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Research Article

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Evaluation of the safety and efficacy of tripterygium wilfordii glycosides for patients with primary sjgren's syndrome : protocol for a prospective, double-blinded, randomized, placebo-controlled clinical trial

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Abstract

Background: As a common autoimmune disease, primary sjogren's syndrome(pss) has limited therapeutic agents. For some patients with Sjogren's syndrome complicated with serious complications, taking glucocorticoid combined with cyclophosphamide treatment can obtain good results. However, the side effects of long-term use of glucocorticoid and cyclophosphamide limit its application in patients without extraglandular manifestations. Some animal experiments have shown that tripterygium wilfordii polyglycosides tablets have immunomodulatory effects. The immunomodulatory function of Tripterygium polyglucoside was found in some animal experiments. Some Single center, small sample, non-randomized control studys have proved that tripterygium wilfordii glycosides can allevitate dry eye,dry mouth and serological immunological abnormalities in the patients with PSS .Therefore, we designed this research to study the effect of tripterygium wilfordii glycosides for patients with primary sjgren's syndrome by measuring the reduction of serum globulin,IgA、IgG、IgM、TNF－α，as well as the extent of dry eye and mouth.

Methods : This study is a 12-week, single-center, prospective, double-blinded, randomized, placebo-controlled clinical trial developed from July 2022 to December 2023. Forty individuals with Primary Sjögren's syndrome without extraglandular manifestations will be recruited and randomly assigned to receive tripterygium wilfordii glycosides or a placebo，and each group will have 20 subjects.

During the 12-week observation period, there will be 4 visits. The decline in serum immunoglobulin IgG, IgM, IgA and tumor necrosis factor –α is the main outcome measure, and change of dry mouth, dry eye : Natural saliva flow rate、Schirmer's test、Tear break-up time and Adverse reactions: damage of blood system, liver and kidney function are the secondary outcome measures.

Discussion: This study will probe the effect of tripterygium wilfordii glycosides in the treatment of pSS and explore possible therapeutic mechanisms. By performing this trial, we hope to provide evidence and data to support further large clinical studies.

Trial registration: Chinese Clinical Trial Registry ChiCTR2200062262. Registered on 31 July 2022.http://www.chictr.org.cn/edit.aspx?pid=175924&htm=4

Keywords: tripterygium wilfordii glycosides, primary sjgren's syndrome, Double-blinded, Randomized, Placebo-controlled

Background

Primary Sjögren's syndrome (pSS) is a systemic autoimmune rheumatic disease characterized by lymphocytic infiltration of exocrine glands, which could lead to heterogeneous and various clinical presentations from siccative symptoms to systemic disease [1]. Approximately one-third of patients with pSS present extra glandular manifestations, and some of these symptoms (e.g.interstitial lung disease, central nervous system [CNS] disease, and renal tubular acidosis) are associated with increased mortality. Abnormal immune response of T and B cells [2–4]recognition of self-antigens (Ro/SSA, La/SSB, and oth-ers), and subsequent activation are crucial for the cascade of events leading to the pSS pathology development [5,6].

To date, there is increased evidence on distinct clinical phenotypes corresponding to several serologic abnormalities, such as B-cell proliferation, present special clinical features; for instance, hypergammaglobulinemia is often accompanied by extraglandular manifestations, especially with cutaneous vasculitis and pulmonary, articular, and renal involvements [7–10].

Because the etiology has not been fully elucidated, the current treatment is limited. The accepted method is to use glucocorticoid in combination with cyclophosphamide, however Because of cyclophosphamide potential tumor, bone marrow suppression, aggravation of infection and other undesirable reactions that many patients cannot tolerate . Tripterygium wilfordii glycosides is a diterpene lactone compound isolated from Tripterygium wilfordii. It has potential pharmacological activity and has been used as an anti-inflammatory, antitumor, antifertility, and immunoregulatory agent. TP inhibits immune responses through various mechanisms. It also shows an inhibitory effect against many kinds of proinflammatory cytokines and adhesion molecules which are secreted by endothelial cells. It also has an ability to inhibit the expression and activity of NF-κB signaling. This further promotes cell apoptosis and prevents the occurrence and development of pathological immune responses[11]. The immunomodulatory function of Tripterygium polyglucoside was found in some animal experiments. Tripterygium wilfordii polyglucoside has been widely used in systemic erythema Lupus, rheumatoid arthritis and refractory glomerulonephritis. Tripterygium wilfordii polyglycosides can down-regulate and inhibit NF - kB pathway and inhibit inflammatory mediators Inhibits inflammatory cytokines such as IL-1, IL-6, IL-8, TNF – α and other secretion, chemokine granulocytes, monocytes/macrophages affected Sound and play an anti-inflammatory role, thereby inhibiting the inflammatory response［12］.

