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Original Article

The Efficacy and Safety of Rituximab in the Treatment of Steroid-dependent or Frequently Relapsing Nephrotic Syndrome in Children

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Abstract ***Purpose:*** To analyse the efficacy and safety of rituximab (RTX) in the treatment of children with steroid-dependent or frequently relapsing nephrotic syndrome (NS). ***Methods:*** A total of 44 children were eligible for inclusion in this study, and they were randomly divided into the control group and the RTX group in a 1:1 ratio. The children in the control group received traditional treatment, that is, steroid and/or calcineurin inhibitors. As well as the traditional treatment, the RTX group was given RTX (375 mg/m^2/time, maximum 500 mg/time, once a week) after the urine protein turned negative. ***Findings:*** After one year of follow-up, there were 17 cases (77.27%) in the RTX group who maintained continuous remission for six months, and 7 cases (31.81%) in the control group. The difference was statistically significant ($p<0.1$). The annual recurrence rate was 54.54% (12/22) in the RTX group and 95.45% (21/22) in the control group, and the difference was statistically significant ($p<0.01$). Compared with the control group, the recurrence-free survival time of the RTX group was significantly longer ($p=0$), the cumulative amount of steroid was reduced ($p<0.05$), and the period of being steroid-free was significantly longer ($p=0$). One case of pneumocystis pneumonia occurred in the RTX group, and there were no serious adverse events. There was no significant difference in the incidence of adverse events between the two groups. ***Conclusions:*** Rituximab is safe and effective in treating children with frequently relapsing or steroid-dependent NS.

Key words *CD19; Children with nephrotic syndrome; Rituximab; Steroid-dependent or frequently relapsing nephrotic syndrome*

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Introduction

Nephrotic syndrome (NS) is a common glomerular disease in childhood. It is a group of clinical syndromes in which the permeability of the glomerular filtration membrane is increased due to various reasons, leading to the loss of a large amount of plasma protein in the urine. It can be divided into primary and secondary NS, according to its aetiology. Primary NS (PNS) accounts for about 90% of nephropathy in childhood, and its basic clinical features are massive proteinuria, hypoalbuminaemia, hyperlipidaemia and varying degrees of oedema.[1] At present, the recognsed first-line treatment for PNS is adequate oral glucocorticosteroids (GC) to induce

remission. Depending on the child's response to the GC, the NS can be classified as steroid-sensitive NS (SSNS), steroid-dependent NS (SDNS), frequent relapse NS (FRNS) and steroid-resistant NS (SRNS). Among them, SDNS accounts for about 45% to 55% of PNS. These children are sensitive to steroids, and those who have relapses within two weeks of two consecutive dose reductions or withdrawals, more than twice in six months or more than four times in one year are called FRNS. For the treatment of children with FRNS/SDNS, large doses of steroid or combined immunosuppressive agents (ISA) are required. Due to repeated illness, the treatment with steroids or immunosuppressants will be prolonged, which will inevitably increase the toxic and side effects on children, and the combined use of multiple drugs will reduce their compliance. In addition, about 35% of children with FRNS/SDNS treated with immunosuppressive therapy still have no remission,[2] causing a bottleneck in clinical treatment. Therefore, it is necessary to explore new therapeutic drugs. Rituximab (RTX) is an anti-CD20 monoclonal antibody commonly used clinically to treat children with refractory nephrotic syndrome. A review of relevant research at home and abroad has found that the vast majority of studies have explored the dosage and use of RTX, its efficacy, its adverse reactions, the correlation between B cell exhaustion and disease recurrence and related factors affecting the efficacy, and relatively positive results have been achieved,[3-7] but there are few reports of randomised controlled studies. In view of this, this single-centre randomised controlled study was conducted in 44 children, aged between 1 and 18 years old, who were treated in the Paediatric Nephrology and Rheumatology Professional Group of the Second Hospital of Hebei Medical University and were clinically diagnosed as having SDNS or FRNS, with steroid dependence or frequent relapses lasting more than two years. The aim of the study was to explore the efficacy and safety of RTX in the treatment of children with FRNS/SDNS in order to guide clinical treatment.

Materials and Methods

Materials

Research Subjects

A total of 44 children with FRNS/SDNS, attending the Paediatric Nephrology and Immunology Rheumatism Professional Group of the Second Hospital of Hebei Medical University between September 2017 and September 2019, were selected for the study. They included 33 males and 11 females, with an average diagnosis age of 4.55±1.99 years old, and an average age of enrolment in the study of 10.34 ±2.64 years old.

