FFICACY OF RITUXIMAB AND RISK FACTORS FOR POOR PROGNOSIS IN PATIENTS WITH CHILDHOOD-ONSET STEROID-RESISTANT NEPHROTIC SYNDROME: A MULTICENTER STUDY

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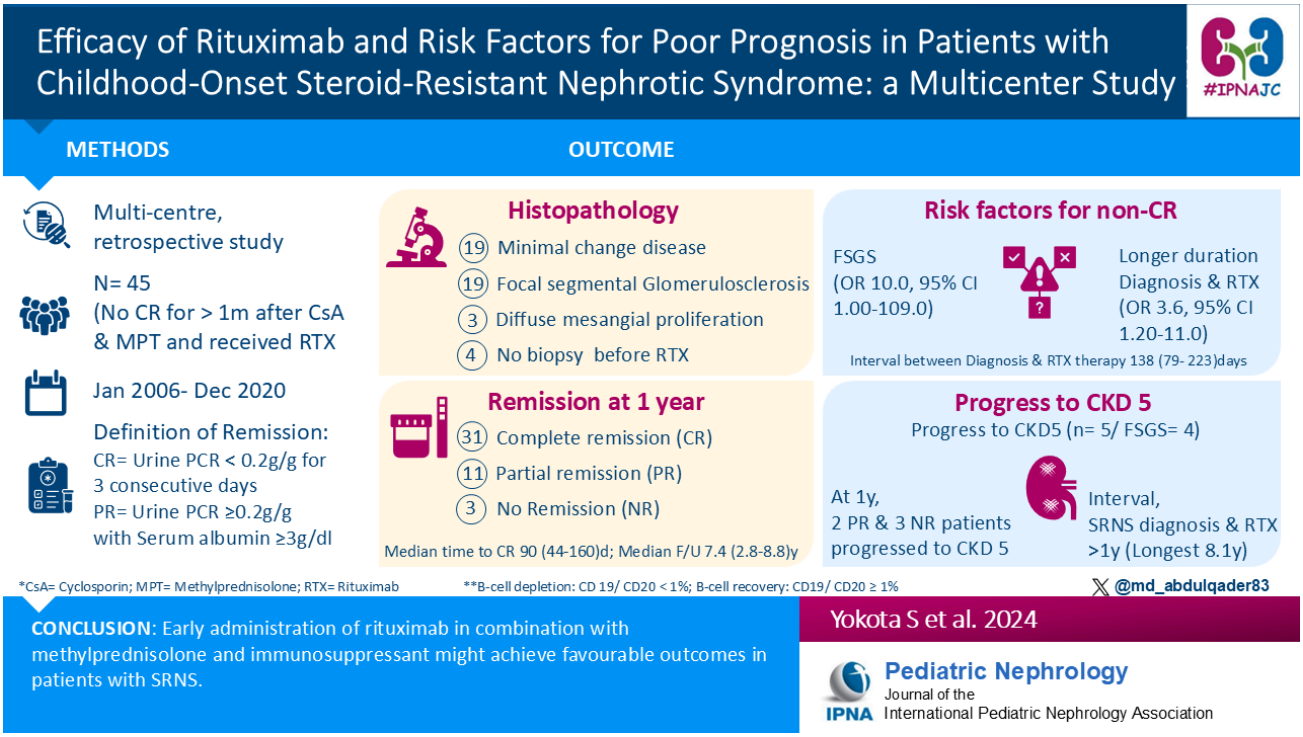
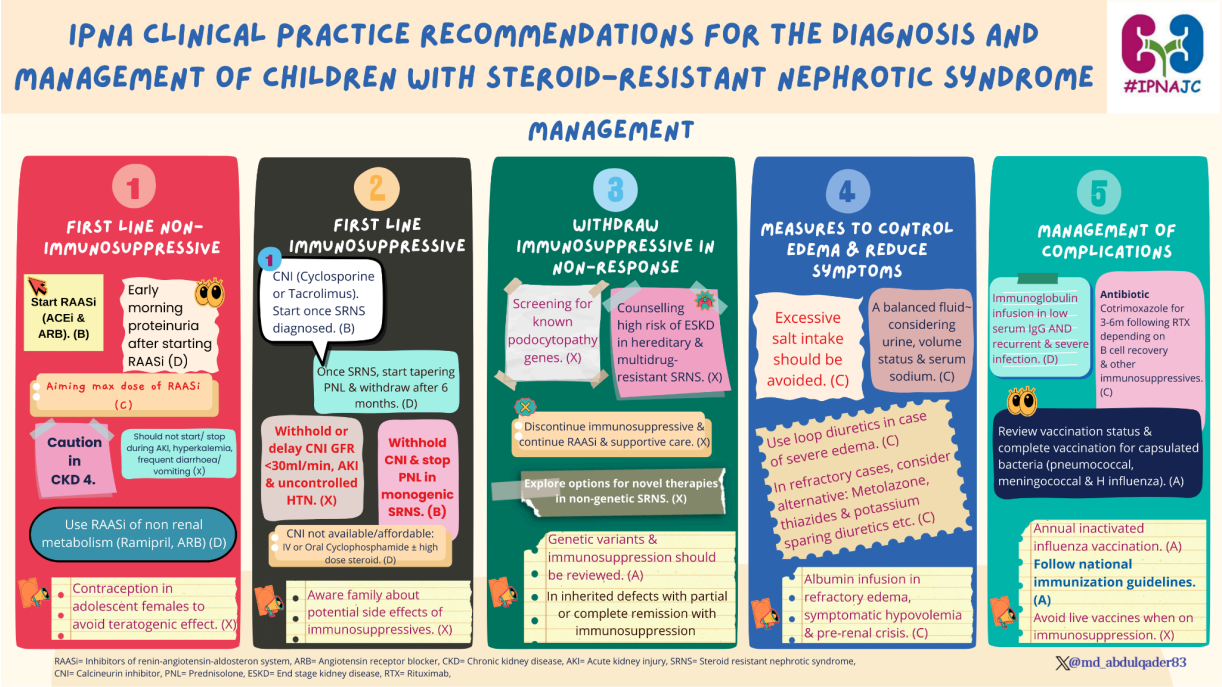