Some single center, small sample, non-randomized control studys have proved that tripterygium wilfordii glycosides can allevitate dry eye, dry mouth and serological immunological abnormalities in the patients with PSS .

At present, there are few studies on the clinical efficacy of tripterygium wilfordii glycosides in the treatment of pSS. In this study, the efficacy and safety of Tripterygium wilfordii glycosides on pSS will be observed by comparing with placebo. We have designed the trial to study the effect of tripterygium wilfordii glycosides in the reducing the level of serum globulin,IgA、IgG、IgM、TNF – α, as

well as in allerviating the extent of dry eye and mouth.

Methods and design

Study objective

The objectives of the experiment are to study the efficacy and safety data of Tripterygium wilfordii polyglycosides therapy for pSS and to screen possible related small molecules/microbial material bases.

Sample size

This study will enroll 40 subjects. Further large-scale RCT trials will estimate the size of the sample according to the results of the main outcome indicators obtained from this study and use the sample content estimation formula to compare the two means to calculate the sample content, $\alpha = 0.025$, $\beta = 0.2$. The sample size ratio of the test group and control group is 1. The follow-up rate is set according to the pre-experiment follow-up rate.

Study design

This is a 12-week, single-center, prospective, double-blinded, randomized, placebo-controlled clinical trial. We used the SPIRIT reporting guidelines to perfect the protocol [13], from July 2022 to December 2023.Forty individuals with Primary Sjögren's syndrome without extraglandular manifestations will be randomly assigned to receive tripterygium wilfordii glycosides or a placebo at a 1:1 ratio. (Figs. 1 and 2).

Recruitment

Patients attending outpatient and inpatient departments of the first affiliated Hospital of Gannan Medical University who meet the 2016 sjogren's syndrome classification criteria and have no significant organ involvement will be included.

Study setting

The frist affiliated hospital of Gannan Medical University will be the only study setting.

The study's key problem

Serum immunoglobulin increased in most patients with Sjogren's syndrome, tumor necrosis factor –α as an inflammatory factor may be involved in the pathogenesis of sjogren's syndrome. This study was to observe whether Tripterygium glycosides could reduce the levels of serum immunoglobulin and tumor necrosis factor in patients with Sjogren's syndrome, and observe the symptoms of dry mouth and dry eye in patients with sjogren's syndrome to judge the efficacy of Tripterygium glycosides in the treatment of primary Sjogren's syndrome.

Eligibility criteria

Inclusion criteria

1) Postmenopausal women and man without fertility requirement

2) Meet the diagnosis of the 2016 ACR/EULAR classification criteria;

3） Accompanied by dry mouth, dry eyes clinical manifestations

4) Sign informed consent.

Exclusion criteria

1)White blood cells less than 3.5×10^9/L.

2)Serious complications or complications of liver and kidney dysfunction, interstitial

pneumonia, cardiovascular and hematopoietic system

3）Associated with other connective tissue diseases

4）Mental disorder

5）Unable to cooperation

6）Drug allergy of Tripterygium glycosides.

7）Take other medications

Randomization and allocation

Adopting simple block group randomization, the allocation ratio will be 1:1. SAS9.2 PROC PLAN will be used to carry out procedure coding and random sequence generation by the methodology team. The random distribution results will be released through the interactive network response random distribution system for clinical research in the First Affiliated Hospital of Gannan Medical University. The random assignment table in the random center will be kept strictly confidential until the end of the study. After the patients are screened as qualified subjects and have given informed consent, the clinicians apply for the randomization system to obtain the randomization results on the internet. Physicians will execute the results according to random grouping and print and paste them on the corresponding position of the case report form (CRF).

Blinding

A double-blinded, placebo-controlled design was adopted, and both the investigators and the subjects will be blinded. All data will be evaluated and statistically processed by a third party after clinical research. The trial will be unblinded if there is a serious adverse event that may be related to the experimental drug, so we can know which group the subject was enrolled in to decide the rescue plan.

Comparisons

Because we selected patients with no significant organ involvement, we used placebo control, and neither group received any combination of other drugs.