Medicine

Generic name: rituximab injection; product name: MabThera; English name: rituximab injection; specification 500 mg/50 ml or 100 mg/10 ml; approval number: National Medicine Standard J20120020, produced by Shanghai Roche Pharmaceutical Co., Ltd.

Inclusion Criteria

a. Aged <18 years old
b. Met the NS diagnostic criteria of the Nephrology Group of the Pediatric Branch of the Chinese Medical Association in 2016
c. With clinical manifestations of FRNS/SDNS[8]
d. Steroid-dependent or frequently relapsing >2 years
e. Receiving RTX treatment for the first time
f. At least 12 months follow-up after RTX treatment

Exclusion Criteria

a. Estimated glomerular filtration rate <60 mL/min/1.73 m^2
b. Active or chronic infection
c. Neutropenia or thrombocytopenia
d. Hard to control hypertension
e. Potential cardiovascular or pulmonary infection
f. Vaccination of live attenuated vaccine one month or less before the start of the study
g. Previous RTX treatment
h. Hereditary causes of NS (WT1, NPHS1, NPHS2, LAMB2 gene mutations)

Methods

Experimental Grouping

The 44 cases finally selected were randomly divided into two groups: A (the control group) and B (the experimental group). SPSS 22.0 was used to generate random numbers, and then these numbers were written on cards, which were sealed in opaque envelopes. The patients randomly selected an envelope and were placed in either group according to the number on the card.

Group A only received traditional treatment, namely glucocorticoids and/or calcineurin inhibitors (CNIs). A total of 22 children were included in this group, including 16 males and 6 females, with an average enrolment age of 10.18±2.36 years old. As well as glucocorticoid and/or

CNI treatment, group B received RTX treatment. A single dose of RTX treatment was given after the urine protein turned negative. A total of 22 children were included in this group, including 17 males and 5 females, with an average enrolment age of 10.5±2.94 years old.

Treatment Plan

With respect to group A, the treatment plan for glucocorticoid and/or CNI followed the evidence-based guidelines for the diagnosis and treatment of steroid-sensitive, relapsed/dependent nephrotic syndrome in children published in the Chinese Journal of Pediatrics in 2017 (2016),[8] while for group B the RTX treatment plan started at 375 mg/m^2 each time, with the maximum dose being 500 mg/time, and one infusion was given in the first week. Whether another dose of RTX was needed depended on the CD19+ cell count level. Ibuprofen was given orally one hour before the RTX to relieve fever and pain, oral cetirizine hydrochloride (<6 years old 5 mg 1/day, ≥6 years old 10 mg 1/day) and methylprednisolone sodium succinate 40 mg were administered by intravenous injection for anti-inflammatory and anti-allergic treatment, and there was continuous ECG monitoring during the infusion of RTX 375 mg/m^2 by intravenous drip (diluted in 5% glucose solution or 0.9% normal saline to a concentration of less than 1 mg/ml). The instillation rate was 50 mg/h in the first hour, and then it could be increased by 50 mg/h every 30 minutes, up to 400 mg/h. If an allergic reaction or a reaction related to the infusion occurred, it was temporarily slowed down or stopped. If the child's symptoms improved, the infusion rate could be increased by half, and the subsequent infusion rate could be 100 mg/h, increasing by 100 mg/h every 30 minutes, up to 400 mg/h. One week after one dose of RTX injection, the CD19+ cell count level was closely checked (the reason for choosing the CD19+ cell count is that it is considered to be a useful B lymphocyte marker after RTX treatment[9]). If the B cells had recovered (CD19+ >5%), a second dose of RTX (same usage and dosage as the first dose) was recommended, or oral mycophenolate mofetil (1000-1200 mg/m^2/d, divided into two doses) was added. If the child relapsed, a second dose of RTX was recommended (the same dosage as the first dose).

Follow-up and Observation Indicators

Clinical Laboratory Indicators

a. Blood routine, and liver and kidney function were reviewed once every three months after enrolment.
b. 24-hour urine protein quantification and urine albumin/creatinine levels were reviewed once every three months after enrolment.
c. The CD19+ cell count was checked once in group B children before RTX treatment and then once every three months after the RTX treatment.
d. Record adverse events.

Observation Indicators

Efficacy: maintenance remission rate 6 months before and after treatment, number of recurrences (6 months, 12 months), annual recurrence rate, cumulative quantity of steroids (12 months), steroid-free duration and recurrence-free survival time within one year of treatment were recorded.

