Trials

STUDY PROTOCOL

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Upadacitinib to improve anxiety in patients with adalimumab-treated psoriatic arthritis: study protocol for a randomized controlled trial

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Abstract

Background Patients with psoriatic arthritis (PsA) often suffer from anxiety disorders. While upadacitinib has shown effectiveness in reducing various disease activity indicators in active PsA, its impact on anxiety disorders in PsA patients needs further investigation.

Methods In this 12-week randomized, open-label, controlled trial, PsA patients with coexisting anxiety were randomly assigned to either the upadacitinib group or the adalimumab group in a 1:1 ratio. The upadacitinib group received a daily dose of 15 mg, while the adalimumab group received 40 mg every 2 weeks. The primary outcome measured the change in Hospital Anxiety Self-Assessment Scale (HADS-A) total scores after the 12-week intervention. Secondary outcomes included changes in the Health Assessment Questionnaire-Disability Index (HAQ-DI), the percentage of participants meeting the ACR20 criteria compared to baseline after 12 weeks, and the percentage of participants achieving a grade 0 or 1 in the psoriasis static Investigator's overall assessment (sPGA) at week 12 with an improvement of at least 2 points from baseline (sPGA 0/1). One-way analysis of variance (ANOVA) was used to compare the means of normally distributed variables between the upadacitinib and adalimumab groups.

Discussion The impact of upadacitinib on anxiety in PsA patients remains uncertain. This 12-week open randomized controlled trial aims to provide insights into disease progression and underscore the importance of addressing PsA-related anxiety during treatment.

Trial registration ChiCTR2400079755. Registered on January 11, 2024, with ChiCTR. https://www.chictr.org.cn/showproj.html?proj=216538

Keywords Psoriatic arthritis, Anxiety, Upadacitinib, Randomized controlled trial

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Introduction

Background and rationale

Psoriatic arthritis (PsA) is a chronic, progressive inflammatory arthritis that often accompanies cutaneous psoriasis. It presents with various musculoskeletal and dermatologic manifestations, including arthritis, peripheral arthritis, dactylitis, and axial spondylarthritis, along with skin and nail issues. These symptoms can manifest individually or in combination [1]. PsA is associated with several comorbidities, including heart disease, metabolic syndrome, and depression. It is a potentially erosive condition, with about 50% of patients experiencing structural damage and functional impairment within 2 years, resulting in irreversible joint damage as the disease advances [2].

Most arthritis patients experience pain and psychological distress (clinically significant depression and anxiety). Pain and anxiety exacerbate each other, but anxiety is often overlooked in the clinical assessment and treatment of arthritis [3]. The increased disease burden in PsA negatively impacts psychological well-being. Depression prevalence in psoriasis patients ranges from 19.2 to 62%, and anxiety can affect as many as 43% of them [4–8]. The presence of both joint inflammation and skin disease in PsA patients may further increase the risk of depression and anxiety [9]. Studies have indicated that the presence of depression or anxiety significantly reduces the likelihood of achieving sustained minimal disease activity (MDA) in PsA patients, with 45.36% failing to attain it [10]. Patients with PsA are at an increased risk of depression and anxiety, which may complicate treatment [11]. Current research suggests that anxiety disorders affect 19% of PsA patients [12, 13]. Only a small percentage of PsA patients (2.4 to 13.5%) were reported to be taking antidepressant or antianxiety medications [14]. This highlights that psychological disorders can both contribute to and exacerbate PsA but are often not adequately addressed in treatment [15]. Biologic treatments for PsA include TNF-α inhibitors, IL-17 inhibitors, and Janus kinase isoform (JAK) inhibitors. Upadacitinib is an oral selective JAK1 inhibitor, part of the cytoplasmic tyrosine kinase family responsible for mediating cytokine signals, such as interferon [16, 17]. A 24-week clinical trial demonstrated that upadacitinib at doses of 15 mg or 30 mg was more effective than placebo in improving PsA signs and symptoms in patients who were poor responders or intolerant to at least one biologic DMARD [18]. In a phase 3 clinical study evaluating upadacitinib in PsA patients who were poor responders to non-biologic DMARDs, upadacitinib treatment at week 24 showed a significantly higher ACR20 response rate compared to adalimumab, with notable differences in the Short Form-36 survey's mental component summary [19]. While upadacitinib's efficacy in improving various disease activity indicators in active PsA has been established, its impact on anxiety in PsA patients requires further investigation.