Interventions

Subjects will be given therapeutic agents (Tripterygium wilfordii polyglycosides) or a placebo. The intervention group received tripterygium wilfordii polyglycoside tablets 20mg three times a day. For the placebo group, the size, appearance, packaging, and administration method will be the same as those of the therapeutic drugs.

Elimination and termination criteria

The elimination criteria are as follows: (1) serious violation of exclusion standards after enrollment, (2) not completing the experimental drug administration during the experimental period as required after enrollment, and(3)incomplete once every month follow-up and no test records available for evaluation.

The termination criteria are as follows: (1) Complications of major organ involvement,(2) severe adverse events, (3) condition deteriorated and required urgent

medical attention, (4) the researcher recommended test termination because of the safety of the subjects, and (5) people unwilling to continue to participate in this study for personal reasons. We will keep in touch with the subjects who drop out to observe any subsequent adverse events and collect data.

Strategies to improve adherence to interventions

The compliance of investigators and subjects is an essential factor in the clinical research process and clinical effects. To ensure compliance, investigators or the designated representative must give detailed information about the clinical trial to the subjects and obtain informed consent after a sufficient and detailed explanation. The compliance evaluation of the subjects will mainly be judged from the status recorded in the subject's log card and the questions asked by the researchers.

Plans to promote participant retention and complete follow-up

First, the investigators will keep in touch with the subjects, and regular telephone follow-ups and reminders for follow-up visits will be implemented. Second, our research system will issue the prescription a day in advance. Third, the subjects will receive free tests. Fourth, transportation subsidies will be given after each follow-up visit to encourage subjects to remain engaged and complete follow-up surveys.

Outcome measures

Primary outcome measure

The reduction of serum immunoglobulin IgG, IgM, IgA and tumor necrosis factor -α measure.

Secondary outcome measures

The secondary outcome measures are as follows: (1) change of dry mouth, dry eye : Natural saliva flow rate、Schirmer's test、Tear break-up time(2) Adverse reactions: damage of blood system, liver and kidney function

Security indicators

Security indicators include the following: (1) liver function (alanine aminotransferase ALT, aspartate aminotransferase AST) and renal function (blood ureanitrogen, creatinine); (2) routine blood tests, routine urine tests, routine stool tests + occult blood; (3)a electrocardiogram. and Data collection and analysis Within the 12-week study period, there will be 4 visits: the first at week 0, the second at 4 weeks ± 3 days, the third at 8 weeks ± 3 days, and the fourth at 12 weeks ±5 days.

Data collection and analysis

Within the 12-week study period, there will be 4 visits:the first at week 0, the second at 4 weeks ± 3 days, the third at 8 weeks ± 3 days, and the fourth at 12 weeks ±5 days. The data collection and completion of the CRF will be performed by two research assistants who will be blinded to the grouping of the participants. The clinical trial monitors will check the quality of data entry regularly. The database after verification will then be checked by logic inspection, and the outliers will be checked with the original laboratory documents, and the final checked database will be converted into an DATA-BASE in the format of the SPSS statistical software pack-age and locked for statistical analysis.

Statistical analysis

All statistical analyses will be performed with the SPSS software (SPSS 20.0, SPSS Inc., Chicago, IL, USA) by statisticians who are independent of the research team and blinded to the group allocation. Data analysis will be based on the intention-to-treat (ITT) principles. All numerical data will be presented as the mean ± SD, and categorical variables will be described with percentages numerical data will be presented as the mean ± SD, and categorical variables will be described with percentages(%). All statistical tests will be two-sided, and $\alpha = 0.05$ will be considered statistically significant. We will use a t-test (or Wilcoxon matched-pairs signed-ranks test if the data are non-normally distributed with uneven variances) to compare the decrease in IgG, IgM, IgA and TNF-α between two groups.

For secondary outcomes, the t-test and Wilcoxon test will be conducted to compare the differences in measurement data (such as index mean, standard deviation, and median) between the groups. Repeated measures analysis of variance will be used to compare multiple measures of the scale among groups. The chisquare test (or Fisher's exact test) and 3×C table will be utilized to determine the differences in the proportion, frequency, and total effective rate of the indices in the therapeutic group and placebo group.

To analyze the influencing factors of curative effects, non-conditional logistic regression analysis will be performed. The χ 2 test or Fisher's exact probability method is used for participants' drop-out and adverse events rate analysis.

Safety analysis

Safety data consist of adverse events and clinical laboratory tests. We will describe specific manifestations of adverse reactions and compare the incidence of adverse events and severe adverse events between the two groups. Changes in laboratory test results before and after the test, abnormal changes, and their relationship with tripterygium wilfordii glycosides will be analyzed.

