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STUDY PROTOCOL

Ruanjian Qingmai Granules for the Treatment of Early Symptomatic Peripheral Arterial Disease: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial Protocol

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Purpose: Peripheral arterial disease (PAD) is a chronic ischemic disease caused by atherosclerosis of the lower extremities, with early clinical symptoms manifesting mainly as intermittent claudication. Current treatment of PAD is based on the control of cardiovascular risk factors. However, even vasoactive drugs are not ideal for improving ischemic symptoms in the lower limbs of PAD patients. Ruanjian Qingmai granules, derived from the classic formula of the late Professor Jiuyi Xi, a famous traditional Chinese medicine doctor in Shanghai, have good clinical efficacy in the treatment of the pattern of blood vessel stasis and obstruction of PAD and have been used by more than 600,000 PAD patients over the past three decades. This study aims to evaluate the efficacy and safety of Ruanjian Qingmai granules in patients with symptomatic PAD.

Patients and methods: A prospective, center-randomized, double-blind, placebo-controlled clinical trial will be conducted at 9 grade A tertiary hospitals in Shanghai. It is anticipated that 250 patients with early symptomatic PAD will be recruited and randomized to the control and intervention groups (1:1 ratio of central randomization). Subjects will be treated with Ruanjian Qingmai granules or placebo at 6 g twice daily for 16 weeks. The primary efficacy indicators are the pain-free walking distance and maximum walking distance. The secondary efficacy indicators are the ankle-brachial index, walking impairment questionnaire, quality of life score, and Chinese medicine syndrome score.

Conclusion: Positive results from this study will demonstrate the efficacy and safety of Ruanjian Qingmai granules in improving ischemic symptoms in patients with symptomatic PAD.

Clinical Registration: This study has been registered with the Chinese Clinical Trials Registry (ChiCTR2200056109, Date: 02/01/2022, https://www.chictr.org.cn/showproj.html?proj=150982).

Keywords: peripheral arterial disease, Ruanjian Qingmai granules, intermittent claudication, efficacy, randomized controlled trial, protocol

Introduction

Peripheral arterial disease (PAD) is a chronic progressive disease caused by inadequate blood flow to the lower extremities due to atherosclerosis, often leading to adverse clinical outcomes such as refractory ischemic ulcers or amputation.[1] PAD currently affects more than 200 million people worldwide[2] and typically presents with intermittent claudication, rest pain, and critical limb ischemia.[3] As a chronic disease with insidious onset, sudden changes in

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condition, and poor prognosis,[4] timely intervention and treatment at an early stage to prevent further worsening of limb ischemia is a critical clinical issue that needs to be addressed today.

Early PAD is difficult to detect or diagnose because of its insidious symptoms. Patients with symptomatic PAD are a group of patients with typical or atypical clinical symptoms in early PAD. The main treatment methods for patients with early symptomatic PAD are exercise therapy, pharmacological control, and revascularization.[5] Exercise therapy, the first-line therapy to improve intermittent claudication, is difficult to achieve due to poor patient compliance.[6] Vasoactive drugs aimed at improving walking impairment in patients with symptomatic PAD, such as cilostazol, beraprost sodium, and pentoxifylline, are not as effective as they could be.[7,8] In a randomized controlled clinical trial, the effect of 6 months of treatment with beraprost sodium was not significantly different from the placebo group.[9] Another study showed that patients treated concomitantly with rivaroxaban and aspirin had a significantly higher risk of major bleeding, although the incidence of critical limb ischemia was reduced.[10] Similarly, a study with a 3-year follow-up found that revascularization for intermittent claudication in patients with symptomatic PAD provided no additional early benefit and even increased the risk of amputation in some patients.[11] Therefore, the aim of this study was to find new treatment options that can be applied in addition to existing therapies for symptomatic PAD to further improve patients' walking ability and slow PAD progression.