Objectives

The aim of this study was to investigate the effectiveness of upadacitinib on psoriatic arthritis patients with anxiety disorders.

Trial design

This will be a 12-week open-label, randomized, controlled trial (RCT) conducted at Shenzhen Traditional Chinese Medicine Hospital. A total of 40 PsA patients with anxiety disorders who meet the study criteria will be randomly assigned in a 1:1 ratio to either the upadacitinib group or the adalimumab group (Fig. 1).

Methods: participants, interventions, and outcomes

Study setting

The study will be conducted at Shenzhen Traditional Chinese Medicine Hospital from January 3, 2024, to January 3, 2026. All participants will provide written informed consent before the study, and they will be thoroughly briefed about the study's purpose, methods, and potential risks.

Eligibility criteria

Inclusion criteria:

Participants meeting the following criteria will be eligible:

(1) Male and female individuals aged 18–75 years
(2) Diagnosis in accordance with the Classification and Diagnostic Criteria for Psoriatic Arthritis (CASPAR) [20]
(3) Active psoriasis diagnosis, with a history of psoriasis and a symptomatic flare-up lasting ≥ 6 months
(4) Hospital Anxiety Self-Assessment Scale (HADS-A) score ≥ 7
(5) Diagnosis of previous or current plaque psoriasis with ≥ 1 (of 66) joint swelling and ≥ 1 (of 68) joint tenderness at screening and baseline

Exclusion criteria:

Participants meeting any of the following criteria will be excluded:

(1) Patients who have used Janus kinase (JAK) inhibitors systemically prior to the study
(2) History of or current diagnosis of an inflammatory joint disease other than psoriasis

