The efficacy and safety of rituximab in the first episode of paediatric idiopathic nephrotic syndrome: An open-label, single-arm, multicentre clinical trial

Trial Registration ID: NCT04783675

Statistical Analysis Plan

The Data Management and Statistical Analysis Plan is directed to support the aims of the study

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Catalogue

1. Introduction

Idiopathic nephrotic syndrome (INS) is one of the most common glomerular diseases in children[1]. The 8-12 weeks treatment with prednisolone/prednisone (PDN) is considered the cornerstone for the initial episode[2,3]. Steroid-sensitive nephrotic syndrome (SSNS) accounts for over 80% of cases, but the 12-month relapse-free survival rate is only approximately 30%[4,5]. And a significant number of patients (up to 50%) may develop frequently relapsing or steroid-dependent nephrotic syndrome (FRNS/SDNS). Additionally, a considerable proportion (up to 42%) of children with SSNS continue to experience relapses into adulthood[6,7]. The frequency of relapse during the first 12-month is correlated with relapse rate into adulthood[2].

Although non-corticosteroid immunosuppressive medications like calcineurin inhibitors (CNI), cyclophosphamide, mycophenolate mofetil, and levamisole can extend periods of remission, they come with potential adverse effects, such as nephrotoxicity, hypertension, seizures, tremors, hirsutism, gum hyperplasia, diabetes mellitus, leukopenia, neutropenia, severe infections, alopecia, infertility, and hemorrhagic cystitis. Monitoring CNI levels is typically necessary to mitigate the risk of nephrotoxicity.

Rituximab, a chimeric anti-CD20 monoclonal antibody used for lymphoma, has shown promise as a maintenance remission treatment for FRNS/SDNS, surpassing the efficacy of other immunosuppressants. Its potential in pediatric NS was discovered incidentally in 2004 when a child with SDNS received rituximab for idiopathic thrombocytopenic purpura[8].

Previous studies have reported acceptable safety profiles for rituximab in pediatric nephrology, with infusion reactions being the most common side effect. The

international Paediatric Nephrology Association (IPNA)[3] and Kidney Disease Improving Global Outcome (KDIGO)[2] guidelines have recommended rituximab for the treatment of FRNS/SDNS by since 2020.

Although rituximab effectively prolongs remission in FRNS/SDNS patients, prolonged exposure to corticosteroids or other immunosuppressants may have already caused side effects. The repeated disruption of immune mechanisms may negatively impact treatment outcomes and prognosis. Currently, although the 12-month relapse-free survival rate of SSNS is only 30%, and at least 50% progress to FRNS/SDNS, there is no consensus on the optimal non-corticosteroid agent, in combination with PDN, for children experiencing the initial episode of SSNS. We hypothesize that early use of rituximab, in addition to PDN, is effective in preventing 12-month relapse in children with the initial episode of SSNS, potentially improving long-term prognosis.

To date, there has been limited research that comprehensively observing variations of T cells, B cells, myeloid cells, NK cells, cytokines in peripheral blood mononuclear cells (PBMC), as well as serum and urine protein biomarker signatures in NS patients before and during rituximab treatment. Understanding the underlying mechanisms and exploring diagnostic and predictive biomarkers would greatly contribute to patient management.

2.Study Objective and Outcomes

2.1 Study Objective

The primary objective is to evaluate the effect of rituximab biosimilar in maintaining remission during the first 12 months of onset in pediatric SSNS patients who achieved

corticosteroid-induced remission.

The secondary objectives include the safety profile and the underlying immunological mechanisms contributing to the effectiveness of the rituximab biosimilar treatment, as well as the relapse-free survival rate at 12 months compared to corticosteroid treatment based on historical controls.

The study also aims to identify potential perturbations in immunological cell subsets as potential predictors of SSNS relapse.

2.2 Outcomes

2.2.1 Primary outcome

The primary outcome is the relapse-free survival rate at 12 months after rituximab biosimilar infusion in children with a first episode of SSNS.