Chinese medicine has a history of several thousand years in the treatment of PAD, and its therapeutic advantages include low side effects, low economic cost, and suitability for long-term use by patients.[12] Ruanjian Qingmai granules, derived from the classical formula of the late Professor Jiuyi Xi, a famous Chinese medicine doctor in Shanghai, have good clinical efficacy in the treatment of the pattern of blood vessel stasis and obstruction in PAD and have been used by more than 600,000 PAD patients over the past three decades. Recent studies have shown that Ruanjian Qingmai granules can alleviate ischemic inflammation,[13] improve the lipid profile,[14] and promote the establishment of collateral circulation.[15] A recent small randomized controlled trial demonstrated the efficacy and safety of Ruanjian Qingmai granules in the treatment of patients with PAD after revascularization.[16] However, stronger clinical evidence is still needed to confirm their effect on improving clinical symptoms in symptomatic PAD under basic treatment. This will open new avenues in the treatment of PAD and provide clinicians with better treatment options.

In summary, researchers will conduct this clinical trial to evaluate the efficacy and safety of Ruanjian Qingmai granules in patients with symptomatic PAD.

Methods

Study Design

This study is a multicenter, prospective, centrally randomized, double-blind, parallel-controlled clinical trial. The study flow (Figure 1) was designed in strict accordance with the SPIRIT statement (Figure S1).

Inclusion and Exclusion Criteria

Patients aged $40 < \text{age} \leq 80$ years who meet the diagnostic criteria of the European Society of Cardiology guidelines for the management of peripheral arterial disease[1] will be included in this study. The subjects must also meet the diagnostic criteria of "pattern of blood vessel stasis and obstruction" in Chinese medicine.[17] The clinical manifestation is intermittent claudication, and the claudication symptoms should be stable for at least 3 months or more. Subjects should have an ankle-brachial index (ABI) of ≤ 0.9 at rest or after exercise and lower extremity artery stenosis or occlusion as indicated by Doppler ultrasound, CTA, MRA, or DSA within one month prior to enrollment. Women of childbearing potential must have a negative pregnancy test and not be breastfeeding at the time of the screening visit. Subjects must be able and willing to attend the scheduled visit and comply with the study procedures; they should agree to participate in this clinical trial and voluntarily sign the informed consent form.

Exclusion criteria include the following: patients with the presence of other diseases affecting walking distance, such as lower extremity ulcers, gangrene, arthrosis, spinal lesions, lower extremity venous disease; patients with current acute or severe limb ischemia, those planning lower extremity revascularization, and those with a history of amputation; patients diagnosed with cardiovascular disease such as unstable angina, myocardial infarction, heart failure (class III–IV),

