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Protocol for an open-label, single-arm, multicentre clinical study to evaluate the efficacy and safety of rituximab in the first episode of paediatric idiopathic nephrotic syndrome

Jialu Liu,[1] Qian Shen,[1] Li Xie,[2,3] Jiyang Wang,[4] Yaxuan Li,[4] Jing Chen,[1] Xiaoyan Fang,[1] Xiaoshan Tang,[1] Biyun Qian,[2,3] Hong Xu [1]

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JL, QS and LX contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Professor Hong Xu; hxu@shmu.edu.cn and Professor Biyun Qian; qianbiyun@sjtu.edu.cn

ABSTRACT

Introduction Rituximab (RTX) effectively prevents relapses in patients with complicated steroid-sensitive nephrotic syndrome (SSNS). The 1-year relapse-free survival rate is approximately 30% in children after the first episode of SSNS treated with standardised corticosteroids. Whether the benefits of RTX extend to the first relapse are unknown. The efficacy and safety of RTX in the first episode of paediatric idiopathic nephrotic syndrome (RTXFIRPedINS) trial (NCT04783675) will assess its effect on the risk of subsequent relapse.

Methods and analysis RTXFIRPedINS is an open-label, single-arm, multicentre trial targeting patients aged 1–18 years with a first episode of SSNS. All patients will receive standardised corticosteroid treatment for 12 weeks. A sample size of 44 patients provides 80% power to detect a 20% increase in the 1-year relapse-free rate, assuming a dropout rate of 10%. After obtaining informed consent and screening, eligible patients will be treated with a single intravenous infusion of 375 mg/m^2 RTX within 1 week after achieving remission. Trimethoprim-sulfamethoxazole will be administered for 3 months after RTX administration to prevent *Pneumocystis carinii* infection. The follow-up period will be 1 year. The primary outcome is the 1-year relapse-free survival rate after RTX infusion. The secondary study outcomes are the number of days from the infusion of RTX to the occurrence of the first relapse, 6-month relapse-free survival rate, the B cell recovery time and treatment-related adverse events. Immunological factors will be studied as predictors of response.

Ethics and dissemination This trial was approved by the Ethics Committee of the Children's Hospital of Fudan University and seven local ethics committees. We will publish our study results in peer-reviewed journals and present them at international scientific meetings.

Trial registration number NCT04783675

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will be conducted as an open-label, single-arm, multicentre clinical study trial coordinated by a large national centre for paediatric nephrology.
⇒ It will provide patients and healthcare providers with first important information about the benefits and risks of rituximab in combination with guideline-recommended prednisone/prednisolone treatment for the first episode of steroid-sensitive nephrotic syndrome in children.
⇒ Limitations include biases in patient selection and outcome evaluation owing to the single-arm design, despite the use of strict eligibility criteria and an objective endpoint.

INTRODUCTION

Idiopathic nephrotic syndrome (INS) is one of the most common paediatric glomerular diseases.[1] Its incidence is the highest in Asians, at 7.14 per 100 000 children per year.[2] The pathogenesis is thought to involve immune dysregulation, systemic circulating factors or inherited structural abnormalities of the podocyte.[3]

The updated International Paediatric Nephrology Association (IPNA) 2020[4] and Kidney Disease Improving Global Outcome (KDIGO) 2020[5] guidelines recommend that children with a first episode of INS should be treated with corticosteroids for a total of 8–12 weeks. Approximately, 85% of patients experience complete remission of proteinuria within 4–6 weeks following guideline-recommended corticosteroids and have steroid-sensitive nephrotic syndrome (SSNS). However, the 1-year relapse-free survival rate is only approximately 30%,[6] and the risk for all relapses is 66.2%–87.4%.[7] Half of these children will experience frequentlyrelapsing nephrotic syndrome (FRNS) or become steroid-dependent nephrotic syndrome (SDNS),[8] and they may experience serious side effects from further steroid treatment or

other immunosuppressive drugs. Therefore, prevention of relapse is an important objective of therapy.

Rituximab (RTX) is a monoclonal antibody against the cluster of differentiation antigen 20 (CD20) on B cells and may be a valuable additional agent for the treatment of children with FRNS/SDNS. Recently, the Cochrane Database of Systematic Reviews[9] reported that in children with FRNS/SDNS, RTX used alone or with other immunosuppressive therapies likely reduces the number of children who relapse at 3, 6 and 12 months. Although the risk of infections may not be increased, infusion reactions may be more common.