- Description: Relapse is defined as the recurrence of nephrotic-range proteinuria, urine protein/creatinine ratio ⩾2 mg/mg or dipstick ⩾3+ on 3 consecutive days in the first morning samples. Dipsticks for proteinuria determination are evaluated daily.
- Time Frame: Within 12-month after rituximab biosimilar infusion.
- Type: time to event variable

2.2.2 Secondary outcomes

(1) The time from the infusion of rituximab biosimilar to the occurrence of the first relapse (day)
   - Time Frame: Within 12 months after rituximab biosimilar infusion.
   - Type: time to event variable

(2) The relapse-free survival rate at 6-month
   - Time Frame: Within six months after rituximab biosimilar infusion.

- Type: time to event variable

(3) The time to the first detection of CD19+ cells above 1% of total CD45+ lymphocytes after CD19+ cell depletion

- Lymphocyte subset (including the percentage of total CD45+ lymphocytes and total CD19+ cells) will be measured by flow cytometry before steroid therapy, before rituximab biosimilar infusion and at 72 hours, 1 month, 3 months, 6 months, 9 months, 12 months after rituximab biosimilar infusion, and at the time of relapse.
- Time Frame: Within 12 months after rituximab biosimilar infusion.
- Type: continues variable

(4) Changes in absolute counts (and/or the percentage) of peripheral blood B cells

- Absolute counts (and/or the percentage) of peripheral blood B cells will be measured by fluorescence-activated cell sorting before steroid therapy, before rituximab biosimilar infusion and at 72 hours, 1 month, 3 months, 6 months, 9 months, 12 months after rituximab biosimilar infusion, and at the time of relapse. The surface markers of B cells are as follows.
- Type: repeatedly-measured continues variable

No.	Immune cell	Surface markers
1	**B CELLS**	
2	Transitional B	CD20+CD19+CD27−CD24hiCD38hi
3	Early transitional B	CD20+CD27−CD21low
4	Late transitional B	CD20+CD27−CD21+
5	Naïve B	CD20+CD27−IgM+IgDhi
6	Memory B	CD20+CD19+CD27+IgD-
7	Switched memory B	CD20+CD19+CD27+CD38lowIgM-IgD-
8	IgM memory B	CD20+CD27+IgMhiIgD±
9	IgG memory B	CD20+CD27+IgG+

10	Plasmablasts	CD20±CD19+CD38hiCD27hiCD24-
11	CD21low B	CD19+CD21lowCD38low

(5) Changes in absolute counts (and/or the percentage) of peripheral blood T cells

- Absolute counts (and/or the percentage) of peripheral blood T cells will be measured by fluorescence-activated cell sorting before steroids therapy, before rituximab biosimilar infusion and at 72 hours, 1 month, 3 months, 6 months, 9 months, 12 months after rituximab biosimilar infusion, and at the time of relapse. The surface markers of T cells are as follows.
- Type: repeatedly-measured continues variable

No.	**Immune cell**	**Surface markers**
1	**CD3+T**	CD3+
2	**CD4+T CELLS**	CD3+CD4+
3	Naïve T	CD3+CD4+CCR7+CD45RA+
4	Central memory T	CD3+CD4+CCR7+CD45RA−
5	Effector memory T	CD3+CD4+CCR7−CD45RA−
6	Treg	CD3+CD4+CD25hiCD127loFoxP3+
7	Tfh	CD3+CD4+CD45RA−CXCR5+
8	Th1	CD3+CD4+CD45RA−CXCR5−CXCR3+
9	Th2	CD45RA−CXCR5−CXCR3−CCR6−CCR4+
10	Th17	CD3+CD4+CD45RA−CXCR5−CCR6+
11	**CD8+T cells**	CD3+CD8+
12	Naïve T	CD3+CD8+CCR7+CD45RA+
13	Central memory T	CD3+CD8+CCR7+CD45RA−
14	Effector memory T	CD3+CD8+CCR7−CD45RA−
15	Revertant memory（TEMRA）	CD3+CD8+CCR7−CD45RA+

(6) Changes in absolute counts (and/or the percentage) of peripheral blood myeloid cells

- Absolute counts (and/or the percentage) of peripheral blood myeloid cells will

be measured by fluorescence-activated cell sorting before steroids therapy, before rituximab biosimilar infusion and at 72 hours, 1 month, 3 months, 6 months, 9 months, 12 months after rituximab biosimilar infusion, and at the time of relapse. The surface markers of peripheral blood myeloid cells are as follows.

