

Treatment effects of Chinese medicine (Yi-Qi-Qing-Jie herbal compound) combined with immunosuppression therapies in patients of IgA nephropathy with high-risk of ESRD (TCM-WINE): study protocol for a randomized controlled trial

Jin-pu Li

China Academy of Chinese Medical Sciences Guanganmen Hospital

Shen Li (✉ lishen58173@163.com)

<https://orcid.org/0000-0002-4097-557X>

Study protocol

Keywords: IgA nephropathy, Immunosuppressive, High-risk IgAN, Yi-Qi-Qing-Jie Formula, Traditional Chinese Medicine

Posted Date: December 9th, 2019

DOI: <https://doi.org/10.21203/rs.2.13775/v2>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published on January 6th, 2020. See the published version at <https://doi.org/10.1186/s13063-019-3989-9>.

Abstract

Background: IgA nephropathy (IgAN) is the most common glomerular disease worldwide. It has a high incidence in Asians and is more likely to progress to end-stage renal disease (ESRD). For high-risk IgAN, which is clinically characterized by massive proteinuria and renal dysfunction, however, there has been no international consensus on treatment options. Compared with other developed countries, IgAN patients in China are often found to have severe kidney function loss at initial diagnosis. Yi-Qi-Qing-Jie Formula Granule (a compound recipe of Chinese medicinal herbs, YQF) has shown potential renal protection in our previous clinical studies. To further confirm the efficacy and safety of YQF in the treatment of high-risk IgAN, we design a prospective double-blind randomized placebo-controlled trial. **Methods/Design:** The TCM-WINE study is a single-center, prospective, double-blind randomized placebo-controlled trial. We plan to randomize 60 participants with biopsy-proven IgAN to YQF combined group (YQF compound, combined with prednisolone, and cyclophosphamide if necessary) and immunosuppression group (placebo-YQF, combined with prednisolone, and cyclophosphamide if necessary). The two groups will enter 48-week in-trial treatment phase and receive post-trial follow-up till study completion (3-year). All patients will receive optimal supportive care. The primary composite outcome is defined as the first occurrence of 40% decrease in estimated glomerular filtration rate (eGFR) from the baseline lasting for 3 months, initiating continuous renal replacement treatment or death due to chronic kidney disease (CKD), during the 3-year study phase. The secondary endpoint events are defined as the mean annual eGFR decline rate (eGFR-Slope, ml/min per 1.73 m² per year) which is calculated by the eGFR regression curve for each eligible patient, and proteinuria remission (prescribed as proteinuria < 0.5g/day) at week 24, 36, 48 during the in-trial phase. The remission rate of symptoms and inflammation status will be evaluated respectively at week 48. Safety monitoring and assessment will be undertaken during the study. **Discussion:** TCM-WINE study will evaluate effects and safety of YQF combined therapy compared with immunosuppression monotherapy on basis of optimal supportive treatment in high-risk IgAN. The evidence from this study will provide a novel, effective and safe Chinese characteristic therapy for high-risk IgAN patients. Trial registration: Clinicaltrials.gov, identifier: NCT03418779. Registered on 18 June 2018. <https://clinicaltrials.gov/show/NCT03418779>

Background

IgA nephropathy (IgAN) is the most prevalent primary glomerular disease worldwide and accounts for 45% of the primary glomerular disease in China which significantly contributes to the global burden of chronic kidney disease (CKD) [1,2]. Patients with IgAN are often diagnosed at young age, and about 30% of the patients develop end-stage renal disease (ESRD) in 10-20 years [1,3]. Proteinuria, decreased kidney function and hypertension at diagnosis are the independent risk factors for progression to ESRD. Among them, persistent proteinuria is the strongest predictor developing ESRD [4-6]. According to the 2016 Oxford Classification of IgAN, mesangial or endocapillary hypercellularity, crescents, segmental glomerulosclerosis, and tubular atrophy/interstitial fibrosis are pathological indicators of poor renal outcome [7].

Latest Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Glomerulonephritis recommends angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs) with up-titration to achieve a maximally tolerated dose, as an initial therapy for progressive IgAN. For those patients with persistent proteinuria >1g per day and estimated glomerular filtration rate (eGFR) >50mL/min/1.73m², a 6-month course of high-dose corticosteroid therapy is suggested despite 3–6 months of optimized supportive care (ACEI, ARB, or both, and blood-pressure controlled). Intensive immunosuppression [corticosteroid with cyclophosphamide (CTX) or azathioprine] is reserved for patients with crescents in more than half of the glomeruli and rapidly deteriorating renal function [8]. A meta-analysis has shown that IgAN patients with more serious pathological features may be more resistant to steroid therapy than slight ones according to the earlier outlined Oxford classification system [9].