Whether the benefits of RTX extend to the first relapse are unknown. The efficacy and safety of RTX in the first episode of paediatric INS (RTXFIRPedINS) trial will test the hypothesis that RTX, in addition to guideline-recommended corticosteroids, safely increases the 1-year relapse-free survival rate in children with a first episode of SSNS.

METHODS AND ANALYSIS

Objectives

The primary objective is to assess whether RTX added to guideline-recommended corticosteroids is effective for maintaining remission for 1 year after infusion in children with a first episode of SSNS. In addition, the trial will examine the number of days from the infusion of RTX to the occurrence of the first relapse, the 6-month relapse-free survival rate, B cell recovery time and treatment-related adverse events. Exploratory endpoints include changes in immunological factors to be studied as predictors of response and relapse.

Design

RTXFIRPedINS is an open-label, single-arm, multicentre clinical trial that has recruited 44 patients from eight hospitals in China. Figure 1 shows the overall design of the study.

Trial participants

The trial participants were patients aged 1–18 years with the first episode of SSNS. Patients were required to achieve complete remission of proteinuria within 4 weeks following the guideline-recommended corticosteroids. Furthermore, patients should not have recently received immunosuppressive agents or live vaccines. The additional inclusion and exclusion criteria are listed in box 1.

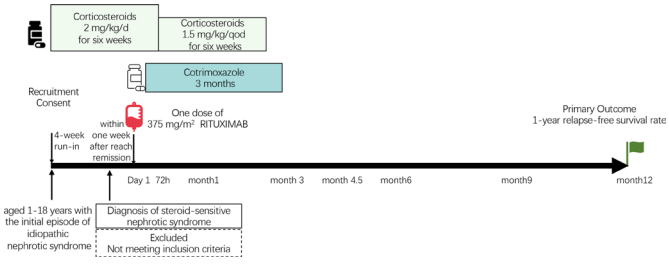

Figure 1 Schematic view of trial design.

Box 1 Inclusion and exclusion criteria of the rituximab in the first episode of paediatric idiopathic nephrotic syndrome trial

Inclusion criteria

1. Children between 1 and 18 years with steroid-sensitive nephrotic syndrome (nephrotic-range proteinuria and either hypoalbuminaemia or oedema when albumin level is not available).
2. An estimated glomerular filtration rate ≥90 mL/min/ 1.73 m^2 at study entry.
3. Remission at study entry.
4. CD20+ cells in peripheral blood ≥1% total lymphocytes.
5. No immunosuppressive agents have been used within 3 months of enrolment, except for the use of corticosteroid to treat nephrotic syndrome.
6. Provision of consent by a legal representative using a document approved by the institutional review board after receiving an adequate explanation of this clinical trial. For children aged 8–18 years, written assent is required using age-appropriate and background-appropriate documents.

Exclusion criteria

1. Diagnosis of secondary nephrotic syndrome.
2. Patients showing one of the following abnormal clinical laboratory values: leucopenia (white cell count ≤3.0×10^9/L); moderate and severe anaemia (haemoglobin <90 g/L); thrombocytopenia (platelet count <100×10^{12}/L); positivity of autoimmunity tests (Antinuclear antibody (ANA), anti-DNA antibody and Antineutrophil autoantibodies (ANCA) or reduced C3 levels; alanine aminotransferase or aspartate aminotransferase >2.5 × upper limit of normal value.
3. Presence of severe or chronic infections within 6 months before assignment: tuberculosis or in whom tuberculosis is suspected; Epstein-Barr virus or cytomegalovirus (CMV) virus; hepatitis B, hepatitis C or hepatitis B virus carrier; HIV or other active viral infections.
4. Live vaccination within last month.
5. Patients with poorly controlled hypertension.
6. Patients with severe brain, heart, liver and other important organs, as well as blood and endocrine system diseases.
7. Presence or history of autoimmune diseases, primary immunodeficiency or tumour.
8. Patients with a known allergy to rituximab and its excipients.
9. Assessed to be unfit for participation by the investigators (patients highly likely to be lost to follow-up or provide inaccurate data, eg, patients with alcohol or other substance misuse disorders, or patients with psychological disorders).