- Type: repeatedly-measured continues variable

No.	Immune cell	Surface markers
1	**non-B/T cells**	CD3-CD20-
2	**Dendritic cells**	CD14-HLADR+
3	plasmacytoid DCs	CD11c-CD123+
4	myeloid DCs/monocytic DCs	CD11c+CD123-
5	**Monocytes**	CD14+HLADR+/−
6	classical monocytes	CD16-HLADR+
7	non-classical monocytes	CD16+HLADR+
8	myeloid derived suppressor cells	CD16-HLADR-
	Other granulocytes and NKs	CD14-HLADR-
9	**Basophils**	CD56-CD123+
10	CD56briCD16neg NKs	CD3-CD20-CD14-CD56briCD16neg
11	CD56dimCD16neg NKs	CD3-CD20-CD14-CD56dimCD16neg
12	CD56dimCD16bri NKs	CD3-CD20-CD14-CD56dimCD16bri
13	CD56negCD16bri NKs	CD3-CD20-CD14-CD56negCD16bri

(7) Changes in concentration of cytokine profiling

- Using a 27-cytokine panel on a Luminex Technology platform and ELISA, changes in concentration of cytokine profiling will be measured before steroids therapy, before rituximab biosimilar infusion and at 72 hours, 1 month, 3 months, 6 months, 9 months, 12 months after rituximab biosimilar infusion, and at the time of relapse. The markers of cytokine profiling are as follows.

- Type: repeatedly-measured continues variable

Product's Name	Commodity number	Methods	Cytokines
Bio-Plex Pro Human Cytokine 27-plex	LX-M500KCAF0Y	Luminex	FGF basic, Eotaxin, G-CSF, GM-CSF, IFN-γ, IL-1β, IL-1rα, IL-2**,** IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12(p70), IL-13, IL-15, IL-17, IP-10, MCP-1(MCAF), MIP-1α, MIP-1β, PDGF-BB, RANTES, TNF-α, VEGF
Human Luminex Discovery Assay	LXSAHM-02	Luminex	IL-18, IL-23
Bio-Plex Pro™ TGF-β 3-plex Assay - 171W4001M	171W4001M	ELISA	TGF-β1、TGF-β2、TGF-β3

(8) The proportion of patients diagnosed with FRNS/SDNS within 12 months.

- Description: FRNS: ≥2 relapses per 6 months or ≥4 relapses per 12 months. SDNS: relapses during therapy with prednisone or prednisolone (either at full dose or during tapering) or within 15 days of prednisone or prednisolone discontinuation.
- Time Frame: At 12-month after rituximab biosimilar infusion.
- Type: binomial variable

3.Study Design

3.1 Design

This is a multicenter, open-label, single-arm trial. Children who are experiencing their first episode SSNS and meet the eligibility criteria outlined in the protocol[9] will be

invited to participate. In this single-arm trial, all enrolled patients will be treated with a single intravenous infusion of 375 mg/m^2 rituximab biosimilar (HANLIKANG) within one week after achieving corticosteroid-induced remission.

To compare the differences in the effects on relapse-free survival rate (at 12-month and 6-month follow up) and the proportion of patients diagnosed with FRNS/SDNS at 12-month follow up between the rituximab biosimilar infusion and steroid therapy without rituximab, a historical control will be selected from a previous trial[5]. The historical control group includes 33 patients receiving prednisolone therapy, and the inclusion and exclusion criteria are consistent with this single-arm trial. Full details of inclusion criteria and prednisolone therapy for historical control patients are described in the previous study[5].