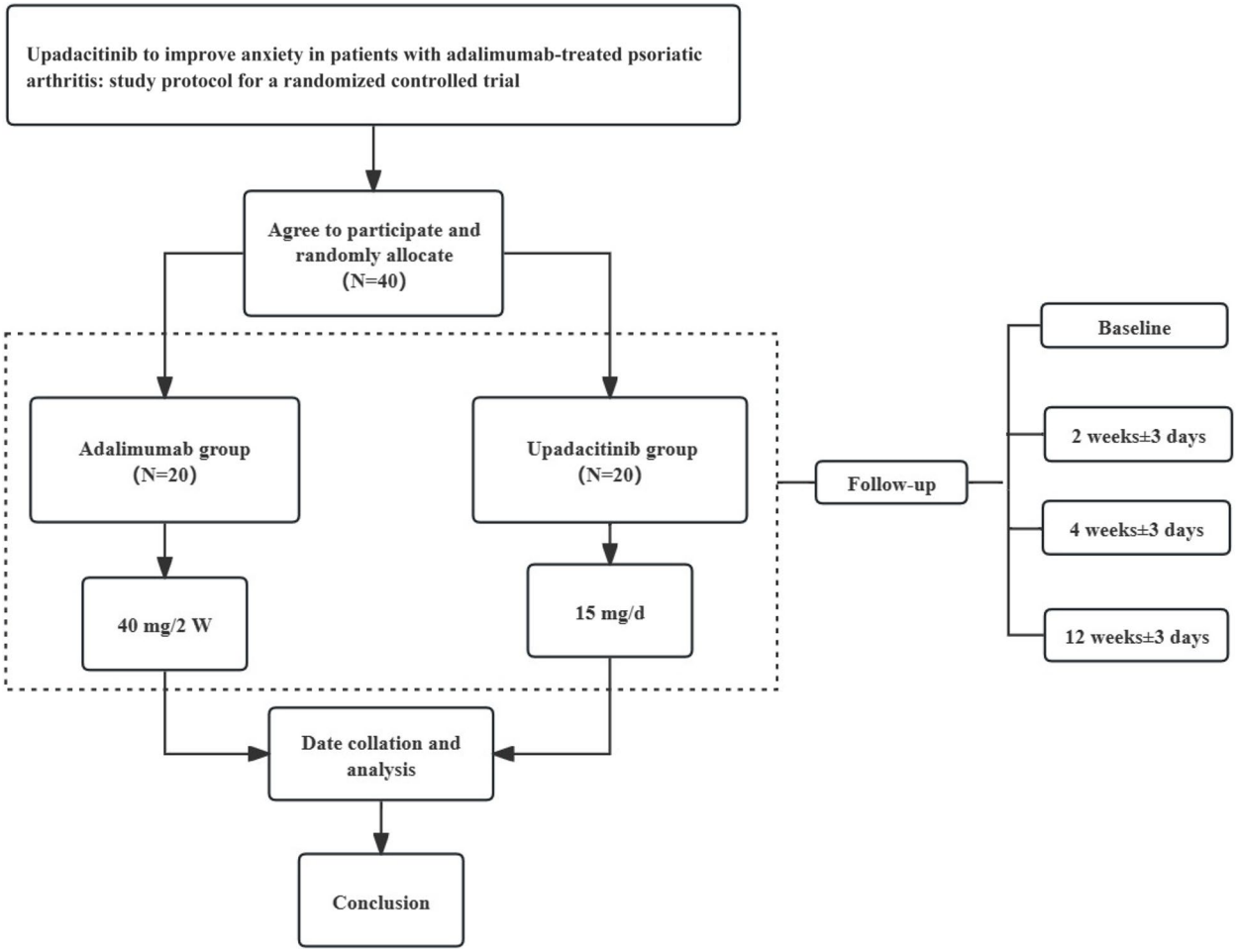

Fig. 1 Trial flow and study design

(3) History of fibromyalgia, reactive arthritis, or axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondylitis
(4) Active tuberculosis or other serious infectious diseases
(5) Concurrent malignant tumors or psychiatric disorders
(6) Unwillingness to discontinue current therapeutic medications before the study
(7) Moderate to severe heart failure

Who will take informed consent?

Patients for this study will be recruited from outpatient clinics and inpatient wards through advertisements on the hospital department's social media platforms and posters placed in public areas of the hospital. These materials will provide information about the study and contact details. Patients who meet the eligibility criteria will be invited to participate in the study and will receive detailed information about the program. All subjects will be required to sign an informed consent form, which will be administered by a clinician.

Additional consent provisions for collection and use of participant data and biological specimens

Participants will be asked for consent to access their medical records and to collect blood samples for blood routine analysis, liver function assessment, kidney function assessment, and measurement of c-reactive protein levels, as well as urine samples for routine urinalysis. The residual blood and urine samples will be destroyed by the Laboratory Department of Shenzhen Hospital of Traditional Chinese Medicine.

Interventions

Explanation for the choice of comparators

A total of 40 patients with psoriatic arthritis with anxiety who met the study criteria. They will be randomly allocated (1:1) to the test and control groups.

Intervention description

The intervention will span 12 weeks, with the first 12 weeks being open-labeled. There are two intervention groups:

(1) Upadacitinib group: participants in this group will receive upadacitinib at a dose of 15 mg once daily for 12 weeks
(2) Adalimumab group: participants in this group will receive adalimumab at a dose of 40 mg every two weeks for 12 weeks
(3) Test period: 12 weeks
(4) During the study, the following examinations will be conducted:

General information assessment, including heart rate, pulse, blood pressure, temperature, height, and weight.

Routine examination, which includes blood routine, urine routine, liver function, kidney function, and c-reactive protein assessment.

(5) Follow-up program: follow-up visits will occur at baseline, 2 weeks ± 3 days, 4 weeks ± 3 days, and 12 weeks ± 3 days from the start of treatment
(6) Frequency of specimen collection:

Patient demographics, such as age, gender, duration of illness, and past medical history, will be collected. Specimen collection will include evaluations and testing of blood routine, urine routine, liver and kidney function, and other systemic damage indicators before treatment, at 2 weeks, 4 weeks, and 12 weeks after treatment.

Research procedures

(1) Screening

Patients meeting the Diagnostic Criteria for Psoriatic Arthritis (CASPAR) and having Hospital Anxiety Self-Assessment Scale (HADS-A) scores over 7 will be considered for inclusion.