However, the benefits of systemic immunosuppression have been questioned in recently completed trials. Conflicting results indicate the presence of severe adverse events (SAEs), which imply long-term immunosuppression must be balanced against benefits carefully [10-12]. Other general immunosuppressants, such as mycophenolate mofetil [13,14], calcineurin inhibitors [15], and targeted immunosuppression regimens, like rituximab [16], targeted release formulation-budesonide [17], the selective enzyme spleen tyrosine kinase inhibitor fostamatinib which was recently completed in a Phase III randomized controlled trial (RCT) (ClinicalTrials.gov, NCT02112838), are waiting for more high-quality trials to assess their safety and efficacy. Above all, for high-risk IgAN, a safe, disease-specific therapy remains limited.

Chinese medicine is gradually accumulating evidence-based application in CKD, which has been widely approved for its positive role in prevention and treatment of IgAN [18-21]. Yi-Qi-Qing-Jie Formula (YQF) was developed from the classical Chinese prescription Yupingfeng San, Yinqiao San and Wuweixiaodu Yin, the main constituents including *Astragali radix* (HUANG QI), *atractylodes rhizome* (BAI ZHU), *Radix Saposhnikoviae* (FANG FENG), *oldenlandia diffusa* (BAI HUA SHE SHE CAO), *Rhizoma Dioscoreae Nipponicae* (CHUAN SHAN LONG), and *raw rhubarb* (DA HUANG). We had conducted an ambispective cohort study [22], which matched 34 high-risk IgAN patients with UTP>3g/24h and eGFR<60ml/min/1.73m² who received YQF combined therapy (treatment group), to 34 patients who received immunosuppression monotherapy (control group) from Peking University First Hospital nephrology department, on basis of renin-angiotensin system blockade (RASB). In conclusion, YQF combined therapy exhibited a potential renal protective effect during the mean follow-up period of 43 months. 5 patients (14.71%) reached ESRD (Figure 1) and there were no SAEs associated with immunosuppressants. In Mitsui's study, which was similar to our treatment protocol, 6 patients (22%) treated with prednisolone and cyclophosphamide reached ESRD during the mean follow-up period of 66.5 months, and 2 patients (7.4%) suffered adverse effects of immunosuppression during treatment [23].

However, the study did not use a standardized clinical study design. Hence, we will conduct a randomized, prospective, double-blind (placebo) controlled trial to confirm that, compared with immunosuppressive therapy alone, YQF combined with immunosuppressive therapy will be superior in

renal function protection and reducing severe treatment-related adverse effects in patients with high-risk IgA nephropathy.

Methods/design

Study design

This is a single-center, prospective, double-blind, placebo-controlled randomized trial. This clinical trial is reported according to the Standard Protocol Interventions: Recommendations for Interventional Trials (SPIRIT) guidelines [24] [study schedule (SPIRIT figure) is outlined in Figure 2, checklist see Additional file 1].

Setting and participants

Sixty high-risk IgAN participants will be followed up until 50% (30 of them) have a composite endpoint or been followed for 3 years. The trial will be conducted at Guang'anmen Hospital, Beijing, China, and was approved by the Ethics Committee of Guang'anmen Hospital (approval number: 2018-055-KY-01) in accordance with the Declaration of Helsinki and the principles outlined in the "Guidelines for Good Clinical Practice" from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Tripartite Guideline (January 1997). Participants will be recruited self-selected or referred from inpatients or outpatients, and hospital-based WeChat advertisement. Potential participants will be pre-screened through WeChat, further assessed by our investigator, and consented for the study. The trial will be conducted with all subjects voluntarily and signed informed consent.

Objectives

Based on optimal supportive care, the trial is aiming to assess the superiority in renal protection and reduction of severe treatment-related adverse events using YQF combined therapy, compared with immunosuppression monotherapy in high-risk IgAN.

Rationale of high-risk IgAN

Several high-quality clinical trials mentioned above [11,12] have respectively interpreted the concept of "high-risk" clinically and pathologically while not specifically. Drawn from the inclusion criteria of above-mentioned trials, this study will define "high-risk" as persistent heavy proteinuria ($\geq 1\text{g/d}$ despite intensive optimal supportive care) with impaired renal function (eGFR 15-60 ml/min/1.73m²).

Inclusion and exclusion criteria

The inclusion criteria are as follows: (1) in accordance with IgAN pathological diagnosis, renal biopsy within 6 months; (2) persistent proteinuria $\geq 1\text{g/d}$ despite at least 8 weeks of optimal supportive care [maximally tolerated RAS blocker which refers to no symptomatic hypotension, no hyperkalemia, and

serum creatinine (SCr) increased not more than 30% of baseline, blood pressure control meeting targets (135/85 mmHg or lower), and dietary management (sodium intake less than 6g/d, protein intake of 0.6-0.8g/kg/d, and low-fat diet)]; (3) eGFR 15 to 60 ml/min/1.73 m², calculated with the use of CKD-EPI Creatinine Equation 2009; (4) patients who maintain regular follow-up at Guang'anmen Hospital, agree to participate and obtain informed consent. (Additional file 2 shows the Informed Consent Form in more detail)