INTRODUCTION

- Childhood idiopathic nephrotic syndrome is largely steroid-sensitive, with 1-3% progressing to refractory steroid-resistant nephrotic syndrome (SRNS), which is resistant to conventional treatments like Cyclosporine A (CsA) and methylprednisolone (MPT).
- Refractory SRNS can lead to chronic kidney disease, with kidney survival rates of 90% for responders compared to 30-40% for non-responders.
- Rituximab (RTX) depletes B-cells and has shown potential in improving kidney survival in SRNS patients, although it has a low remission rate of up to 46%.

- When combined with MPT and followed by other immunosuppressants, the complete remission rate can rise to 70%.



AIM AND OBJECTIVES:

This multicenter, retrospective observational study aims to identify risk factors for failure to achieve remission one year after RTX treatment and assess long-term kidney function in pediatric SRNS patients.

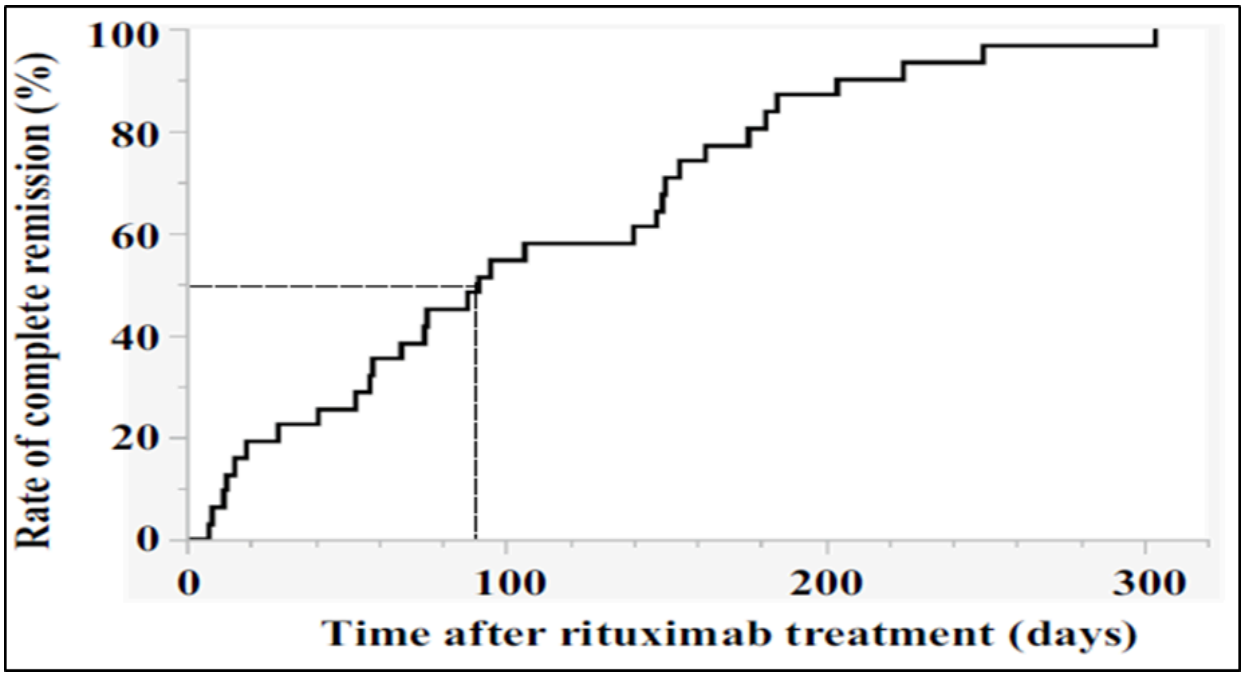
METHODOLOGY

- ***Inclusion criteria*** focused on children who did not achieve complete remission after a month of CsA and MPT treatment before receiving RTX.
- ***Exclusion criteria*** included genetic abnormalities, inability to be followed for one year, and missing data. Data were collected from four medical centers in Japan from January 2006 to December 2020.

- ***Definitions:***
  - *Complete Remission (CR):* Defined as a urinary protein-to-creatinine ratio of less than 0.2 g/gCr for three consecutive days.
  - *Partial Remission (PR):* Indicated by a ratio of ≥ 0.2 g/gCr with serum albumin ≥ 3.0 g/dL.
  - *No Remission (NR):* Characterized by a urinary ratio ≥ 0.2 g/gCr and serum albumin < 3.0 g/dL.
  - *B-cell Depletion:* Determined by a CD19 or CD20 ratio of < 1.0%, with recovery at ≥ 1.0%.
- ***Pathological Findings:***
  - *Minimal Change Disease:* Normal glomeruli on microscopy.
  - *Focal Segmental Glomerular Sclerosis (FSGS):* Localized and segmental sclerosis
  - *Diffuse Mesangial Proliferation (DMP):* Increased mesangial cells and extracellular matrix.
- ***Treatment Protocols:***
  - ***Rituximab*** is administered to pediatric SRNS patients when other treatments, like MPT and Cyclosporine A (CsA), are ineffective.
  - Rituximab is given at a dosage of 375 mg/m², with one to four doses, and additional doses for those not achieving complete remission after B-cell recovery.