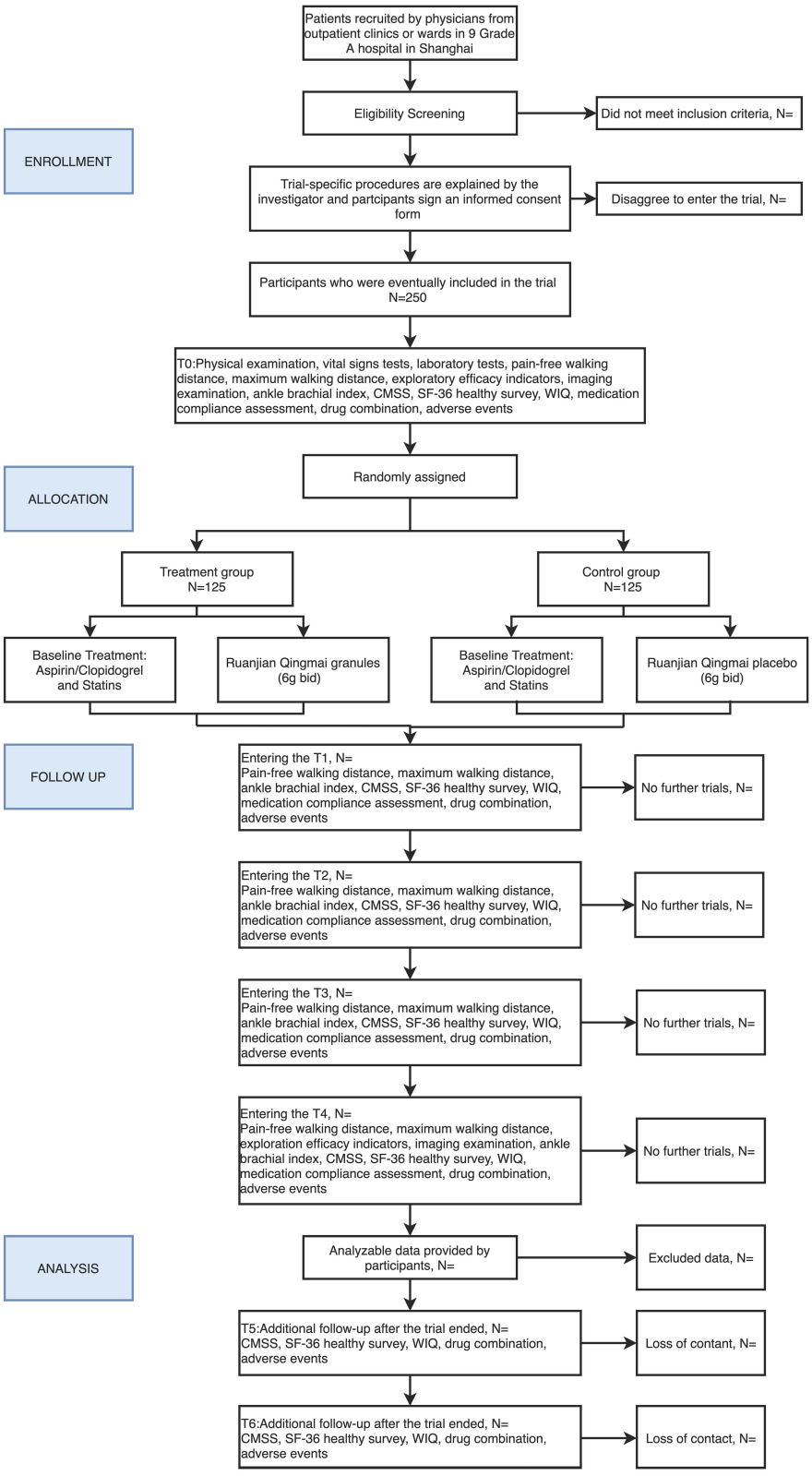

Figure 1 The flow diagram of the trial. T0, 0–1 day treatment (baseline); T1: 4 week treatment; T2: 8 week treatment; T3: 12 week treatment; T4: 16 week treatment; T5: 20 week or 1 month after treatment; T6: 24 week or 2 month after treatment; CMSS: Chinese medicine syndrome score; SF-36, 36-Item Short-Form; WIQ, Walking Impairment Questionnaire.

and transient ischemic attack within the past 3 months; patients with severe poor glycemic control (defined as HbA1c >10. 0%) and severely inadequate blood pressure control (defined as systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg); patients with occlusion of the common femoral and femoral-iliac arteries or occlusion of the arteries above the groin; patients with inflammatory vascular diseases such as multiple aortitis, thrombo-occlusive vasculitis, and other non-PAD; patients with abnormal liver or renal function, malignancy, psychiatric abnormalities, etc., who are considered by the investigator to be unsuitable for this study; patients with previous allergy to any of the investigational drugs or excipients or a history of allergy to other similar products; and patients who have participated in clinical trials of other drugs within the previous 6 months.

Case Drop-Out and Management

All subjects who sign the informed consent form will be screened and qualified for inclusion in the study, regardless of when or why they withdraw, and they will be defined as drop-out cases if they do not complete the observation period specified in the protocol. Those who recover before the end of treatment and discontinue treatment of their own volition will not be considered drop-out cases.

In this study, the following patients will be considered to have dropped out: (1) Participants with poor medication compliance, a final dose less than 80% or greater than 120% of the expected dose, use of concomitant medications prohibited by this protocol, or unilateral changes in the treatment regimen; (2) Patients who are natural dropouts or are lost to follow-up during the trial, including those who show treatment efficacy during treatment but are unable to complete the entire course of treatment, resulting in incomplete information and other factors that affect the assessment of efficacy and safety; and (3) Cases in which serious adverse events or complications occur that make it inappropriate to continue the trial and cause the trial to be terminated.

After a subject is dropped, the investigator should contact the subject, if possible, to inquire about the reasons, record the last treatment time, and complete the assessment items that can be completed. In cases of withdrawal from the study due to allergic reactions, adverse reactions, or treatment failure, the investigator should provide appropriate treatment according to the actual situation, as well as complete the efficacy assessment form and the "reason for drop-out" section of the case report form (CRF). The CRF should be completed for all patients enrolled and treated, whether or not they drop out.