The exclusion criteria are as follows: (1) secondary IgAN; (2) comorbidity of other primary or secondary glomerular diseases; (3) comorbidity of severe primary diseases such as cardiovascular, hepatic, cerebral, hematopoietic system diseases or mental disorders; (4) allergy or intolerance to the experimental medication (e.g., RAS blockers, prednisolone, cyclophosphamide, YQF compound and its placebo compound) ; (5) contraindications of immunosuppression therapy: acute and chronic infectious diseases, malignancies, leukopenia, thrombocytopenia, gastrointestinal hemorrhage, ulcers of stomach or duodenum, post-transplantation; (6) pregnant or lactating women; (7) unwilling to participate in this study, failure to accept or tolerate Chinese medicine compound; (8) history of alcohol or drug abuse; (9) poor compliance, loss to follow-up; (10) participation in another clinical investigation.

Randomization and masking

In the case that the subjects are eligible to participate and have signed informed consent, 30 patients in each group of the YQF group and the control group will be randomly selected in 1:1 ratio after run-in phase. A central stochastic system developed by the Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences, which based on SAS 9.4.3 (SAS Institute, Cary, NC, USA), will perform the randomization. Independent experts will generate the randomization sequence which will be concealed in opaque, sealed and stapled envelopes. Participants, investigators, and other all members with clinical involvement in the trial will be masked to the treatment assignment for the duration of the trial. Relevant personnel have clear division of labor and strict permission restrictions. The masking will be removed only if the participant occurs severe side effects that need to terminate the trial.

Interventions

Run-in period (pre-trial, 4 weeks)

Eligible participants will enter a run-in period for 4 weeks, during which they will receive an optimized basic treatment, including living behavior management (smoking cessation, alcohol restriction, weight control, low-salt and proper protein diet), maximum tolerated dose of ACEI or ARB, blood pressure control to a target below 135/85 mmHg, controlling glycated hemoglobin ≤7% by using insulin or oral hypoglycemic agents in diabetics, reaching targets in serum uric acid (UA) (<420umol/L in male, <360umol/L in female) by uric acid-lowering medications in hyperuricemia, and stopping other Chinese medicine treatments.

Treatment period (in-trial, 48 weeks)

At the end of the run-in period, participants who fulfill all eligible criteria and no exclusion criteria, will be randomized to either the YQF combined immunosuppression therapy (YQF group) or matching placebo combined with immunosuppression therapy (control group) in a double-blind fashion with a total treatment period of 48 weeks. Both groups will continue their basic treatment as mentioned above in the pre-trial phase.

Immunosuppression therapy. oral prednisolone (0.5-0.8 mg/kg/d, exact dose decided by the investigator, maximum dose not exceeding 60 mg/d) for 8 weeks, then tapered by 5~10 mg/d every 4 weeks, with a total treatment period of 24-32 weeks. Participants with persistent proteinuria $\geq 1\text{g/d}$ after 8-weeks of corticosteroid monotherapy, will receive 0.8-1.0g of intravenous cyclophosphamide (CTX) every 4 weeks, total dose of not exceeding 8g (exact dose decided by the site Investigator). If severe CTX-related adverse events occur, such as alanine transaminase (ALT) exceeding the upper limit of 2 times, infections requiring hospitalization, granulocytes $< 3.0 \times 10^9/\text{L}$ and platelets $< 50.0 \times 10^9/\text{L}$, stop using CTX, symptomatically treated and record adverse events. The frequency of detection is increased to once every 2 weeks, and the trial is terminated if persistent infection or myelosuppression occurs.

YQF Formula Granule. obtained from Sichuan Xinlv Yao Co. (Chengdu, Sichuan, China), manufacturing process complying with Chinese GMP. The compounds are blends of individual herbal extract from YQF formula (consist of: *astragalus membranaceus*, *saposhnikovia divaricata*(turcz.) *schischk*, *Flos Lonicerae*, *Angelica Sinensis*, *Dioscorea Nipponica*, *hedyotis diffusa willd*, *rhubarb*, *Spatholobus Suberectus*), dissolved in 150ml boiled water and taken orally twice a day.

YQF placebo. obtained from Sichuan Xinlv Yao Co. (Chengdu, Sichuan, China), manufacturing process complying with Chinese GMP. Major component: malt dextrine, with similar appearance and the package, dissolved in 150ml boiled water and taken orally twice a day.

Follow-up period (post-trial)

All participants will continue their previous basic treatment agents.

Follow-up assessments

Participants will be visited at regular intervals, for a planned mean of at least 3 years until the end point occurs. In run-in period and treatment period, study visits occur every 4 weeks until week 24, and every 12 weeks face-to-face or by telephone in consideration of choice of the participants and investigators, till the end of the trial. The measurements will be performed at qualified laboratories during the follow-up period.