Enrolment

All patients affected by INS in the nephrology units of the registered hospitals were evaluated for recruitment. A preliminary interview was conducted to verify the eligibility criteria. A study coordinator described the project and delivered the informational material. Eligible participants received standard prednisone/prednisolone treatment after blood sample collection. They participated in a 4-week run-in period, during which instructions on urine collection and dipstick readings were carefully reviewed, and compliance was assessed until complete remission was reached (urine protein/creatinine ratio ≤0.2 mg/mg or negative or trace dipstick on three or more consecutive occasions in first morning samples).

Table 1 Clinical trial schedule

	Screening period	Observation period		Follow-up period						
Visit	V0	V1		V2	V3	V4	V5	V6	V7	Relapse
Day	Within 28 days	RTX administration period		28±7	91±7	133±7	182±7	273±7	365±7	Within 3 days
		Before RTX	Within 72 hours after RTX							
Obtaining informed consent	√	√								
Background survey	√									
Medical examination	√	√	√	√	√	√	√	√	√	√
Height/weight/blood pressure/pulse	√	√	√	√	√	√	√	√	√	√
Urinalysis	√	√	√	√	√	√	√	√	√	√
Complete blood count and biochemistry (kidney function, liver function, lipid status-cholesterol and triglycerides, and albumin)	√	√	√	√	√	√	√	√	√	√
Lymphocyte subset testing	√	√	√	√	√	√	√	√	√	√
Immunoglobulin examination	√	√	√	√	√	√	√	√	√	√
Peripheral blood B cell, T cell and myeloid cell subsets	√Before corticosteroids	√	√	√	√		√	√	√	√
Chest X-ray	√									√
Echocardiography and ECG	√									√
Any adverse report yes/no (if yes—describe in full detail)		√	√	√	√	√	√	√	√	√
Use of any other drugs	√	√	√	√	√	√	√	√	√	√

RTX, rituximab.

After confirming all the inclusion/exclusion criteria, secondary registration was performed.

Written informed consent from the parent or guardian and the child's assent (online supplemental material) was obtained before any study-related procedures were performed.

Study period

Investigators will conduct observations and examinations in accordance with the prescribed schedule (table 1).

The study period began on the date consent was obtained and will end on the date of completion of the observation period. Dipsticks for proteinuria determination are evaluated daily. Study visits are scheduled for the screening period as follows: at RTX administration; at 1, 3, 4.5, 6, 9 and 12 months after RTX administration; and at the time of relapse. Each visit will include the collection of information regarding potential endpoints, adverse events and concomitant therapies. Vital signs will be recorded. Urinalysis, complete blood count, biochemistry, immunoglobulins and lymphocyte subpopulations will be evaluated according to the standard laboratory practice. A study coordinator will maintain ongoing

contact to minimise dropouts. Follow-up visits will be performed at the same institution or by local nephrologists if travel is impossible.

Intervention

RTX was infused intravenously at a dose of 375 mg/1.73 m^2 (maximum dose: 500 mg) within 1 week of achieving complete remission. Every 100 mg of RTX was diluted in 100 mL of normal saline and infused at a rate of 25 mL/hour for the first 30 min. Thereafter, the rate was doubled every 30 min to a maximum of 100 mL/hour.

Interventions were administered in an inpatient setting at the nephrology units of the registered hospitals. Interventions were discontinued if the investigator determines that continuation continuing would result in a significant safety risk.

Related medications

The initial treatment for nephrotic syndrome (NS) is daily prednisone/prednisolone 2 mg/kg/day or 60 mg/m^2/day (maximum 60 mg/day) for 6 weeks and then 1.5 mg/kg/day or 40 mg/m^2 (maximum 40 mg/day) on alternate days for another 6 weeks.

To prevent infusion reactions, 30 min before the RTX infusion, the patient should be administered antipyretic and analgesic drugs, such as acetaminophen/ibuprofen, once at a regular dose. Antiallergy medications, cetirizine hydrochloride/cyproheptadine/loratadine, should be administered once at a regular dose. Before RTX infusion, oral corticosteroids will be switched to methylprednisolone 1.6 mg/kg intravenously once.

To prevent *Pneumocystis carinii*, trimethoprim-sulfamethoxazole (SMZ) was administered for 3 months from the beginning of the RTX treatment (day 1), the prophylactic dose of trimethoprim (TMP) will be 3 mg/kg on alternate days and the maximum dose of SMZ will be 960 mg on alternate days.