Termination Criteria

Drug discontinuation is the premature discontinuation of study treatment for any reason by a subject who has been randomized to participate in the study. Subjects are free to withdraw from the study intervention and/or the study at any time for any reason, without giving a reason and without penalty or consequence. The investigator may also terminate a subject's participation in the study at any time if the subject's clinical condition so requires. Criteria for subject discontinuation include (1) noncompliance and/or significant deviation from the study protocol; (2) lack of satisfactory efficacy, need for in-subject intervention, or the investigator's determination that the subject requires other treatment; (3) safety concerns; (4) loss to follow-up; (5) withdrawal of informed consent; (6) discontinuation of the drug according to the judgment of the investigator to maximize patient benefit; and (7) termination of the study by the sponsor.

In all cases, the reason for withdrawal and the withdrawal date must be recorded on the CRF and in the subject's medical record. Subjects must be followed up to determine whether the reason for withdrawal was an adverse event. If so, this must be reported by following the adverse event reporting procedures.

In all cases, the reason and date of withdrawal must be recorded on the CRF and in the subject's medical record. Subjects must be followed up to determine if the reason for withdrawal was an adverse event. If so, this must be reported by following the adverse event reporting procedures.

If a subject withdraws from the study or the study intervention is terminated early, all planned procedures at the end of the study should be included on the CRF. Subjects who withdraw will not be replaced, regardless of the reason for withdrawal. All participants whose adverse events persist at the time of withdrawal or at the end-of-study follow-up visit must be followed at appropriate intervals until the adverse event resolves or the condition is judged to be no longer clinically significant or becomes chronic and can be fully and clearly defined.

Patient Recruitment

Patients will come from the outpatient clinics and wards of traditional Chinese medicine surgery or vascular surgery at 9 Grade A tertiary hospitals in Shanghai. The nine hospitals include (1) Shanghai TCM-Integrated Hospital, Shanghai University of Traditional Chinese Medicine; (2) Longhua Hospital, Shanghai University of Traditional Chinese Medicine; (3) Shuguang Hospital, Shanghai University of Traditional Chinese Medicine; (4) Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine; (5) Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine; (6) Zhongshan Hospital, Fudan University; (7) Pudong Hospital, Fudan University; (8) Shanghai Sixth People's Hospital, Shanghai Jiao Tong University; and (9) Renji Hospital, Shanghai Jiao Tong University. The trial is led by the Diagnosis and Treatment Center of Vascular Disease, Shanghai TCM-Integrated Hospital, Shanghai University of Traditional Chinese Medicine.

Blinding and Grouping

Approximately 250 subjects are expected to be enrolled in this study and randomized in a 1:1 ratio to either the treatment group or the control group, stratified by ABI (≥ 0.6 and < 0.9, ≥ 0.4 and < 0.6, < 0.4), Fontaine class, and sex (male, female). Allocation is expected to be completed in 9 centers. A center-randomized system will be used. The randomization method for this study is stratified block randomization, and the electronic data capture (EDC) system is linked to the randomization system. After the screening period, once a subject's eligibility for enrollment is confirmed, the EDC system will be logged into for randomization and drug distribution, the randomization number and drug number for that subject will be obtained, and the corresponding study drug will be obtained and administered to the subject according to the drug number provided by the system. Each randomization number and drug number will correspond to one subject, and the same randomization number or drug number will not be used repeatedly. In the event of an emergency, such as participant pregnancy, drug toxicity, or drug overdose, an urgent unblinding procedure will be conducted. The data management personnel will access the unblinded data through the EDC system and inform the clinical researchers accordingly. Additionally, they must record the time, location, and reason for the urgent unblinding.