3.2 Trial Sites (Coordinators):

The trial will be conducted in eight hospitals in China. Children's Hospital of Fudan University, Shanghai: Hong Xu (PI, lead investigator), Qian Shen (Co-PI, principal investigator), Jialu Liu (coordinator); Anhui Provincial Children's Hospital, Anhui: Fang Deng (PI), Shaohang Fang (coordinator); Children's Hospital affiliated to Zhengzhou University, Henan: Cuihua Liu (PI), Shufeng Zhang (coordinator); Wuhan Children's Hospital, Hubei: Xiaowen Wang (PI) , Daojing Wang (coordinator); Shandong Provincial Hospital, Shandong: Shuzheng Sun (PI), Jing Wang (coordinator); Xuzhou Children' Hospital, Jiangsu: Ruifeng Zhang (PI), Tingting Yuan (coordinator); Children's Hospital of Nanjing Medical University, Jiangsu: Aihua Zhang (PI) , Chunhua Zhu (coordinator); and the First Affiliated Hospital of Sun Yat-sen University, Guangdong: Xiaoyun Jiang (PI), Mengjie Jiang(coordinator).

3.3 Interventions

Since this is a single-arm study, all enrolled patients who meet eligibility criteria will be treated with rituximab infusion. Rituximab will be 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 rituximab will be diluted in 100 mL of normal saline and infused at a rate of 25 mL/hour for the first 30 mins. Thereafter, the rate will be doubled every 30 mins to a maximum of 100 mL/hour. Interventions will be administered in an inpatient setting at the nephrology units of the registered hospitals. Details are included in the protocol[9].

3.4 Sample Size

This study is a single-arm study. The sample size is based on the expected rate of the primary treatment effect endpoint and the size of the effect of rituximab biosimilar treatment. According to previous literature[4], the 12-month relapse-free survival rate is approximately 30% in children with the first episode of SSNS after prednisone/prednisolone treatment. Based on which, we estimated that at a two-sided alpha level of 0.05, with an assumed dropout rate of 10%, a sample size of 44 would provide 80% power to detect a 20% increase in the relapse-free rate in patients receiving rituximab biosimilar treatment as compared with the traditional treatment.

4.Analysis Populations

4.1 Study population data sets

The following populations will be defined in the analysis. Primary analysis for the primary objective will be based on the intention-to-treatment population.

- **Intention-to-Treat population**

  Intention-to-treat (ITT) population will be defined as all patients who meet the eligibility criteria, are enrolled in the study, and receive the rituximab biosimilar intervention.

- **Safety population**

  This population will be defined as all patients who received the RITUXIMAB intervention.

4.2 Study Close Date

The data collection close date for this SAP is the date on when the last patient completed the follow-up 12-month. After 12 months, the patient will continue to receive routine clinical follow-up.

4.3 Data Cleaning

The data will then be checked to ensure that there are no erroneous entries and that all missing data is properly coded. Any changes will be made on the database.

4.4 Data Check-up

Once all data have been inputted and checked, the database will be locked and a data download request made. The data will be downloaded into SPSS and Stata formats for statistical analyses.

5. Statistical Analyses

5.1 Primary Outcome Analysis

5.1.1 Primary analysis

The primary analysis will be based on the ITT population as defined above. The primary outcome is a time to event outcome. The Kaplan-Meier method will be used to generate survival curves, and obtain estimation of 12-month relapse-free survival rate and median survival time with their 95% confidence intervals (CIs).

5.1.2 Secondary analysis

The difference in the 12-month relapse-free survival rate between the two treatments will be compared using Cox proportional hazards regression model, and adjusted for age at onset of diseases (continuous variable), sex (categorical variable), the time of remission induced by corticosteroid (continuous variable), the hazard ratio (HR) and its 95% CI will be reported. If the proportional risk assumptions for performing Cox regression model are not met, the Kaplan-Meier method will be used to estimate the 12-month relapse-free survival rate for the two treatments, and a rate difference with 95%CI will be reported[10].