In cases of relapse, if there is an infection, the coinfection will be controlled first. If the patients cannot achieve complete remission within 7 days, they will be treated with prednisone/prednisolone at a daily dose of 60 mg/m^2 until complete remission is achieved for at least 3 days and then the dose will be reduced to 40 mg/m^2 on alternate days for at least 4 weeks. The treatment for subsequent recurrences will be based on the clinical guidelines.

Outcome definitions

Efficacy outcomes

The primary outcome for the evaluation of the effect of RTX added to guideline-recommended corticosteroids is the 1-year relapse-free survival rate in children with a first episode of SSNS (relapse definition: recurrence of nephrotic-range proteinuria, urine protein/creatinine ratio ≥2 mg/mg or dipstick ≥3+ on 3 consecutive days in the first morning samples). Secondary outcomes are as follows: the number of days from the infusion of RTX to the occurrence of the first relapse, the 6-month relapse-free survival rate and the time to the first detection of CD19+ cells above 1% of total CD45+ lymphocytes after CD19+ cell depletion. Using fluorescence-activated cell sorting, the effect of RTX on peripheral blood B cells, T cell and myeloid cell subsets will be studied as biomarkers of response and relapse, before and after infusion of RTX within 72 hours; at 1, 3, 6 and 12 months; and when a relapse occurs.

Safety outcomes

Only serious adverse events of interest will be recorded. The number of participants with treatment-related adverse events, as a binary variable (1/0), will be assessed using common terminology criteria for adverse events (CTCAE) v5.0. The variable is assigned a '1' if any adverse events occur, including infusion-related reactions (within 24 hours of infusion); symptoms including fever, chills and rash, flushing, angioedema, nausea, urticaria/rash, fatigue, headache, throat irritation, rhinitis, vomiting, hypotension and bronchospasm; infection (upper respiratory tract infection, hepatitis B virus reactivation, herpes zoster infection, pneumocystis pneumonia, sepsis, etc); persistent hypogammaglobulinaemia, leucopenia or neutropenia; encephalopathy, fatal pulmonary fibrosis, ulcerative colitis, Crohn's disease or fulminant myocarditis.

Statistical methods

The 1-year relapse-free survival rate and 95% CI will be assessed. Relapse-free survival is defined as the date from the injection of RTX until the first relapse or the last follow-up, whichever occurs first. The Kaplan-Meier method will be used to assess relapse-free survival. Potential risk factors assumed to affect the time to the first relapse will be assessed using a Cox proportional hazards regression model. Secondary endpoints, including time to relapse, 6-month relapse-free survival rate, B cell depletion period and treatment-related adverse events, will be analysed. Peripheral blood B cells, T cell and myeloid cell subsets will be explored.

Sample size

The present study design is an exploratory single-arm study. The sample size is based on the expected rate of the primary efficacy endpoint and the anticipated size of the effect of RTX treatment. According to previous literature, the 1-year relapse-free survival rate is approximately 30% in children with the first episode of SSNS after standardised prednisone/prednisolone treatment.[6] Based on this previous study,[6] we estimated that a sample size of 44, with the assumption of a 10% dropout rate, would provide 80% power to detect a 20% increase in the relapse-free rate between the traditional method and RTX treatment at a two-sided alpha level of 0.05.

Patient and public involvement

No patients were involved in the study's design.

ETHICS AND DISSEMINATION

This study is being conducted according to the Declaration of Helsinki. This study was first approved by the

Ethics Committee of the Children's Hospital of Fudan University (2020-545-2). In total, seven other participating hospitals received approval from their local ethics committees: Ethics Committee of Anhui Provincial Children's Hospital (EYLL 2021–008); Ethics Committee of Children's Hospital affiliated to Zhengzhou University (2021 H-K19); Ethics Committee of Wuhan Children's Hospital (2021R138-F01); Biomedical Research Ethics Committee of Shandong Provincial Hospital (SWYX:2021–472); Xuzhou Children's Hospital Medical Ethics Committee (2021-05-13-H13); Independent Ethics Committee (IEC) of Children's Hospital of Nanjing Medical University (202110112–2); and IEC for Clinical Research and Animal Trials of the First Affiliated Hospital of Sun Yat-sen University (2021–772).