Trial Drugs

Ruanjian Qingmai granules are composed of sargassum, ostreae concha, typhae pollen, sedi herba, and siegesbeckiae herba. The Ruanjian Qingmai granules and the placebo used in this study are packaged and labeled by Shanghai Liantang Pharmaceutical Co. in accordance with standard operating procedures (SOPs), guidelines for quality management practices in drug manufacturing, guidelines for quality management practices in clinical trials, and relevant laws and regulations. The specific Chinese herbal ingredients in Ruanjian Qingmai granules are listed in Table 1. The placebo is a one-tenth active ingredient preparation of the original drug, and its packaging, specifications, color, odor, and taste are identical to those of Ruanjian Qingmai granules. The investigator will ensure that a responsible person (eg, pharmacist) receives the study medication supplied by the investigator. The investigator or pharmacist will maintain a list of study treatment products and records of counts. Study drug counts must be documented throughout the trial.

Table 1 Components of Ruanjian Qingmai Granules

Chinese romanization	Scientific name	Family	Using parts	Original dosage (g)	Daily dosage(g)
Pu Huang	*Typha. angustifolia* L.	Typhaceae	Dried pollen	15	1.8
Hai Zao	*Sargassum pallidum* (Turn.) C. Ag	Sargassaceae	Dried Algae	15	1.8
Chui Pen Cao	*Sedum sarmentosum Bunge*	Crassulaceae	Dried whole herb	30	3.6
Xi Xian Cao	*Siegesbeckia orientalis* L.	Asteraceae	Dry above ground part	10	1.2
Mu Li	*Ostrea gigas* Thunberg	Ostreidae	Shell	30	3.6

Interventions

The treatment group will receive Ruanjian Qingmai granules (6 g/pack) twice daily with lukewarm water. The control group will receive placebo in the same dose and manner. Treatment will last for a total of 16 weeks. Concomitant medications allowed during the treatment period include medications for the basic treatment of PAD patients (such as aspirin, clopidogrel, and statins) and medications for the treatment of comorbidities (such as antihypertensive, hypoglycemic, lipid-lowering, and anticoagulant medications). However, the use of vasodilators that directly treat PAD, such as cilostazol and beraprost sodium, is prohibited. The use of Chinese herbal preparations that have been shown to significantly relieve PAD symptoms, such as ginkgo biloba capsules and Tongmai granules, is also prohibited. Patients' medications used within 4 weeks prior to randomization will be recorded in the original file and on the CRF. All concomitant medications used during the patient's study period, including the name of the medication, the dose used, the frequency of use, and the time of use, must be collected and reported on the CRF. Concomitant medications should be kept to a minimum throughout the study. If there are any concerns, the sponsor must be consulted, and the decision to withdraw from the study may need to be made jointly by the sponsor and the investigator if the patient is taking medications that may interfere with the determination of study efficacy. At each follow-up visit during the treatment period, the investigator must assess the subject's compliance with the study drug, including compliance with the basic treatment. Compliance with study drug use will be recorded on the CRF for each subject. The investigator will decide whether the subject needs to be withdrawn from the study based on the subject's assessment of compliance.

Efficacy Indicators

The primary efficacy endpoints for this study are the change from baseline in terms of the pain-free walking distance and maximum walking distance after 16 weeks of treatment. Secondary efficacy indicators are the changes from baseline for the Chinese Medicine Syndrome Score, Walking Impairment Questionnaire (WIQ) score, and 36-Item Short-Form (SF-36) health survey at weeks 4, 8, 12, and 16. Exploratory efficacy indicators include pre- and posttreatment changes in carotid/superficial femoral artery intima-media thickness and carotid/superficial femoral artery vascular stiffness, as well as changes in serum levels of inflammatory factors (including interleukin (IL)-1β, IL-6, IL-8, Il-10, C-reactive protein (CRP), serum amyloid A protein (SAA), and tumor necrosis factor-α (TNF-α)) in patients before and after treatment.

Safety

An adverse event is defined as the occurrence or worsening of any symptom, condition, syndrome, or disease that occurs in a subject during the observation period of a clinical trial and that would affect the patient's health. It also includes clinically relevant conditions identified during laboratory or other diagnostic procedures, such as those that require unplanned diagnostic procedures or that result in withdrawal from the trial, or laboratory tests that exceed 20% of normal values and are considered abnormal. The most frequently observed adverse reactions to this drug in clinical practice are loss of appetite and constipation. However, it is important to note that drug allergy and abnormalities in liver and kidney function cannot be ruled out. From the time participants are randomized, the investigator will closely monitor each participant for evidence of treatment intolerance and clinical or laboratory evidence of adverse events.