Adverse events management

The type, degree, occurrence time, duration, treatment measures, treatment process, and follow-up results of adverse events that occurred during the trial will be recorded in the case report form, and the correlation between the adverse events and the experimental drugs will be evaluated on the basis of comprehensive consideration of the complications and combined use of drugs, which will also be recorded in detail by the physician. For non-serious adverse events, the observation physician may decide whether to suspend observation based on the disease condition. Cases in which drugs are withdrawn due to adverse events will be followed up and the lab security indicators will be reexamined. For serious adverse events, drug use will be stopped immediately. Regardless of whether it is related to the experimental drug, the investigators will report to the Ethics Committee of the First Affiliated Hospital of Gannan Medical University within 24 h after its occurrence. If a serious adverse event occurs during the course of the study, the research team and the hospital will be responsible for subsequent treatment and financial compensation.

Protocol amendments

If a protocol change is required, the risk to the subject will be fully assessed and reviewed by the Ethics Committee, and all members will be notified after the new scheme has been approved through email and face-to-face meetings.

Confidentiality

Subjects have independent codes and only enter codes when uploading test data. An encryption system will be utilized to upload and store data. The final statistical process will be administered by a third party.

Discussion

As a single-center study, this study has obvious limitations. Small sample size and single center data are subject to selection bias. As the first randomized, double-blind, placebo-controlled clinical trial to investigate the efficacy of tripterygium wilfordii polyglycosides tablets in patients with primary Sjogren's syndrome without visceral injury. We are not sure whether 3 months of follow-up is a predictor of efficacy. In order to exclude the interference of other drugs, only patients with Sjogren's syndrome without major organ involvement were selected as the research objects in this trial, which cannot explain the efficacy of tripterygium wilfordii polyglycosides tablets in Sjogren's syndrome patients with organ involvement. What's more, the side effects of long-term use of tripterygium wilfordii polyside tablets and the economic benefit ratio of long-term use need to be further confirmed by multi-center and large-sample clinical trials.

Trial status

This trial information is available on chictr.org.cn,July31,2022. The study was funded on September 14, 2020. Our trial enrollment period was from July 2022 to December 2023.

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Protocol amendment

An ethical amendment approval will be required if the protocol needs to be modified.

Confidentiality

All appropriate and necessary precautions will be taken to keep medical data and personal information permanently confidential. Provenance and peer review Not commissioned; externally peer reviewed.

Authors' contributions

JYJ, GDB, LRP, DXF,JYJ ,ZSH,HJ designed the protocol. JYJ and LRP wrote the draft. GDB conceived the study and revised the manuscript critically for important intellectual content. JYJ edited the manuscript and contributed to the final draft. LRP and DXF are responsible for statistical analysis. JYJ is the director of the trial. ZSH,HJ are responsible for the follow-up.All authors have carefully read and approved the final manuscript. The trial sponsor was responsible for the selection of research units, researchers, and drug resources. The costs for purchasing drug and publishing the article are supported by the funders.

Funding
This study is funded by Science and Technology Program of Jiangxi Provincial Administration of Traditional Chinese Medicine. The funding body was not involved in the design of the study and will not have any role in the data collection, data analysis, or data publication.
Availability of data and materials
The result of this study will be disseminated via peer-reviewed publications and conference presentation. Al the data will be available upon request.
Declarations
Ethics approval and consent to participate
This study has been approved by the Medical Ethics Committee of the First Affiliated Hospital of Gannan Medical University(No. LLSL-2022072704). All patients are required to sign an informed consent form before they join into the study. Clinical investigators must make sure that the participant knows very well the whole process of the study, the benefits and risks she/he will get whether she/he is in an experiment group or a control group.
Consent for publication
Not applicable.
Competing interests
The authors declare that they have no competing interests.
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Dissemination policy
Regardless of the size and direction of the validity of the test results, they will be published.
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Fig.1 Flow diagram for the study