Laboratory measurements including: (1) urine tests: 24h urine total protein (UTP) measured using biuret method, albumin/creatinine ratio (ACR) ; (2) blood tests: serum creatinine, albumin (ALB), blood urea nitrogen (BUN), uric acid (UA), blood glucose (GLU), total cholesterol (CHO), electrolytes (K, Na, Cl), triglyceride (TG), alanine transaminase (ALT), aspartate aminotransferase (AST), hemoglobin (HGB), white blood cell count (WBC), and platelets (PLT).

General conditions inspection includes body weight, appetite, excretory functions, stamina, mobility, sleep, etc. Vital signs inspection includes temperature, respiration, pulse and blood pressure. Rational symptoms and chronic inflammation status will be recorded by investigators on case report forms (CRFs) as syndrome scores for effectiveness assessment. Each symptom is scored on a 4-point scale ranging from 0 (absent) to 3 (severe), and a total symptom score is calculated by adding together the values for all 3 symptoms. Similarly, we get a total chronic inflammation status score (see Additional file 5).

The final follow-up duration will be continued until the occurrence of primary end point or keeping visit up to 3 years (Figure 3).

Outcome measures definition

The primary composite end point is defined as the first occurrence of 40% decrease in eGFR from baseline eGFR, progression to continuous renal replacement, or death due to renal disease.

The secondary composite end points are defined as (1) main outcome measurement: the mean annual reduction in eGFR based on SCr (eGFR-slope); (2) proteinuria remission (prescribed as proteinuria <0.5g/d) at week 24, 36, 48 in treatment period, and month 6, 12, 24, or 36 if possible. The remission rate of symptoms and inflammation status will be evaluated at week 48, respectively.

Adverse events and safety

Adverse events and SAEs will be inspected at each follow up, including infections requiring hospitalization, thromboembolic events, hepatic dysfunction, hematopoietic disorders, fracture or osteonecrosis and new onset diabetes. SAEs are defined according to the definitions of Good Clinical Practice (GCP) by the China Food and Drug Administration (CFDA). The researcher will report the events to the principal investigator and the Ethics Committee within 24 hours of occurrence of the SAE, who will give a final decision on whether or not to continue the study treatment and identify appropriate support for the patients involved. Furthermore, treatment interruption due to any events and relevant measures will be recorded on the CRFs. The influence of all adverse events will be analyzed at the end of the trial.

Termination and withdrawal

Participants will be withdrawn from the trial in any of the following situations: (1) SAEs related with immunosuppression: severe infections (e.g., pulmonary infection requiring ventilatory support), serious granulocytopenia/thrombocytopenia (e.g., $WBC < 2.0 \times 10^9/L$, $PLT < 20 \times 10^9/L$); (2) participants or investigators fail to obey the study protocol; (3) participants behave poor compliance, experimental medications are taken less than 30%; (4) termination requested by data and safety monitoring board, ethics committee or study principal investigator: in the best interest of the participants, the investigator can request for termination of individual participation if the study treatment is of insignificant clinical benefit.

Sample size calculation

On basis of our recent trial from above [22], eGFR-Slope after 12-month treatment as the primary endpoint, we define $\delta=(\mu_1-\mu_2)/\sigma$, σ as the pooled standard deviation (sample size calculation, see Additional file 4), where μ is the treated mean, respectively. We calculate $\delta=0.994$, approximately equivalent as 1.0, according to the look-up table of counts (Medical Statistics Method, PH Jin, Shanghai Medical College Press, see Additional file 3), using $\alpha=0.05$ and $\beta=0.1$, we require a sample size of 46 participants. Assuming 25% dropout adaptation and in view of $n=30$ as a rule of thumb for a small size clinical trial, we plan to recruit 60 patients for this study (30 patients per group).

Statistical analysis

Investigators will fill the CRFs as making follow-up observations by interviewing the participants. Paper CRFs will be interpreted into database by those investigators in order to ensure data validity. An independent statistician will unblind and extract clean data from final database for analysis after locking. Data analysis of treatment effect and safety follows the intention-to-treat principle. Investigators can access the final database only when both data analysis and study are complete. The endpoint events will be described by Kaplan-Meier method and the between-group difference will be compared using log-rank test. T-test will be used for scale variables, chi-square test or variance analysis will be used for binomial and nominal variables, nonparametric test will be used for ordinal variables. The eGFR-slope will be calculated as the individual slopes obtained from individual linear regressions of eGFR during the follow-up period. All analyses will be performed using SPSS software version 23.0 (IBM Analytics). Differences are considered to indicate statistically significant for 2-sided $P < 0.05$.

Quality control and monitoring

A Data and Safety Monitoring Board (DSMB) will be established to monitor the performance of the overall study, ensure safety and welfare of participants, and review quality of the data on regular meetings. The DSMB, which is independent of the present trial, consists of three members, including a clinical nephrologist, a statistician and an ethical specialist (see Additional file 6). The DSMB will assess that participants receive good clinical care and that safety concerns are interpreted and addressed appropriately. Moreover, the DSMB will make recommendations and decisions on any modification of the protocol, even termination of the study based on the interim analysis of efficacy and safety. In order to improve compliance with the protocol until completion, we will intensify patient management through one-to-one WeChat follow-up by designate researchers. Participants' medical records (including CRFs, consent forms, etc.) will be archived securely and used only within the validity period.