All adverse events occurring during the study will be followed until they resolve or are judged to be no longer clinically relevant or until they become chronic and can be adequately characterized (all follow-up results will be reported to the sponsor). Since it is impossible to predict how long the above follow-up will take, the investigator will record follow-up data generated after the subject completes the poststudy visit. Full details of this follow-up will be described in the study report, as appropriate. If an adverse event progresses to a serious event during the follow-up or if a new serious event that cannot be excluded as being related to the investigational product occurs in a subject, the investigator must report the information immediately to the sponsor.

Trial Procedure

Subjects will be required to have 5 face-to-face follow-up visits after the treatment: on the day of randomization and at week 4, week 8, week 12, and week 16. In addition, they will be required to receive 1 telephone follow-up visit per month for 2 months after the completion of treatment (Table 2).

Table 2 Time Schedule of Enrollment, Intervention, General Information, and Efficacy Indicators and Measures of the Trial

Time point	Intervention period (T1~T4)						Follow-up period (T5~T6)	
	Screening stage	T0:0–1 day treatment (baseline)	T1:4 week treatment	T2:8 week treatment	T3:12 week treatment	T4:16 week treatment	T5:20 week 1 month after treatment	T6:24 week 2 month after treatment
Enrollment								
Eligibility screening	√							
Informed consent	√							
Allocation		√						
Intervention								
Ruanjian Qingmai granules/Placebo		√	√	√	√	√		
General information								
Demographic data	√							
Physical examination and vital signs tests[a]	√	√				√		
Laboratory tests[b]		√				√		
Pregnancy tests[c]	√							
ECG	√					√		
Efficacy indicators and measures								
Pain-free walking distance		√	√	√	√	√		
Maximum walking distance		√	√	√	√	√		
Exploratory efficacy indicators [d]		√				√		
Imaging examination[e]		√				√		
Ankle brachial index	√	√	√	√	√	√		
CMSS		√	√	√	√	√	√	√
SF-36 healthy survey		√	√	√	√	√	√	√
WIQ		√	√	√	√	√	√	√
Medication compliance assessment		√	√	√	√	√		
Drug combination	√	√	√	√	√	√	√	√
Adverse events		√	√	√	√	√	√	√

Note: [a]If the screening phase and T0 occur on the same day, the physical examination and vital signs assessment for T0 may be exempted. Vital signs tests includes heart rate, body temperature, respiratory frequency blood pressure, and saturation of blood oxygen. [b]Laboratory tests include blood routine examination, liver function tests, renal function tests, coagulation function tests, D-dimer tests, blood lipid tests, fasting blood glucose tests, and HbA1c tests. [c]Only women of childbearing age are allowed to participate in pregnancy tests. [d]The exploratory study will be conducted only in selected hospitals. Exploratory efficacy indicators include carotid/superficial femoral artery intima-media thickness, carotid/superficial femoral artery vascular stiffness, and serum levels of inflammatory factors [including interleukin (IL)-1β, IL-6, IL-8, IL-10, C-reactive protein (CRP), serum amyloid A protein (SAA), and tumor necrosis factor-α (TNF-α)]. [e]Choose from Doppler ultrasound, MRA, DSA, or CTA. ECG, electrocardiogram; CMSS, Chinese medicine syndrome score; SF-36, 36-Item Short-Form; WIQ, Walking Impairment Questionnaire.

Abbreviations: ABI, ankle brachial index; ANOVA, analysis of variance; CI, confidence interval; CRF, case report form; CRO, contract research organization; CRP, c-reactive protein; EDC, electronic data capture; FAS, full analysis set; IL, interleukin; LOCF, last observation carried forward; PAD, peripheral arterial disease; PPS, per protocol set; SAA, serum amyloid A protein; SOPs, standard operating procedures; SS, safety analysis set; TNF-α, tumor necrosis factor-α; WIQ, walking impairment questionnaire.