  - Patients are screened for tuberculosis and hepatitis prior to treatment.
  - ***MPT consists of intravenous methylprednisolone*** at 30 mg/kg/day for three days, continued until complete remission is achieved.
- ***Outcomes:***
  - ***Primary Outcome:*** were measured the rates of complete remission (CR), partial remission (PR), and no remission (NR) one year after rituximab treatment.
  - ***Secondary Outcomes:*** Secondary outcomes focused on
    - *Identifying risk factors for non-CR* and were analyzed through univariate and multivariate methods,
    - *Evaluating long-term prognosis* using estimated glomerular filtration rate (eGFR) data,
    - *Analyzing the relationship between disease status at one year and* long-term outcomes,
    - *Assessing adverse events related to the treatment.*

RESULTS

- ➔ The study analyzed 45 pediatric patients with steroid-resistant nephrotic syndrome (SRNS) from four medical centers, with 31 (69%) being initial non-responders. The median time from diagnosis to rituximab treatment was 138 days.
- ➔ Histopathological findings indicated minimal change disease (42%), focal segmental glomerular sclerosis (FSGS) (42%), and diffuse mesangial proliferation (7%).
- ➔ At the time of rituximab (RTX) administration, Cyclosporine A (CsA) was the main single-agent immunosuppressant used in 54% of patients, dropping to 40% afterward. Other agents like mycophenolate mofetil (MMF) and mizoribine were also utilized. Combination therapies included CsA with MMF (20%) and CsA with mizoribine (13%), while one patient received tacrolimus with MMF. After RTX, the use of the CsA and MMF combination increased to 31%, along with other combinations tailored to individual patients.
- ➔ Notably, three patients on dialysis successfully transitioned off treatment.
- ➔ One year post-treatment, outcomes were complete remission (CR) in 69%, partial remission (PR) in 24%, and no remission (NR) in 7%, with a median time to CR of 90 days and a median follow-up of 7.4 years. Eighteen percent of patients required additional rituximab doses, and 87% received MPT after rituximab.



The Kaplan–Meier curve illustrates the relationship between the time from rituximab treatment and the achievement of complete remission (CR) in patients who reached CR. The median time to CR was 90 days.