Safety: Any adverse events were recorded.

Main Experimental Equipment

a. The 24-hour urine was processed, using the pyrogallol red colorimetric method, and placed in the Beckman Coulter AU-5800 biochemical analyser for the 24-hour urine protein level to be detected.
b. The fasting blood from the child was processed using the scattering rate turbidimetric method and then placed in a special protein analyser (model Siemens BNII-02) for the level of immunoglobulin to be detected, and the peripheral blood CD19+ cell count was detected using the BD FACSCalibur™ automatic flow cytometry system (the USA).

Related Definitions

a. Maintenance remission rate = complete remission rate + partial remission rate; no remission: morning urine protein ≥(3+); partial remission: morning urine protein positive ≤(2+) and/or disappearance of oedema and serum albumin >25 g/L; complete remission: blood biochemistry and urine examination are completely normal.
b. Relapse: 24-hour urine protein ≥50 mg/kg, or morning urine protein/creatinine (mg/mg) ≥2.0, or morning urine protein changes from negative to (3+) to (4+) for three consecutive days.
c. Relapse-free survival time: the time from enrolment to the first recurrence.
d. B cell depletion: CD19+ cell count <5/μl or <1%.

Statistical Analysis Methods

SPSS 22.0 statistical software was used for statistical analysis. Count data was expressed as a percentage, and a χ^2 test or Fisher's exact probability test was used for

comparison between groups. Measurement data conforming to the normal distribution were expressed as mean ± standard deviation ($x \pm s$), and those of non-normal distribution were expressed as the median (upper quartile, lower quartile) [M (P25, P75)]. A t-test was used to compare the two groups with normal distribution data, and a Mann-Whitney U test was used for non-normal distribution data. The survival curve was constructed using the Kaplan-Meier method, and the comparison between survival curves was performed using a Log-rank test. A value of $p<0.05$ was regarded as statistically significance, and $p<0.01$ means a significant difference, while $p>0.05$ means no statistical significance.

Results

General Baseline Data

The clinical case data of 44 children with FRNS/SDNS are shown in Table 1. There was no significant difference in gender composition, age at diagnosis, age at enrolment, course of disease before enrolment, previous steroid and immunosuppressive treatment, and pathological composition between the two groups.

The Comparison of the Continuous Remission Rate in 6 Months, the Recurrence Frequency in 6 and 12 Months and the Annual Recurrence Rate

After one year of medication, the frequency of recurrence in the two groups was lower than before enrolment, and the difference was statistically significant ($p<0.05$). Compared with group A, there was no significant difference in the frequency of recurrence within 6 months and 12 months, the sustained remission rate within 6 months, and the annual recurrence rate in group B before enrolment, while the differences between the two groups after enrolment were statistically significant ($p<0.05$). See Table 2.

The Comparison of the Cumulative Quantity of Steroids and Steroid-free Duration

The accumulation of steroids in both groups was lower than it was before enrolment ($p<0.05$). There was no significant difference in the steroid-free duration of group A before and after enrolment ($p>0.05$), but there was a significant difference in the steroid-free duration of group B after enrolment ($p<0.01$). In group B, the steroid levels were decreased within three to four months of the treatment. Compared with group A, there was no significant difference

Table 1 Comparison of general baseline data between the two groups

Item		Group A (n=22)	Group B (n=22)	Statistics	P value
Male/female (cases)		16/6	17/5	χ^2=0.121	0.728
Age of diagnosis (years)		4.50±1.90	4.59±2.13	t=-0.150	0.882
Age of enrollment (years)		10.18±2.36	10.50±2.94	t=-0.396	0.694
Course of disease before enrollment (years)		5.68±1.81	5.59±2.04	t=0.156	0.876
Pathological type	MCD (cases)	4	7		
	FSGS (cases)	1	1		
	Not performed (cases)	17	14	χ^2=1.034	0.083
Past medication history	Oral GC (cases)	20	20		
	GC granules (cases)	9	8		
	CTX (cases)	6	8		
	CsA (cases)	2	3		
	TAC (cases)	15	16		
	MMF (cases)	6	6		
	Leflunomide (cases)	3	2	χ^2=0.019	0.997

MCD: minimal change nephropathy; FSGS: focal segmental glomurular sclerosis; GC: glucocorticoid; CTX: cyclophosphamide; CsA: cyclosporine A; TAC: tacrolimus; MMF: mycophenolate mofetil

in the cumulative amount of steroid and the steroid-free duration of children in group B before enrolment, but the difference between the two groups after enrolment was statistically significant ($p<0.01$). See Table 3.