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Sample Size Calculation

The change in intermittent claudication distance from baseline was used as the primary efficacy indicator, and the sample size was estimated using the superiority test. In current clinical trials of similar studies, the improvement in walking distance is generally approximately 30 meters.[18] Therefore, we assumed that the difference between the mean values of the effect between the treatment group and the control group was 30%, the standard deviation $\sigma = 30\%$, the superiority margin $\Delta = 20\%$, the type I error level $\alpha = 0.05$, the power $(1 - \beta) = 0.8$, and the sample ratio of the treatment group to the control group was 1:1. The required sample size for each group was calculated using PASS software 2017 (NCSS LLC., Kaysville, U.T., USA) as n = 112 cases each, for a total of 224 cases. With a dropout rate of 12%, a total of approximately 250 cases would be needed, with 125 cases in the treatment group and 125 cases in the control group.

Statistical Analysis

The data collected for this trial will be divided into the full analysis set (FAS), the per protocol set (PPS), and the safety analysis set (SS). The FAS refers to all patients who are randomized to a group, start treatment, and receive at least 1 evaluation with relevant efficacy assessments. The missing data in the efficacy portion of the FAS will be imputed using the last observation carried forward (LOCF) method. The PPS population is defined as patients who complete treatment as per protocol, who have no significant protocol deviations, who complete all evaluation components, and whose data set will be determined at the time of the poststudy data review. The SS includes all patients who are randomized to groups, use the study drug at least once and have postdose safety assessment data.

Baseline patient data will be analyzed according to the FAS. Continuous variables that follow a normal distribution will be expressed as the mean ± standard deviation, and continuous variables that do not follow a normal distribution will be expressed as the median (interquartile range). Categorical variables will be expressed as counts (rates). T tests, nonparametric tests, or chi-squared tests will be used to test whether patients adhere to the random assignment, depending on the data characteristics.

Primary efficacy indicators, secondary efficacy indicators, and exploratory efficacy indicators will be analyzed based on the FAS and PPS, and analysis of variance (ANOVA) will be used for comparisons between the two groups. In addition, based on the analysis of the covariance model, the difference in the scores of each scale before and after treatment will be used as the response variable, baseline scores will be included in the model as covariates, the test center and group will be used as independent variables, and the difference between groups will be considered statistically significant if the P value of the between-group comparison is <0.05. The test for superiority of the treatment group over the control group will be performed using an analysis of covariance model that estimates the 95% confidence interval (95% CI) for the difference between the pre- and posttreatment mean scores of the treatment and control groups with respect to the corrected mean (treatment group-control group). If the lower limit of the 95% CI is greater than 0, the superiority of the treatment group over placebo will be established. The p value for the comparison between the treatment and control groups will be reported; if $P < 0.05$, the difference between the groups will be considered statistically significant. If the difference between the pre- and posttreatment mean scores do not follow a normal distribution, sensitivity analyses will be performed using the Wilcoxon rank-sum test.

The SS will be used to estimate the incidence of adverse reactions, total incidence of adverse reactions, incidence of serious adverse reactions, and total incidence of serious adverse reactions.

Missing data in the efficacy portion of this study will be imputed using the LOCF method, and missing values will not be imputed in the safety assessment.

Data Management

Data management is coordinated by initiating or authorizing an independent contract research organization (CRO) in accordance with data management SOPs. The data management will document all study-specific processes and definitions. CRF retrieval and correction processes will be referenced on the CRF instructions. Medical terminology coding will be performed using MedDRA.

To collect data in the most efficient manner, the investigator or designee should enter data (including laboratory values, if applicable) into the CRF immediately after the subject visit, and the CRF and any supporting documentation should be available for retrieval at any time.

The study database will be soft-locked after all data collected in accordance with the study protocol have been received and cleaned according to the relevant SOPs. The database will be hard-locked when a (blind) data review meeting has been held and all data-related decisions have been made and reflected in the database.

Quality Control

The trial sponsor will implement and maintain quality assurance and quality control systems based on written SOPs to ensure that the trials are conducted and the data are generated, recorded, and reported in accordance with the protocol, GCP, and applicable regulatory requirements.

The trial sponsor or its designee may arrange for the inspection or audit of clinical trials at any or all of the trial sites. The inspector is independent of the sponsor's clinical monitoring and program management team. The audit may include an on-site review of regulatory documents, the CRF, and source documents. The investigator is authorized to have direct access to these documents.

