinical decision-making on active RA and possibly be incorporated into future guidelines.

Trial Status

This protocol is version 1. The trial is currently enrolling participants, the recruitment began in 1st November 2018, and we will complete the recruitment in 1st November 2020.

Abbreviations

RA: rheumatoid arthritis; HQGZWWT: Huang Qi Gui Zhi Wu Wu Tang; ACR: American College of Rheumatology; CAM: complementary and alternative medicine; DMARDs: Anti-rheumatic drugs; NSAIDs: Non-steroidal anti-inflammatory drugs; CRC: clinical research coordinator; ACR: American College of Rheumatology; HAQ-DI: Health Assessment Questionnaire - Disability Index; ESR: Acute phase reactant value such as Erythrocyte Sedimentation Rate; CRP: C-reactive Protein; SF-36: 36-item Short-Form Health Survey Questionnaire; VAS: visual analogue scale; AIS: Athens Insomnia Scale.

Declarations

Availability of data and materials

Not applicable.

Consent for publication

Not applicable.

Acknowledgements

QS, QQL and YJW supervised and coordinated the clinical trial, conceived of the study and revised the manuscript critically for important intellectual content.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

YL, YRW and ZJX are co-first authors of this manuscript, contributing equally in designing, conducting the trials and drafting the manuscript. All authors will participate in the design of the study and performing

the trial. QQL will supervise the clinical trial. LL, JCM, LBX, XHG, MY, XJC, QS and YJW are responsible for recruiting the participants. YL, and ZJX will participate in statistical analysis. All authors have read and approved the final manuscript.

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Ethics approval and consent to participate

Human ethics approvals were obtained from the the Research Ethical Committee of Longhua hospital, affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China (approval Number: 2018LCSY024). All adult participants will provide written informed consent before participating.

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Table

Due to technical limitations, the table is only available as a download in the supplemental files section.

Figures

Figure 1

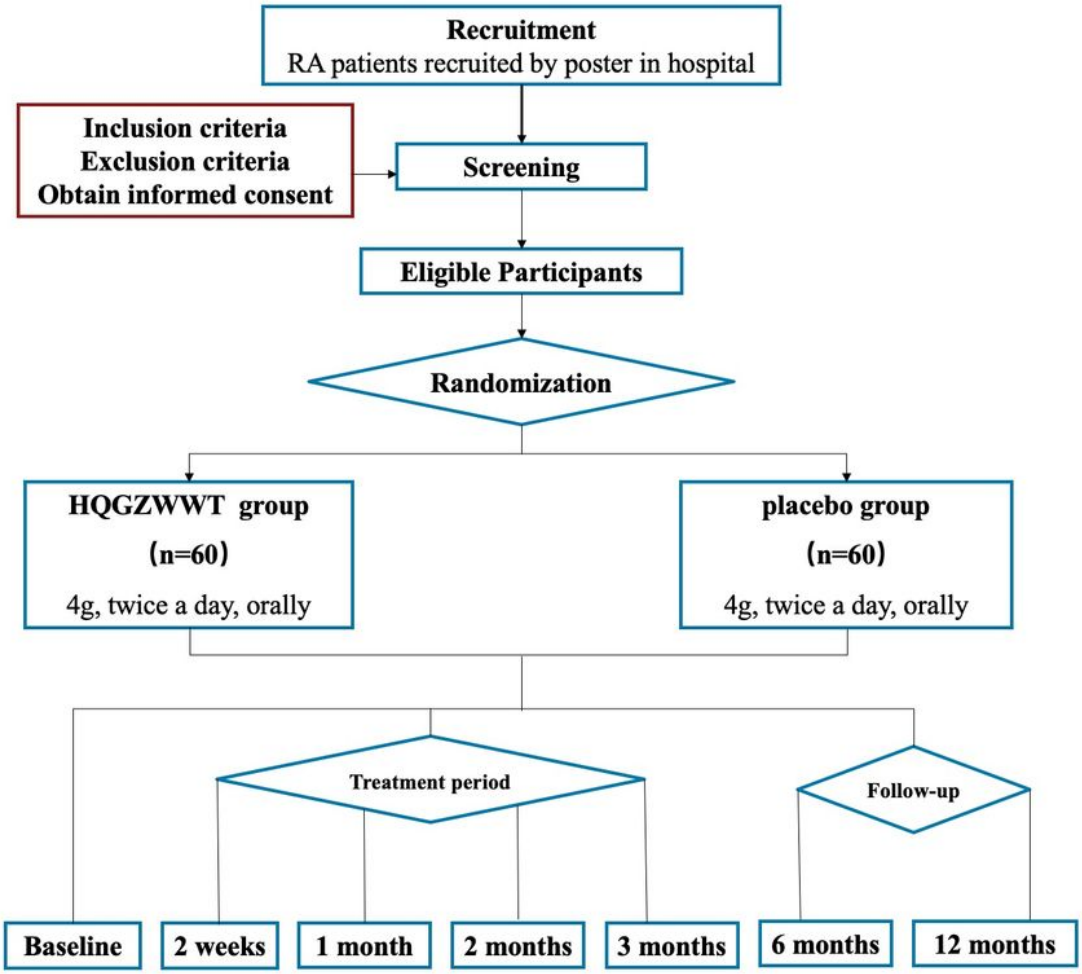

Figure 1

Project overview. RA, rheumatoid arthritis; HQGZWWT, Huangqi GuiZhi WuWu Tang.

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