Intention-to-treat analysis will be used for subjects who dropout or withdraw from the study, which includes every subject who is randomized according to randomized treatment assignment regardless of whether he/she receives the treatment of this group or not, should finally be included in the assigned group for statistical analysis of efficacy.

Last observation carried forward method will be applied in missing data of longitudinal observations.

Discussion

IgAN is considered to be an autoimmune disease, it is logical that immunosuppression therapy may be effective [10,26]. As the therapeutic benefits of intensive supportive care show, it's the cornerstone of treatment in IgAN. Recently completed high-profile RCTs with rigorous standardization and optimization of supportive management have focused on the outcomes of additional immunosuppression. STOP-IgAN trial [11] showed that the additional immunosuppression therapy (oral corticosteroids plus CTX and azathioprine) did not exert substantial renal protection for those with eGFR 30-59 ml/min/1.73m², including one death due to sepsis related to steroids. However, the trial excluded patients with 24hUTP >3.5g, eGFR <30 ml/min/1.73m², or eGFR decreased more than 30% at the end of 6-month run-in phase which often underlies relatively high risk in disease progression and a better response to steroids. In TESTING study [12], after a 3-month run-in phase of optimal supportive treatment, recruiting participants with 24hUTP >1g and eGFR of 20-120 ml/min/1.73m², was terminated because of two deaths of infection and excess SAEs in methylprednisolone group. Early results could not demonstrate definite treatment efficacy in steroid therapy though they have shown indication in short-term potential renal benefits. Both trials highlight the safety concerns about immunosuppression, and necessary to seek for approach which is alternative, safe and effective in high-risk IgAN.

Traditional Chinese medicine has initiative proved promising effects regarding safety and renoprotection with some RCTs in chronic kidney diseases, for instance, *Abelmoschus manihot* [27], however, it is notable that this trial excluded patients with impaired renal function (eGFR <60 ml/min/1.73m²) and nephrotic syndrome. In clinical practice, we also get patient feedback of symptomatic amelioration with respect to application of Chinese medicine. Therefore, we conduct TCM-WINE, a prospective, double-blind, single-dummy controlled, randomized trial, aiming to evaluate safety and long-term outcomes with YQF herbal compound compared to immunosuppression monotherapy in treating high-risk IgAN. In conclusion, the results of TCM-WINE will provide clinical evidence for the efficacy and safety of YQF compound, moreover, this trial will serve as an important step toward new era of treatment in high-risk IgAN.

Trial status

Recruitment for this study began on 4 July 2019 (protocol version 03, 22 November 2019). It's estimated that recruitment will be completed in August 2020.

Abbreviations

ACEI: Angiotensin-converting enzyme inhibitor; ACR: Albumin/creatinine ratio; ALT: Alanine transaminase; ALB: Albumin; ARB: Angiotensin-receptor blocker; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; CFDA : China Food and Drug Administration; CRF: Case Record Form; CHO: Total cholesterol; CKD: Chronic kidney disease; CTX: Cyclophosphamide; DSMB: Data and Safety Monitoring Board; eGFR: Estimated glomerular filtration rate; ESRD: End-stage renal disease; GCP: Good Clinical Practice; GLU:

Blood glucose; HGB: Hemoglobin; IgAN: Immunoglobulin A nephropathy; KDIGO: Kidney Disease: Improving Global Outcomes; PLT: Platelets; RASB: Reninangiotensin system blockade; RASB: Reninangiotensin system blockade; RCT: Randomized controlled trial; SAE: Severe adverse event; SCr: Serum creatinine; SPIRIT: Standard Protocol Interventions: Recommendations for Interventional Trials; TG: Triglyceride; UA: Uric acid; UTP: Urine total protein; WBC: White blood cell count; YQF: Yi-Qi-Qing-Jie Formula Granule.

Declarations

Funding

This study is supported by the Beijing Municipal Science & Technology Commission (grant number: Z181100001718123) and the special research projects of national traditional Chinese medicine clinical research demonstration base of Guang'anmen Hospital (grant number: 2017S379). The funding body has no role in the design, conduct, or analysis of the study.

Acknowledgements

We are grateful to Professor Ji-cheng Lv, Renal Division, Department of Medicine, Peking University First Hospital for advice on trial design, Dr. Li-yun He, Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Sciences and her team for randomization by their central stochastic system. The authors are also grateful to the Beijing Municipal Science & Technology Commission and Guang'anmen Hospital for funding this study.

Availability of data and material

The trial results will be published through publication in a peer-reviewed journal and poster or oral presentations in conferences. The datasets generated or analyzed during the current study will available from the corresponding author upon reasonable request.