Discussion

The purpose of this study is to evaluate the efficacy of Ruanjian Qingmai granules in the treatment of patients with symptomatic PAD. Intermittent claudication, as a major clinical symptom in patients with symptomatic PAD, is also an important cause of decreased quality of life and work ability in patients with early PAD.[19] The cause of intermittent claudication in patients with PAD is chronic ischemia of the lower limbs, and the pain-free walking distance and maximum walking distance of patients are the two determinants that reflect walking ability.[20] Previous studies have shown that vasoactive drugs can improve the pain-free walking distance in patients with symptomatic PAD,[7,21,22] but there are many drawbacks, such as widespread side effects, suboptimal efficacy, and lack of consensus recommendations.[19,21] As a famous classic prescription for PAD in Shanghai, Ruanjian Qingmai granules have obtained good patient feedback in clinical practice for more than 30 years. Early use of Ruanjian Qingmai granules may benefit patients with symptomatic PAD. This will provide more drug strategies to treat early symptomatic PAD patients and thereby improve these individuals' quality of life and social participation.

ABI, which is the ratio of ankle systolic blood pressure to arm systolic blood pressure, is a noninvasive method to assess the degree of lower extremity perfusion impairment[20] and has been recommended in several guidelines for use in patients with PAD.[5,23] This study will use the ABI as a secondary indicator to observe whether lower extremity perfusion improves after patients are treated with Ruanjian Qingmai granules. The WIQ and SF-36 health surveys will be used to subjectively assess the patients' walking function and quality of life. Meanwhile, the study will also analyze changes in the patients' serum inflammatory cytokine levels (including IL-1β, IL-6, IL-8, Il-10, CRP, SAA, and TNF-α) before and after treatment and explore the therapeutic mechanism of Ruanjian Qingmai granules from the perspective of inflammation regulation. Inflammation has been shown to be related to atherogenesis and the progression of atherosclerosis in several studies.[24] At present, most treatments for PAD are aimed at controlling cardiovascular-related risk factors, often neglecting the intervention of inflammation within the blood vessels themselves.[25] In contrast, traditional Chinese medicine has a unique advantage in regulating inflammation in the body.[26] Our previous study found that Ruanjian Qingmai granules could reduce inflammatory responses by downregulating the expression of IL-17A and IL-21 through regulation of the JAK2/STAT3 signaling pathway.[13] Network pharmacological analysis suggests that Ruanjian Qingmai granules may exert anti-inflammatory effects to treat PAD.[27] The present study will further investigate the effects of Ruanjian Qingmai granules on the levels of various inflammatory factors in PAD patients based on previous studies, providing a foundation for future in-depth studies on the modulation of inflammatory responses in PAD patients by the drug.

This study also has several limitations. It only includes patients with symptomatic PAD and will not observe the efficacy of the drug in patients with asymptomatic PAD (Fontaine I stage) or in patients with intermediate to advanced disease (Fontaine II~IV stage). Some patients with PAD may have concomitant cardiopulmonary disease, which may interfere with

the assessment of their walking ability. Notably, the study was initiated during the COVID-19 pandemic, and the decrease in exercise tolerance in patients after novel coronavirus pneumonia may also affect the assessment of walking ability.

Conclusion

This is a multicenter, prospective, center-randomized, double-blind, placebo-controlled clinical trial that has the potential to provide an effective treatment option for patients with symptomatic PAD.

Trial Status

The trial was started on April 01, 2022, and is expected to stop enrolling patients on April 01, 2024, and to end on December 31, 2024, for observation and follow-up.

Ethics Approval and Consent to Participate

The clinical trial was reviewed by the Ethics Committee of Shanghai TCM-Integrated Hospital, Shanghai University of Traditional Chinese Medicine on November 15, 2021 (No. 2021-015-1). It was registered in the Chinese Clinical Trial Registry on February 01, 2022 (registration number: ChiCTR2200056109, website: https://www.chictr.org.cn/showproj.html?proj=150982). All subjects and their families signed an informed consent form. The study was conducted in accordance with the tenets of the Declaration of Helsinki. Subjects' privacy will be protected to the maximum extent possible, and identifying information will be concealed. The collected biological specimens will be used for exploratory research purposes and will be retained until the conclusion of this trial. Subsequently, they will be handed over to a professional institution for unified destruction.

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Disclosure

The authors report no conflicts of interest in this work.

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