Survival Analysis

The recurrence-free survival curves of the two groups are shown in Figure 1. A Log-rank test was used to compare them ($\chi^2=16.233$, $p=0$), and the survival curves of the two groups were significantly different. The cumulative recurrence-free survival rate of group B (the RTX treatment group) was significantly higher than that of group A (the traditional treatment group), and the recurrence-free survival time was significantly prolonged. The median recurrence-free survival time of group A was five months, 95% confidence interval (3.894, 6.106). Since the cumulative recurrence-free survival rate of group B was greater than 50% after one year of follow-up, the median recurrence-free survival time of group B could not be obtained.

Adverse Reactions

The adverse events are shown in Table 4. Among the 22 children treated with RTX, 10 cases (45.45%) had mild infusion reactions, such as fever, chest discomfort, vomiting or a rash, which was alleviated by the administration of antihistamine or a reduction in the infusion rate. There was no need to stop the infusion, and all the children were able to tolerate the subsequent RTX administration. Seven children (31.82% of those receiving RTX treatment) had infections (mostly mild ones) after the RTX treatment, and 14 children developed pneumocystis pneumonia 54 days after the treatment, which was alleviated after active treatment, and there were no deaths. Overall, 14 children (63.64% of those receiving RTX treatment) had adverse reactions.

Discussion

Children with FRNS/SDNS account for about 50% of children with PNS, which is a common refractory NS in clinical practice. At present, immunosuppressant agents are commonly used in clinic to alleviate the disease, mainly by affecting the immune pathway of T lymphocytes. However, the immune dysfunction of B lymphocytes also

Table 2 Comparison of remission rate, recurrence frequency, and annual recurrence rate between the two groups

Item		Group A (n=22)	Group B (n=22)	Statistics	P value
Maintenance remission rate within 6 months		7 (31.81%)	17 (77.27%)	$\chi^2=9.167$	0.002
Complete remission		2 (9.09%)	9 (40.91%)		
Partial remission		5 (22.72%)	8 (36.36%)		
Recurrence within 6 months	Before enrollment	2 (1,2)	2 (1,2)	Z=-0.283	0.777
Frequency (times / half a year)	After enrollment	1 (0,1)[a]	0 (0,0.25)[b]	Z=-3.170	0.002
Recurrence within 12 months	Before enrollment	3 (2,4)	3 (2,4)	Z=-0.254	0.800
Frequency (times / half a year)	After enrollment	2 (1,3)[c]	0.5 (0,1)[d]	Z=-4.484	0
Annual recurrence rate		21 (95.45%)	12 (54.54%)	$\chi^2=0.121$	0.004

Note: The frequency of recurrence within 6 months is compared with that before enrollment, [a]Z=-3.365, P=0.001, [b]Z=-5.520, P=0. The frequency of recurrence within 12 months is compared with that before enrollment, [c]Z=-2.015, P=0.044, [d]Z=5.188, P=0.

Table 3 Comparison of the cumulative amount of steroid and steroid-free duration between the two groups

Item		Group A (n=22)	Group B (n=22)	Statistics	P value
Cumulative amount of steroid (mg/(kg*d))	Before enrollment	0.39±0.11	0.37±0.17	Z=-0.823	0.411
	After enrollment	0.27±0.16[e]	0.15±0.13[f]	Z=-2.949	0.003
Steroid-free duration (month)	Before enrollment	2.45±1.07	2.94±1.31	Z=-1.344	0.179
	After enrollment	1.60±1.69[g]	5.91±3.52[h]	Z=-3.740	0

Note: Compared with the cumulative amount of steroid before enrollment, [e]Z=-2.525, P=0.012, [f]Z=-4.333, P=0; Compared with the steroid-free duration before enrollment, [g]Z=-1.934, P=0.053, [h]Z=-2.955, P=0.003.

plays an important role in the pathogenesis of the disease. Therefore, taking B cells as a therapeutic target is a feasible approach.