Authors' contributions

Shen Li and Ji-cheng Lv discussed and designed the trial. Shen Li and Jin-pu Li drafted and finalized the manuscript. Shen Li reviewed the final version. All authors approved the final version of the manuscript.

Competing interests

No competing interests.

Consent for publication

Not applicable.

Ethics approval and the consent

This study has been approved by the Ethics Committee of Guang'anmen Hospital (approval number: 2018-055-KY-01). Patients who agree to participate and sign the informed consent will be involved.

References

- [1] Wyatt RJ, Julian BA. IgA nephropathy. *N Engl J Med*. 2013;368(25):2402-2414.
- [2] Li LS, Liu ZH. Epidemiologic data of renal diseases from a single unit in China: analysis based on 13,519 renal biopsies. *Kidney Int*. 2004;66(3): 920-923.
- [3] Le W, Liang S, Hu Y, et al. Long-term renal survival and related risk factors in patients with IgA nephropathy: results from a cohort of 1155 cases in a Chinese adult population. *Nephrol Dial Transplant*. 2012;27(4):1479-1485.
- [4] Reich HN, Troyanov S, Scholey JW, Cattran DC. Toronto Glomerulonephritis Registry. Remission of proteinuria improves prognosis in IgA nephropathy. *J Am Soc Nephrol*. 2007;18(12):3177-3183.
- [5] Lv J, Shi S, Xu D, Zhang H, Troyanov S, Cattran DC, Wang H. Evaluation of the Oxford Classification of IgA nephropathy: a systematic review and meta-analysis. *Am J Kidney Dis*. 2013; 62: 891-899.
- [6] Zhang C, Zeng X, Li Z, Wang Z, Li S. Immunoglobulin A nephropathy: current progress and future directions. *Transl Res*. 2015; 166: 134–44.
- [7] Trimarchi H, Barratt J, Cattran DC, et al. Oxford Classification of IgA nephropathy 2016—the role of crescentic lesions: an update from the IgA Nephropathy Classification Working Group. *Kidney Int*. 2017 May;91(5):1014-1021.
- [8] Kidney Disease: Improving Global Outcomes group. KDIGO Clinical Practice Guideline for Glomerulonephritis. *Kidney International Supplements*. 2012;2: 209–217.
- [9] Yang P, Chen X, Zeng L, Hao H, Xu G. The response of the Oxford classification to steroid in IgA nephropathy: a systematic review and meta-analysis. *Oncotarget*. 2017;8(35):59748–59756.
- [10] Tesar V, Troyanov S, Bellur S, et al. Corticosteroids in IgA Nephropathy: A Retrospective Analysis from the VALIGA Study. *J Am Soc Nephrol*. 2015 Sep;26 (9): 2248-58.
- [11] Rauen T, Eitner F, Fitzner C, et al. Intensive supportive care plus immunosuppression in IgA nephropathy. *N Engl J Med*. 2015;373(23):2225-2236.
- [12] Lv J, Zhang H, Wong MG, et al. Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy. *JAMA*. 2017;318(5): 432-442.
- [13] Tang SC, Tang AW, Wong SS, Leung JC, Ho YW, Lai KN. Long-term study of mycophenolate mofetil treatment in IgA nephropathy. *Kidney Int*. 2010;77(6):543–549.

- [14] Hou JH, Le WB, Chen N, et al. Mycophenolate Mofetil combined with Prednisone versus full-dose Prednisone in IgA Nephropathy with active proliferative lesions: A randomized controlled trial. *Am J Kidney Dis.* 2017 Jun;69(6):788-795.
- [15] Song YH, Cai GY, Xiao YF, et al. Efficacy and safety of calcineurin inhibitor treatment for IgA nephropathy: a meta-analysis. *BMC Nephrol.* 2017;18(1):61.
- [16] Lafayette RA, Canetta PA, Rovin BH, et al. A randomized, controlled trial of rituximab in IgA nephropathy with proteinuria and renal dysfunction. *J Am Soc Nephrol.* 2017;28(4):1306–1313.
- [17] Fellstrom BC, Barratt J, Cook H, et al. Targeted-release budesonide versus placebo in patients with IgA nephropathy (NEFIGAN): a double-blind, randomized, placebo-controlled phase 2b trial. *Lancet.* 2017;389(10084):2117–2127.
- [18] Wang YJ, He LQ, Sun W, Lu Y, Wang XQ, Zhang PQ, et al. Optimized project of traditional Chinese medicine in treating chronic kidney disease stage 3: a multicenter double-blinded randomized controlled trial. *J Ethnopharmacol.* 2012;139(3):757–64.
- [19] Zhong Y, Menon MC, Deng Y, Chen Y, He JC. Recent advances in Traditional Chinese Medicine for kidney disease. *Am J Kidney Dis.* 2015;66:513–22.
- [20] Peng T, Yang XD, Li DR, Guo L, Xia Q, Hu Z. Observation of effect of Huang Kui capsule combined with valsartan in the treatment of IgA nephropathy. *Chin J Integr Tradit West Nephrol.* 2010;11:723–4.
- [21] Efficacy and Safety of *Abelmoschus manihot* for Primary Glomerular Disease: A Prospective, Multicenter Randomized Controlled Clinical Trial. *Am J Kidney Dis.* 2014;64(1):57-65.
- [22] Shen LI, Mo-yang DONG, Xiang-rong RAO, et al. Effect of Yiqi Qingjie Formula combined with immunosuppressive therapies on IgA nephropathy with high-risk factor: a propensity score matching analysis. *Chinese Journal of Integrated Traditional and Western Medicine.* 2019; doi: 10.7661/j.cjim.20190429.010. [Article in Chinese with English abstract].
- [23] Mitsuiki K, Harada A, Okura T, Higaki J. Histologically advanced IgA nephropathy treated successfully with prednisolone and cyclophosphamide. *Clin Exp Nephrol.* 2007; Dec;11(4):297-303.
- [24] Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ.* 2013;346:e7586
- [25] Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. *Am J Kidney Dis.* 2010;55:622–7.
- [26] Kim JK, Kim JH, Lee SC, et al. Clinical features and outcomes of IgA nephropathy with nephrotic syndrome. *Clin J Am Soc Nephrol.* 2012;7(3):427–436.