Fig.2 Participant timeline

Appendix 1 Model informed consent form

Appendix 2 SPIRIT checklist

Figures

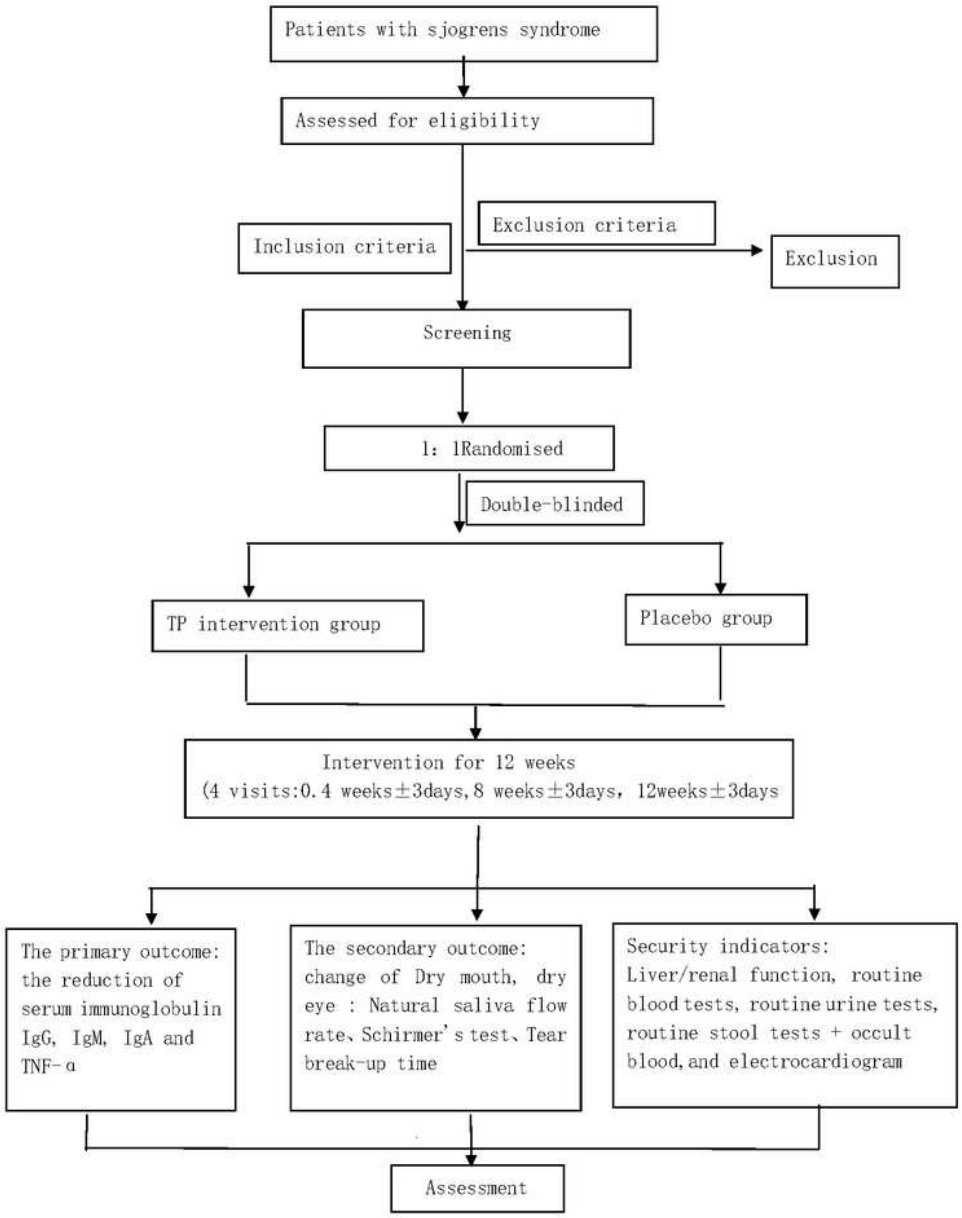

Fig. 1 Flow diagram for the study

Figure 1

Flow diagram for the study

Timepoint	Study period				
	Visit 0	**Visit 1 (0)**	**Visit 2 (4weeks±3days)**	**Visit 3 (8weeks±3days)**	**Visit 4 (12weeks±3days)**
	Screening And consent	**Allocation**	**Post-allocation**		**Clost-out**
Enroll					
Eligibility screening	√				
Informed consent	√				
Allocation		√			
Intervention					
TPintervention		√	√	√	
Placebo		√	√	√	
Assessment					
Underlying disease	√	√	√	√	√
Medication	√	√	√	√	√
Serum IgG/A/M,TNF-α		√	√	√	√
Security indicators		√	√	√	√

Fig. 2 Participant timeline

Figure 2

Participant timeline

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Appendix1consent.pdf
- Appendix2SPIRITchecklist.pdf