(2) Enrollment

Participants will be randomly assigned to either the test or control group. Both groups will receive treatment for 12 weeks.

(3) Treatment scheme

The experimental group will receive oral upadacitinib at a daily dose of 15 mg. The control group will receive injections of adalimumab at a dose of 40 mg once every 2 weeks.

(4) Laboratory indicators

Various laboratory indicators will be assessed, including heart rate, pulse, blood pressure, temperature, height, weight, blood routine, urine routine, liver function, kidney function, and CRP.

(5) Follow-up

Follow-up visits will occur at baseline, 2 weeks ± 3 days, 4 weeks ± 3 days, and 12 weeks ± 3 days from the start of treatment.

(6) Data and specimen collection

Participant demographics, including age, gender, disease duration, and medication history, will be recorded. Biochemical tests, such as blood routine, urine routine, liver function, kidney function, and CRP will be conducted at follow-up visits. Participants will complete relevant scales, such as HADS-A and HAQ-DI. Biospecimens will be collected for testing and subsequently destroyed.

Criteria for discontinuing or modifying allocated interventions

Criteria for discontinuing

(1) Participants withdraw the trial spontaneously
(2) Pregnancy
(3) Adverse events that persuade investigators to urge participants to leave the trial as early as possible
(4) Incomplete data affects the assessment of efficacy and safety
(5) Participants have poor compliance with the research protocol, and exercise adherence rate is not within the range of 80–120%

Relevant concomitant care permitted or prohibited during the trial

Associated concomitant care not permitted or prohibited in this trial.

Provisions for post-trial care

When the participants complete the trial, they will receive standardized treatment based on the guideline.

Outcomes

Primary outcome

The primary outcome is the change in Hospital Anxiety Self-Assessment Scale (HADS-A) total scores after 12 weeks of treatment between the upadacitinib and adalimumab groups.

Secondary outcomes

(1) Change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) after 12 weeks: the Health Assessment Questionnaire-

Disability Index (HAQ-DI) is a patient-reported questionnaire designed to assess the difficulty individuals face in completing tasks in eight functional domains over the past week. These domains include dressing, getting up, eating, walking, hygiene, reaching, grasping, errands, and household chores. Participants rate their ability to perform each task on a scale ranging from 0 (no difficulty) to 3 (unable to complete). The scores for each task are then averaged to calculate a total score, which ranges from 0 (indicating no disability) to 3 (indicating a severe, highly dependent disability). A negative change in the total score from baseline at week 12 signifies an improvement in the participant's functional abilities

(2) Percentage of participants meeting ACR20 Criteria at week 12 compared with baseline: this outcome measures the percentage of participants who meet the ACR20 criteria at week 12 compared to baseline. Meeting the ACR20 criteria involves fulfilling the following three improvement criteria: ≥ 20% improvement in the number of 68 pressure-painful joints; ≥ 20% improvement in the number of 66 swollen joints; ≥ 20% improvement in at least three of the following five parameters: (a) physician's overall assessment of disease activity, (b) patient's overall assessment of disease activity, (c) patient's pain assessment, (d) Health Assessment Questionnaire-Disability Index (HAQ-DI), (e) high-sensitivity C-reactive protein (hsCRP)

(3) Percentage of participants achieving a grade 0 or 1 Static Psoriasis Investigator's Overall Assessment (sPGA) at week 12 with an improvement of at least 2 points from baseline (sPGA 0/1): this outcome measures the percentage of participants who attain a grade 0 or 1 in the psoriasis sIGA at week 12 with an improvement of at least 2 points from baseline. The sIGA is a 5-point scale ranging from 0 to 4 based on the investigator's evaluation of the average elevation, erythema, and scaling of all psoriatic lesions during the current visit. Lower scores on the sIGA indicate less severe psoriasis, with grades defined as follows: 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		
TIMEPOINT(week)	−1	0	2	4	12
ENROLMENT					
Eligibility screen	X				
Informed consent		X			
Demographic characteristics		X			
Medical and medication history		X			
Review Criteria		X			
Randomization		X			
Allocation		X			
INTERVENTIONS					
Upadacitinib			←	—	→
Adalimumab			←	—	→
ASSESSMENTS					
HADS-A		X	X	X	X
HAQ-DI		X	X	X	X
Hs-CRP		X	X	X	X
Vital signs		X	X	X	X
Physical examination		X	X	X	X
Blood routine		X	X	X	X
Urine routine		X	X	X	X
Liver function		X	X	X	X
Kidney function		X	X	X	X
CRP		X	X	X	X
Combined medication		X	X	X	X
Adverse Event			X	X	X