[27] Zhang L, Li P, Xing CY, et al. Efficacy and Safety of Abelmoschus manihot for Primary Glomerular Disease: A Prospective, Multicenter Randomized Controlled Clinical Trial. Am J Kidney Dis. 2014 Jul;64(1):57-65.

Tables

Table 1 Baseline characteristics of participants in our former ambispective cohort study

	Treatment group (N =34)	Control group (N =34)	<i>P</i>
Age, y	38.50 ±11.62	38.21 ± 13.05	0.92
Male, N (%)	64.71	55.88	0.31
SBP (mmHg)	126.18±11.68	124.94±13.64	0.69
DBP (mmHg)	74.71±14.35	77.97±10.06	0.28
UTP (g/24h)	3.85□3.19 - 4.89□	3.82□2.36 - 5.89□	0.78
SCr (umol/L)	154.82 ± 70.58	175.53 ± 80.01	0.26
eGFR (ml/min/1.73m ²)	47.43 ±14.75	46.52 ± 22.61	0.84
Alb (g/L)	35.29 ±3.37	34.71 ± 6.68	0.64

Values for continuous variables are given as mean ± standard deviation. The non-normal variables are presented as median and □interquartile range□. Alb=albumin, DBP=diastolic pressure, eGFR=estimated glomerular filtration rate, N=intention-to-treat patients number, SBP=systolic pressure, SCr=serum creatinine, UTP=urine total protein.

Table 2 Renal function and proteinuria changes at the end of the in-trial phase

	Treatment group (N =34)	Control group (N =34)	Odds Ratio (95%CI)	P
Δ eGFR (ml/min/1.73m ²)				
6m	14.16±11.55	-0.45±13.97	4.70	0.00
12m	16.67±18.09	-2.72±16.34	4.52	0.00
eGFR-Slope (ml/min/1.73m ² per month)	1.39±1.51	-0.26±1.39	4.69	0.00
Proteinuria reduction(g/24h)				
6m	1.93[1.54 - 2.74]	1.60[0.97 - 2.97]	0.85	0.39
12m	2.48[1.70 - 3.38]	1.81[1.29 - 3.90]	0.16	0.87
Proteinuria complete remission, N (%)	5 (14.71)	9 (26.47)	2.09[0.62-7.05]	0.37

M=month, N=number of patients in the respective population, Δ eGFR=[after-treatment]-[before-treatment], proteinuria complete remission was defined as proteinuria<0.5g/d after treatment.

Additional File Legends

File 1. SPIRIT checklist doc

File 2. Informed consent form doc

File 3. Look-up table pdf from Medical Statistics Method, PH Jin, Shanghai Medical College Press