Participation in this study is voluntary. All participants have the right to withdraw at any time. The study protocol was issued on 5 January 2021, and the amendment number is 1.3 (last updated on 3 December 2021). All data are kept confidential in accordance with institutional policies. The results will be submitted to peer-reviewed journals. Any publications and presentations of the results will require review and approval by the authors of this protocol. Data will be available to researchers with a clear research plan, with the appropriate team in place to undertake the work. The individual participant data collected during the trial (including the data dictionary) will be available, after de-identification, when the article has been published with no end date. All proposals will need the approval of authors before data release.

Trial status

This study is registered at https://clinicaltrials.gov (NCT04783675). Patient enrolment started in April 2021 and was closed in January 2022 when 44 patients were enrolled. The study will end in January 2023.

DISCUSSION

NS carries a high risk of relapse; therefore, alternative treatment options are required. We will assess the efficacy and safety of RTX combined with standard treatment in children with a first episode of SSNS in a single-arm study. The goal is to achieve a 1-year relapse-free survival rate of 50%.

Recently, RTX has been shown to improve the treatment of complicated FRNS/SDNS.[9 10] The main pathological findings in patients with INS include minimal change disease (MCD). For adults with MCD for whom corticosteroids may be relatively contraindicated, the KDIGO 2020 recommends RTX as an initial therapy.[5] To date, few clinical trials have considered RTX for initial treatment, and a trial of its use at initial presentation is ongoing: a French trial in adult MCD (NCT03970577).[11]

The time to the first relapse and long-term outcomes reported previously may help us choose an appropriate treatment for the first episode of NS. Following the first episode, 70%–90% of children with SSNS relapse 1 year after disease onset.[12] Data from a meta-analysis[6] demonstrated that the median time to relapse was 63 days after cessation of 12 weeks of corticosteroids. Relapse-free rates at 3, 6, 12 and 24 months after the end of continuous therapy were 71%, 44%, 29% and 23%, respectively.[6] The overall 1-year relapse rate of first-onset INS in our unpublished data from China was similar to the results of the previous meta-analysis.[6] The primary outcome will be assessed at 1 year because most of the first relapses occur within 6–12 months after corticosteroid withdrawal, and the secondary endpoint will be at 6 months.

Studies have shown that B cells participate in the immunological dysregulation of INS.[13] The reducing effects of RTX were delayed over time. B cells begin to recover 3–4 months after infusion, while memory B cells, particularly IgM memory B cells, remain low during the first year and then start to regenerate.[14]

Assessing the relationship between clinical response or relapse and peripheral blood B cell, T cell and myeloid cell subsets may help improve the understanding of the pathology of NS. INS in children occurs predominantly in men, with a sex ratio of 3:1 for unknown reasons.[15] Normal immune cell subsets also differ by age and sex, and uncovering the reasons for this may lead to pathogenetic insights.

This study has several limitations. We speculated that RTX might be more effective in patients from the time of initial onset. The estimation of a 20% increase in the relapse-free rate was based on a recent Cochrane review in FRNS/SNDS patients.[9] Approximately, 30% of children who may be relapse-free but are treated with RTX in this study. We expect to identify new markers in this study that can predict the relapse and the treatment effect so that the indications for RTX administration can be clarified. Further studies are needed to validate the efficacy and safety of RTX in a cohort with a higher probability of predicted relapse. Although the single-arm design of this study may incur some bias regarding patient selection and outcome evaluation, several strategies have been used to minimise these biases, such as strict eligibility criteria, objective endpoints and independent assessment of safety data. Furthermore, all participating paediatricians underwent mandatory training programme before patient enrolment.

The results of this study may support the use of RTX in children with a first episode of SSNS and provide information on its safety in clinical practice. Improvements in the quality of life will be accomplished via long-term remission, which should be of great benefit to both children with NS and their families.

Author affiliations
[1]Department of Nephrology, Children's Hospital of Fudan University, National Children's Medical Center, Shanghai, China
[2]Clinical Research Institute, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[3]Shanghai Clinical Research Promotion and Development Centre, Shanghai Hospital Development Centre, Shanghai, China

[4]Department of Immunology, School of Basic Medical Sciences, Fudan University, Shanghai, China

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Contributors HX was involved in conception and trial design. JL, QS, LX, JW, YL, JC, XF, XT, BQ and HX participated in the execution and coordination. QS and JL drafted the manuscript. LX and BQ are responsible for statistical analysis. All coauthors critically reviewed and revised the initial draft and approved the final version of the manuscript.

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ORCID iD

Hong Xu http://orcid.org/0000-0001-7617-0872

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