Fig. 2 SPIRIT figure of enrolment, interventions, and assessments. HADS-A, Hospital Anxiety Self-Assessment Scale; HAQ-DI, Health Assessment Questionnaire-Disability Index; Hs-CRP, high-sensitivity C-reactive protein; CRP, C-reactive protein

Participate timeline

The participant timeline is depicted in Fig. 2.

Sample size

This study aims to assess the efficacy of upadacitinib in managing anxiety symptoms in PsA patients. The primary outcome measure is the difference in the total score of the Hospital Anxiety Self-Assessment Scale (HADS-A) between the upadacitinib group and the adalimumab group after a 12-week treatment period. As this trial was a differential test, the sample size was not pre-determined. However, it was ultimately decided that a sample size of 20 cases in each group, resulting in a total of 40 cases across both groups, would be appropriate.

Recruitment

Participants will be recruited from Shenzhen Traditional Chinese Medicine Hospital between January 3, 2024, and January 3, 2026. A total of 40 adult psoriatic arthritis (PSA) patients with anxiety will be included. Once a patient is confirmed eligible, a physician will review the study procedures and requirements with the patient and ensure their commitment to the study and their acceptance of randomization. Written informed consent will be obtained from each participant, and baseline evaluations will be performed, scheduled immediately by the physician assistant.

Assignment of interventions: allocation

Sequence generation

The statistician will generate the random list by block randomization with variable block length, implemented using the PROC PLAN for SAS 9.4 statistical software.

Concealment mechanism

After the sequence is generated, Dr. Zhiying Zhan performs a concealment allocation mechanism, sequentially numbered, opaque, sealed envelopes that can be duplicated when needed.

Implementation

Dr. Zhiying Zhan (Fujian Medical University School of Public Health) generated the allocation sequence; doctors will enroll participants, and the nurse will assign participants to interventions.

Assignment of interventions: blinding

Who will be blinded

The design of this study is open-label. The assigned study investigator will be known for both patients and all research staff. Research data collectors and the outcome adjudicators will be blinded during the study.

Procedure for unblinding if needed

The design is open label with only outcome adjudicators being blinded, so unblinding will not be required.

Data collection and management

Plans for assessment and collection of outcomes

Demographic data on participants will be collected, including age, gender, disease duration, medication history, and comorbid medications. In addition, participants will be followed up four times (baseline, 2 weeks, 4 weeks, and 12 weeks after test) with physical examination and blood routine, urine routine, biochemicals, c-reactive protein (CRP), anti-hemolytic streptococcal "O" (AS0), rheumatoid factor (RF), blood sedimentation rate (ESR), and high-sensitivity C-reactive protein (hs-CRP). The Health Assessment Questionnaire Disability Index (HAQ-DI), the Hospital Anxiety Self-Rating Scale (HADS-A), and Static Psoriasis Investigator's Overall Assessment (sPGA) were recorded. The biological samples will be destroyed by the Laboratory of Shenzhen Hospital of Traditional Chinese Medicine after testing. The case report form (CRF) is used to assess and collect outcomes and baselines and is maintained by the designated data management assistant and imported into the clinical trial database. Clinical trial databases are created by designated data administrators who are responsible for the regular management and maintenance of the databases.

Plans to promote participant retention and complete follow-up

Follow-up will be conducted at baseline, 2 weeks ± 3 days, 4 weeks ± 3 days, and 12 weeks ± 3 days. Any missing or incorrect data will be detected by software system. In such case, the original CRFS will be checked to correct or complete every piece of data.

Data management

Trial data are collected and stored according to GCP guidelines. The CRF for each participant should be filled out in a timely manner. All data will be double-entered by the site personnel or the coordinating investigator. Original documents and CRFs will be stored in the study office. The clinical trial database is managed and maintained by the appointed data manager.