File 4. Sample size calculation xls

File 5 Syndrome scale in CRF doc

File 6 DSMB members doc

Supplementary files

See editorialmanager system

Figures

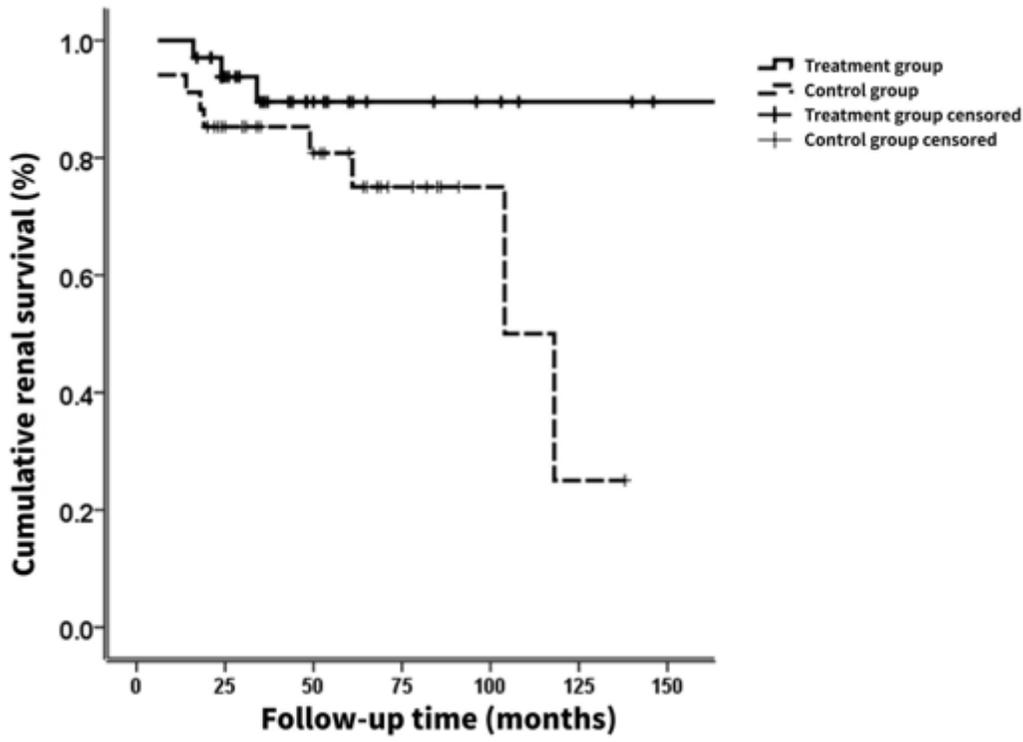


Figure 1

Cumulative renal survival curves

		STUDY PERIOD										
		Enrolment	Allocation	Post-allocation								Close-out
TIMEPOINT		-4w	0	4w	8w	12w	16w	20w	24w	36w	48w	After 48w
Eligibility screen /Informed consent		X										
Allocation			X									
INTERVENTIONS:												
Optimal supportive care												
YQF group	YQF compound +immunosuppression therapy											
Control group	YQF compound placebo +Immunosuppression therapy											
Primary Outcome Measurement	eGFR (CKD-EPI Equation)	X	X	X	X	X	X	X	X	X	X	X
	ESRD*/ Death**	X	X	X	X	X	X	X	X	X	X	X
Second Outcome Measurement	24hUTP	X	X	X	X	X	X	X	X	X	X	X
Other assessments	General condition, vital signs inspection & syndrome scores	X	X	X	X	X	X	X	X	X	X	X
	Serum potassium	X	X	X	X	X	X	X	X	X	X	X
	Blood routine	X	X	X	X	X	X	X	X	X	X	X
	Liver function	X	X	X	X	X	X	X	X	X	X	X
	Adverse events			X	X	X	X	X	X	X	X	X

* End stage kidney disease requiring ongoing maintenance dialysis or renal transplantation

** Death due to kidney disease.

Figure 2

Study schedule * End stage kidney disease requiring ongoing maintenance dialysis or renal transplantation. ** Death due to kidney disease.

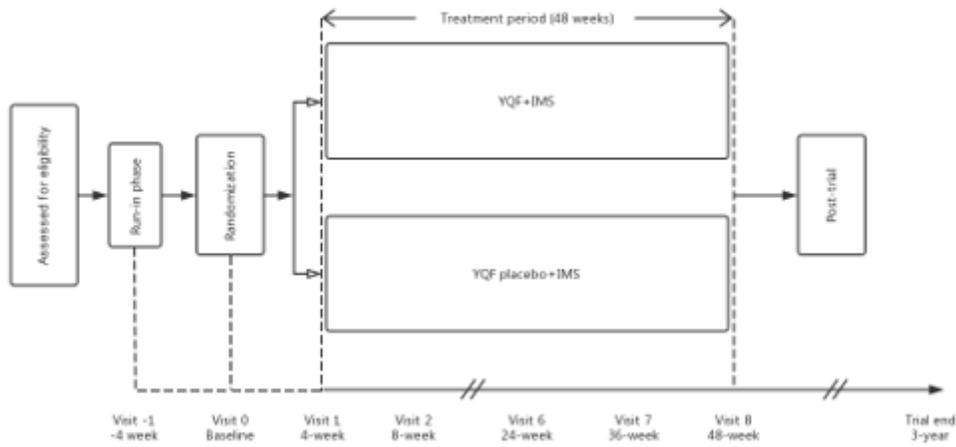


Figure 3

Clinical trial flow diagram

Supplementary Files

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

- [SPIRITFigure.doc](#)
- [Additionalfile6DSMB.pdf](#)
- [1SPIRITchecklistofTCMWINEver1.75.pdf](#)
- [Additionalfile5syndromescaleinCRF.pdf](#)