5.1.3 Subgroup analysis of the primary outcome

Subgroup analyses for the primary outcome will be performed using the same Kaplan-Meier method as the primary analysis above. We will stratify patients by age, gender and the time of remission induced by corticosteroid. Age will be divided into <4 years group and ⩾4 years group. Gender will be divided into male and female. The time of remission induced by corticosteroid will be divided into <10 days group and ⩾10 days group. Survival curves, the 12-month relapse-free survival rate at fixed time points, and median survival time with their 95% CIs will be reported by Kaplan-Meier method.

The log-rank tests will be used to test the differences between subgroups.

5.2 Secondary Outcome Analysis

Secondary outcome analyses will be based on the ITT population unless specified. Categorical outcomes will be summarized by number (%) of patients with event. Continuous outcomes will be summarized as medians and ranges. Time to event outcomes will be analysed using Kaplan-Meier method, survival curves, the 12-month relapse-free survival rate at fixed time points, and median survival time with their 95% CIs will be reported.

For repeatedly-measured continuous variables (absolute and/or the percentage changes of peripheral immunological biomarkers at follow-up visits from the baseline, including counts of B cells, T cell and myeloid cell subsets and cytokines levels in peripheral blood), mean differences of the change of biomarkers across the eight follow-up visits will be tested using mixed-effects linear regression models, treating the change as the dependent variable, time-point of the follow-up visit (categorical variable: 1= baseline, 2= before rituximab biosimilar, 3=72 hours after rituximab biosimilar, 4=1 months after rituximab biosimilar, 5=3 months after rituximab biosimilar, 6=6 months after rituximab biosimilar, 7=9 months after rituximab biosimilar, and 8=3 months after the treatment) as the fixed effect, id number of subjects as the random effect, baseline values of immunological biomarkers (absolute counts and/or the percentage) , age (years), weight (kg) and height (m) at baseline, and sex (binary variable: 1=male, 2=female) as the covariates, and using a restricted maximum likelihood fit model. Adjusted means and standard errors at each visit will be compared by margin estimation. A P value for time visit <0.05 will be used to indicate a significant treatment effect for that time as compared with the baseline (before treatment), when the overall model P value is <0.05.

5.3 Predictors of rituximab response (Relapse vs. Nonrelapse)

To explore the potential relationship between serum levels of immune biomarkers and relapse, we will conduct an analysis of cytokines and chemokines in the patients' peripheral blood at various time points of the trial.

Changes of immunological biomarkers (counts of B cells, T cell and myeloid cell subsets and cytokines levels in peripheral blood) at follow-up visits from the baseline (before rituximab biosimilar infusion) will also be treated as repeatedly-measured continuous variables. To investigate immunological biomarkers associated with relapse of SSNS, treating the change of immunological biomarkers as the dependent variables, relapse of SSNS (binary variable: 1=yes and 0=no), time-point of the follow-up (categorical variable: 1= baseline, 2= before rituximab biosimilar, 3=72 hours after rituximab biosimilar, 4=1 months after rituximab biosimilar, 5=3 months after rituximab biosimilar, 6=6 months after rituximab biosimilar, 7=9 months after rituximab biosimilar, and 8=3 months after rituximab biosimilar, and interaction between relapse status and time as the fixed effects, id number of subjects as the random effect, and baseline of immunological biomarkers (absolute counts and/or the percentage), age(years), weight (kg) and height (m) at baseline, and sex (binary variable: 1=male, 2=female) as the covariate, multilevel mixed-effects linear regression models will be constructed respectively for each parameter using a restricted maximum likelihood method. Adjusted mean group differences of the change of biomarkers and standard errors at each visit will be analysed by margin estimation.