Confidentiality

The confidentiality measures are as follows. The research information obtained for this trial will be represented by a unique number, and the coded information will be

stored securely to prevent disclosure of the subject's privacy. The identity of the subjects will not be disclosed when the research information and data obtained from this study are published at scientific meetings or in scientific journals. Third parties will be prevented from knowing the subjects' private information and the personal date involved in the study.

Statistical methods

Statistical methods for primary and secondary outcomes

Statistical analysis will be conducted using the SAS 9.4 statistical software, and all data will be presented as mean ± standard deviation (SD) or percentage (%). Differences in demographic data, anthropometric measurements, blood biochemical parameters, and health-related physical fitness components between baseline and week 12 will be analyzed using paired *t*-tests. One-way analysis of variance (ANOVA) will be employed to compare the mean values of normally distributed variables between the two groups. Statistical analysis was carried out using SPSS (version 26), and a two-tailed significance level of 0.05 was used for all tests. A *p*-value less than 0.05 is considered statistically significant.

Methods for additional analyses (e.g., subgroup analyses)

No subgroup analysis will be performed in this study. The investigator will obtain these interim results and make the final decision to terminate the trial.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

Strategies will be put in place to increase follow-up and promote adherence, like phone calls twice a week and texting. In the event of missing data, this will be dealt with accordingly using additional statistical analyses (e.g., imputation). The primary analysis will be an intention-to-treat analysis. All patients receiving study medication will be included in the ITT analysis.

Plans to give access to the full protocol, participant-level data, and statistical code

Data is available upon reasonable request and should be addressed to sailing1980@126.com.

Oversight and monitoring

Composition of the coordinating center and trial steering committee

The trial steering committee comprises three members, including two senior rheumatologists and a statistician, who will oversee the trial. The committee is separate from the research team with no conflict of interest.

Composition of the data monitoring committee, its role and reporting structure

The data monitoring committee consists of three members, two senior rheumatologists and a statistician, who will ensure the safety and quality of data. The committee is independent of the research team and has no conflict of interest. They are in charge of recruiting, treating, and following up on study participants, as well as reporting severe adverse events and serious, unexpectedly suspected adverse events. During the visit, they will interview investigators, review research documents and subject enrollment, and confirm compliance with the study protocol.

Adverse event reporting and harms

Common side effects that may occur in patients receiving upadacitinib for psoriatic arthritis in this study include upper respiratory tract infections, shingles, acne, and headaches. Adalimumab is associated with the most frequently reported adverse reactions, which include infections such as nasopharyngitis, upper respiratory tract infections, sinusitis, injection site reactions (such as erythema, itching, bleeding, pain, or swelling), headaches, and musculoskeletal swelling. Clinical psychologists are available to administer interventions to research participants facing persistent or exacerbated anxiety symptoms, should the existing treatments prove ineffective. Furthermore, serious hematological, neurological, and autoimmune reactions have been documented. In case of any discomfort or adverse events during the study, participants are strongly advised to promptly contact their doctor.

Frequency and plans for auditing trial conduct

We will audit the study protocols for participant enrollment, consent, eligibility, and allocation to research groups; adherence to trial interventions and policies to protect participants, including reporting of harm; and data collection completeness, accuracy, and timeliness. Over the course of the study, we will do at least one onsite monitoring visit every month. The process will be independent from investigators.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees)

Any changes to the protocol that may affect the conduct of the study need to be approved by the Ethics Committee of Shenzhen Traditional Chinese Medicine Hospital before implementation and in accordance with local regulations and health department requirements.

Dissemination plans

All presentations and publications will prioritize preserving the integrity of the primary research objectives. Data that could potentially compromise the study's objectives will not be disclosed until the results become available. The steering committee will engage in discussions to determine the appropriate timing for presenting final data at meetings. Primary outcomes will be disseminated through publication in abstract books and articles.

Discussion

PsA is a chronic and progressive inflammatory joint condition linked with psoriasis. It often co-occurs with inflammatory bowel disease, eye problems, and metabolic syndrome, along with physical symptoms and skin issues. This significantly increases the social and emotional burdens on patients, negatively impacting their quality of life and leading to higher rates of depression, anxiety, and suicide compared to other inflammatory arthritis conditions [21]. Studies have confirmed that the severity of the disease is closely linked to increased symptoms of depression and anxiety.