CD20 is a surface antigen expressed during the differentiation of B lymphocytes as they mature. RTX is a human mouse chimeric anti-CD20 monoclonal antibody. The main mechanism of RTX is as follows:

a. It binds and aggregates with the Fc segment of macrophages, monocytes and natural killer cells in the human body to induce the lysis of CD20+ B lymphocytes;
b. RTX binds to CD20 and complement C1q to activate the complement cascade to form a membrane attack complex, thereby promoting the lysis of CD20+ B lymphocytes;
c. The combination of RTX and CD20 can also initiate the signal transfer pathway mediated by Caspase-3, thereby inducing CD20+ B lymphocyte apoptosis. In addition, some researchers have discovered a mechanism of action independent of CD20+ B lymphocytes, that is, RTX can directly affect glomerular podocytes to reduce urine protein;
d. It immediately recognises the acid sphingomyelinase-like phosphodiesterase 3 expressed by podocytes and stabilises the podocyte skeleton by binding to its side chain amino acids;[10]
e. It can be combined with the acid sphingomyelinase expressed by Th17 cells to inhibit Th17's release of the inflammatory factor interleukin-17 through transmembrane signal transduction, reduce the damage of inflammatory response to podocytes and reduce podocyte apoptosis.[11] Of the above five items, the mechanism of item four is an important theoretical basis for the application of RTX to NS.[12,13]

Table 4 Comparison of the safety of the two groups

Item	Group A (n=22)	Group B (n=22)	*P* value
Total (cases)	12	14	
Infusion reaction	NA	10	
Infection	4	7	
Serious adverse events	1	1	0.572

NA: cases without infusion treatment.

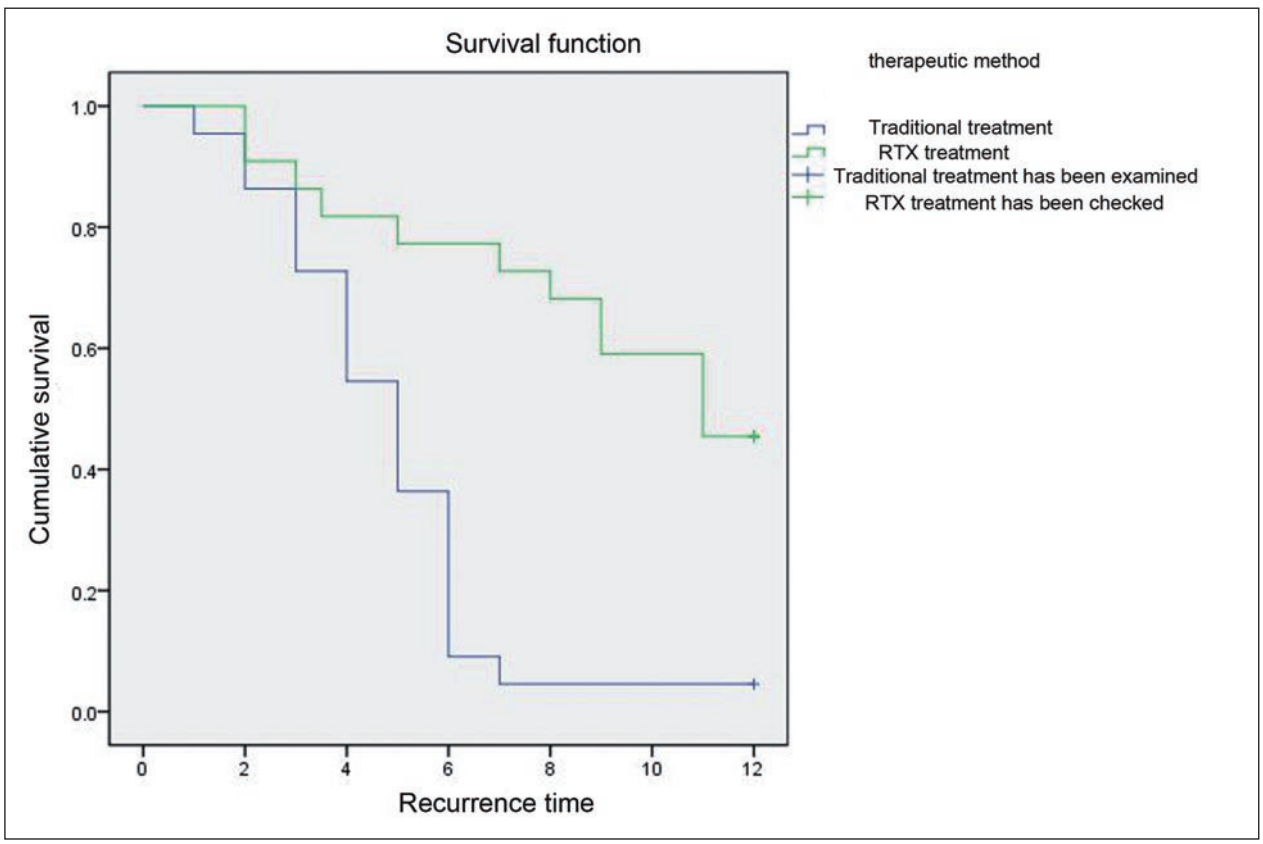

Figure 1 Comparison of survival curves between the two groups.