5.4 Handling of Missing Data

According to the reasons for the missing data, different data imputation methods will be used. Missing baseline covariates will be imputed using simple imputation methods in the covariate adjusted analysis based on the covariate distributions, should the missing values for a particular covariate be less than 5%. For a continuous variable,

missing values will be imputed from random values from a permutated normal distribution with mean and SD calculated from the available sample. For a categorical variable, missing values will be imputed from random values from a uniform distribution with probabilities P1, P2, …, and Pk from the sample. For randomly missing data, multiple imputations (MI) will be used to handle the missing data in analyses. We do not assume the condition that missing of covariate variable at baseline would be over 5%.

5.5 Analysis of other secondary outcomes

Other statistical methods may be used if deemed necessary.

6.General Considerations for Data Analyses

R software, version 4.1.2 (R Foundation for Statistical Computing) will be used to perform all data analyses and generate majority of data displays. STATA (version 17.0) may also be used for some data analyses and generating statistical graphs. All analyses for the primary and secondary outcome variables will be primarily based on the ITT population. Two-sided test and P value will be reported. Regression models for repeated measurement will be used for outcomes that are repeatedly measured, and group differences at the prespecified time point will be computed and reported. Only the primary outcome, the relapse-free survival rate at 12 months after rituximab biosimilar infusion, the relapse-free survival rate at 6 months and the proportion of patients diagnosed with FRNS/SDNS within 12 months will be compared with the historical control group, because the cytokine and immunity biomarkers are not available in the control group.

6.1 Data Summaries (baseline characteristics)

Descriptive statistics will summarize the baseline characteristics (see "7. Study variable list") for all treated subjects. Continuous variables will be presented as means and standard deviations or medians and ranges. Categorical variables will be summarized as the absolute frequency and percentage of subjects (%). All baseline presentations will identify subjects with missing measurements.

The differences in continuous variables between the two treatments (rituximab biosimilar treatment vs. corticosteroid treatment) and two group subjects (relapse vs. nonrelapse) will be analyzed using the or the t-test or Mann-Whitney U test, and differences in categorical variables will be analyzed using the Chi-square test or Fisher's exact test.

6.2 Graphical / Table Displays

Mean values for some continuous outcomes will be plotted. The Kaplan-Meier method will be used to generate survival curves. P values will be calculated with the use of the log-rank test in the subgroup analyses for the primary outcome. Hazard ratio and 95% CIs will be calculated with the use of Cox proportional-hazards model. The proportional-hazards assumption of progression-free survival will be examined.

7. Study variable list

Variable	Variable interpretation	Variable Type
center	Name of center	Text
center_no	Number of center	Text
name	Initials of subject	Text
id	Study ID of subject	Number

date_start	Date of enrollment	Date
date_end	Date of end	Date
investigator	Initials of investigator	Text
arm	Intervention allocation	Categorical
date_birth	Date of birth	Date
gender	Male / Female	Binary
Height	Height at baseline in meters	Continuous
weight	Body weight at baseline in kilograms	Continuous
Body mass index	Weight in kilograms divided by the square of the height in meters at baseline	Continuous
The time of remission induced by corticosteroid	The days of remission induced by corticosteroid	Continuous
Days from remission to rituximab infusion	Days from remission to rituximab infusion	Continuous
Days from corticosteroids to rituximab infusion	Days from corticosteroids to rituximab infusion	Continuous
Serum albumin	Serum albumin (g/dL)	Continuous
Serum total protein	Serum total protein (g/dL)	Continuous
Serum creatinine	Serum creatinine (mg/dL)	Continuous
Estimated glomerular filtration rate	Estimated glomerular filtration rate (mL/min/1.73 m^2)	Continuous
Adverse event	Number of adverse events	Continuous
The duration for corticosteroids	The duration for corticosteroids (weeks)	Continuous
Perturbations in immunological cell subsets	Absolute counts and/or the percentage of T cells, B cells, myeloid cells, NK cells in peripheral blood mononuclear cells	Continuous

Cytokines	Cytokines (concentration）	Continuous

8.Reference

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