Despite these severe effects, healthcare providers often overlook and underestimate the psychological and social impact of PsA on patients. Although the exact cause of PsA remains unknown, it is now understood that both innate and adaptive immune cells, along with pro-inflammatory cytokines, play a role in its development. PsA involves the infiltration of immune cells into the joints, including activated T cells, dendritic cells, macrophages, and intrinsic lymphocytes, resulting in the production of high levels of pro-inflammatory cytokines. Many of these cytokines and immune responses are regulated by the JAK-STAT signaling pathway.

Adalimumab, a tumor necrosis factor α inhibitor utilized in the treatment of psoriatic arthritis, demonstrated effectiveness with acceptable safety profiles in pivotal phase III trials [22]. A randomized double-blind phase 3 trial [23] revealed that greater improvements were witnessed with upadacitinib at 15 mg and 30 mg compared to adalimumab in achieving 20%, 50%, and 70% improvement according to the American College of Rheumatology (ACR20/50/70 responses) at week 24 [24]. Both doses of upadacitinib were established as non-inferior to adalimumab. A clinical trial has demonstrated a significant correlation between reduced depression and anxiety scores over a 6-month period in psoriasis patients treated with biologics, including adalimumab ($p < 0.005$) [25]. Therefore, adalimumab was utilized as the positive control drug in our study. Biologic therapies for psoriasis have proven effective in reducing both the severity of the disease and symptoms related to depression and anxiety. Upadacitinib, which selectively targets JAK1, has shown good efficacy in objective scores measuring psoriasis disease activity, minimal disease activity, and regression of adhesion pemphigoid. However, there is still room for improvement in addressing anxiety symptoms.

It is important to note that this study has limitations. It is not blinded, which may introduce bias that could influence the study's outcomes. Additionally, the sample size should be expanded in future studies to enhance the robustness of the findings.

In this study, our goal is to investigate the potential improvement in anxiety symptoms among psoriatic arthritis patients treated with upadacitinib. Such treatment is expected to not only slow down the progression of psoriatic arthritis but also alleviate anxiety, ultimately leading to improvements in psychological well-being.

Trial status

The revised version V20231213 of this protocol on December 13, 2023, has been approved by the Institutional Medical Ethics Committee of Shenzhen Traditional Chinese Medicine Hospital. The recruitment will begin on January 3, 2024, and this study will be completed on January 3, 2026.

Abbreviations

RCT	Randomized controlled trial
PsA	Psoriatic arthritis
HADS-A	Hospital Anxiety Self-Assessment Scale-Anxiety
HAQ-DI	Health Assessment Questionnaire-Disability Index
sIGAStatic	Investigator's overall assessment
ANOVA	One-way analysis of variance
MDA	Minimal disease activity
OR	Odds ratio
TNF	Tumor necrosis factor
IL	Interleukin
JAK	Janus kinase
DMARD	Disease-modifying antirheumatic drug
ACR	American College of Rheumatology
CASPAR	Classification and Diagnostic Criteria for Psoriatic Arthritis
HsCRP	High-sensitivity C-reactive protein
SD	Standard deviation
STAT	Signal transducer and activator of transcription

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Not applicable.

Authors' contributions

JL and EJ designed the trial. JL, ZW, JZ, HG, and HT drafted the manuscript. SZ, SH, JW, Zzhang, and ZL conducted the research. ZZhan was responsible for the statistical analyses. All authors participated in the manuscript revision.

Authors' information

Not applicable.

Funding

This study has been funded by the investigator. No funding was available for this study.

Availability of data and materials

The doctors will have access to the final trial dataset.

Declarations

Ethics approval and consent to participate
The study is approved by the Institutional Medical Ethics Committee of Shenzhen Traditional Chinese Medicine Hospital (approval number: K2023-122–02). All subjects are required to sign the written informed consent forms.

Consent for publication
Model consent form has given to participants and authorized surrogates.

Competing interests
The authors declare they have no competing interests.

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