At present, the research and application of RTX treatment for children with FRNS/SDNS by scholars at home and abroad is becoming more extensive. Ito et al[14] conducted a multicentre retrospective study and included 55 children with FRNS/SDNS who were treated with RTX. During follow-up, 51% (28 cases) of children relapsed. A multi-centre randomised controlled study in South Korea[15] studied the efficacy of RTX in the treatment of children with FRNS/SDNS. The results showed that the 6-month sustained remission rate of the RTX group was significantly higher than that of the control group, and the recurrence rate of the RTX group was significantly lower than that of the control group. Fujinaga et al[16] used a single dose of RTX as a rescue treatment for 10 children with SDNS to study its efficacy. The results showed that the number of relapses at 12 months was significantly reduced. In this paper, a single-centre randomised controlled study method was used to randomly divide 44 children with FRNS/SDNS with a course of more than 2 years into a control group and an RTX group in a 1:1 ratio. The control group used traditional treatment programs (steroids and/or CNIs), and the RTX group was given RTX as well as traditional treatment. The maximum dose was no more than 500 mg/ time, and the second dose could be given after B cell reconstitution or recurrence. The results showed that there were 17 children (77.27%) in the RTX group who maintained continuous remission for six months without recurrence, while there were only 7 children (31.81%) in the control group (p=0.002); the annual recurrence rate in the RTX group was 54.54% (12/22), and in the control group it was 95.45% (21/22), which was similar to the results of the multicentre randomised controlled study in South Korea carried out by Fujinaga et al. In their study, the number of patients with steroid resistance in group A was 20 (partial remission + no remission), and the number in group B was 13. Moreover, the combined use of RTX was found to reduce steroid resistance.[16] reported a study of 10 children with SDNS who were given a single dose of RTX treatment and also showed that RTX treatment could reduce the cumulative quantity of steroids. During the follow-up period of more than one year, the average quantity of steroids was reduced from 0.39 mg/ (kg•d) to 0.15 mg/ (kg•d). This is similar to the results of this paper. Iijima et al[17] reported the results of a randomised placebo-controlled study that found the median time to recurrence in the RTX treatment group was longer than that of the placebo group. The survival time of the two groups in this paper showed that the RTX group was significantly longer than the control group, but because the cumulative recurrence-free survival rate of the RTX group was greater than 50% after one year of follow-up, the median recurrence-free survival time of group B could not be obtained. At present, most studies have concluded that RTX is safe in the treatment of SDNS in children, and its adverse reactions are relatively mild, most of them being infusion reactions.[18] There are still some shortcomings in this study. First, the sample size is relatively small, so there may be some errors in the research results, and second, because of the short follow-up time of some children, the long-term prognosis could not be studied.

Conclusion

RTX is effective in the treatment of children with FRNS or SDNS. It can increase the remission rate, reduce the annual recurrence rate, reduce the quantity of steroids taken and prolong the recurrence-free survival time. In addition, the incidence of adverse events is small, and they tend to be mild. Most of the manifestations are allergic-like reactions during the infusion process, and only a few children have serious adverse reactions such as pneumocystis pneumonia. However, it is necessary to expand the sample size and extend the follow-up time in the future to understand the long-term prognosis after RTX treatment.

Statement of Ethics

This study was conducted in accordance with the declaration of Helsinki.This study was conducted with approval from the Ethics Committee of The Second Hospital of HeBei Medical University.Written informed consent was obtained from all parents/local guardians.

Author Contributions

Su QX have made substantial contributions to conception and design, Qi XJ, Shen YN and Dou ZY acquisition of data, analysis and interpretation of data; Rong ZH and Zhao X have been involved in drafting the manuscript and revising it critically for important intellectual content; Yu B, Wang YX and Wang XL have given final approval of the version to be published.

Conflict of Interest

The authors have no conflicts of interest to declare.

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