Table 2 Comparison between patients with and without CR

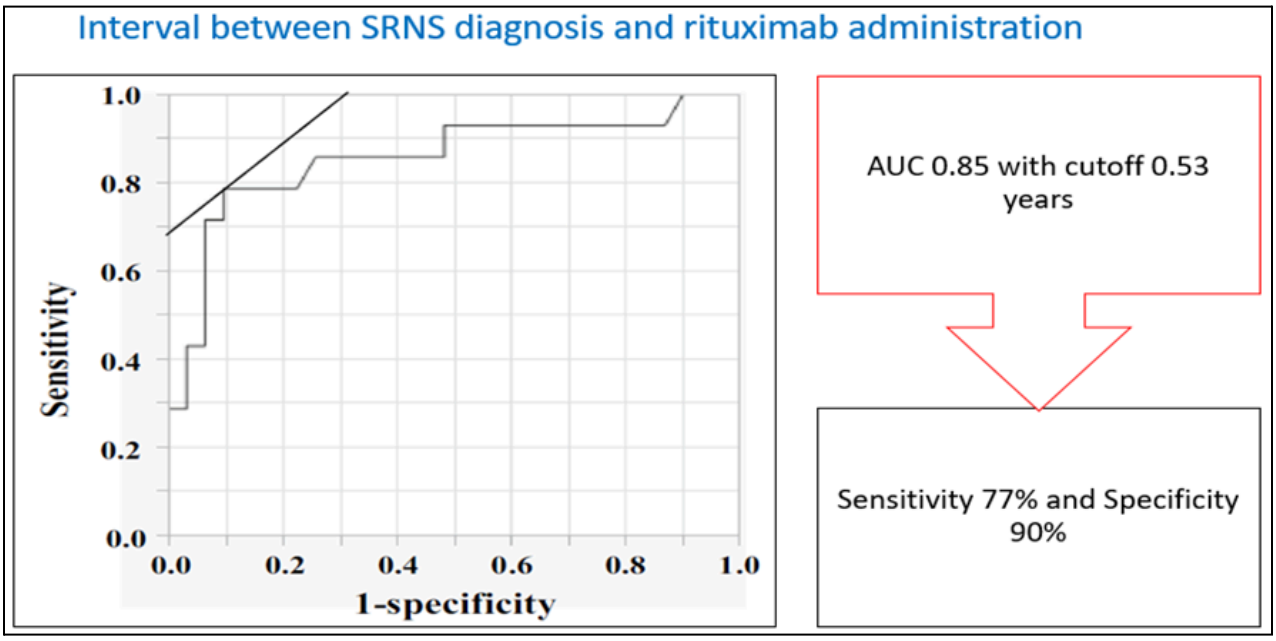
	CR group (n = 31)	Non-CR group (n = 14)	*P* value
Male sex	14 (45)	9 (64)	0.23
FSGS	8 (29)	11 (85)	<0.001
Initial non-responder	18 (58)	13 (93)	0.01
Cr-eGFR < 60 mL/min/1.73 m^2 at rituximab administration	5 (16)	3 (21)	0.67
Age at SRNS diagnosis	6.6[3.1–11.3]	10.8[5.7–12.3]	0.09
Age at rituximab administration (years)	6.6 [2.9–11.8]	11.0 [4.7–12.8]	0.11
Duration of CNI from SRNS diagnosis to rituximab administration	2[1.25–4.0]	7[5.0–25]	<0.001
Duration of any immunosuppressive agents from SRNS diagnosis to rituximab administration	2[1.25–4.0]	7[5.0–25]	<0.001
Interval between SRNS diagnosis and rituximab administration (days)	96 [74–151]	298 [192–1,090]	<0.001
The number of rituximab doses	1[1-2]	1[1-2]	0.66
Additional rituximab administration within one year	18 (58)	6 (43)	0.52
MPT within one year after rituximab administration	25(80)	14(100)	0.15

➔ Multivariate analysis identified FSGS *(odds ratio 10.0; 95% CI, 1.00–109.0; p = 0.0498)* and delayed rituximab administration *(odds ratio 3.6; 95% CI, 1.20–11.0; p = 0.02) as* significant risk factors for poor response.

Table 3 Risk factors for non-CR in univariate and multivariate analysis

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
FSGS	13.8	2.5–76.4	0.003	10.0	1.0–109.0	0.0498
Initial non-responder	9.4	1.1–81.0	0.04	5.3	0.3–95.0	0.26
Interval between SRNS diagnosis and rituximab administration (years)	3.0	1.2–7.4	< 0.001	3.6	1.2–11.0	0.02

CI, confidence interval; CR, complete remission; FSGS, focal segmental glomerulosclerosis; SRNS, steroid-resistant nephrotic syndrome



- ➔ At the last observation, five patients were diagnosed with chronic kidney disease stage G5 (CKD G5). None of the 31 patients with CR had a Cr-eGFR < 60 mL/min/1.73 m², while two with PR and all three with NR had CKD G5.
- ➔ Among those with CKD G5, four were initial non-responders with FSGS, and genetic testing revealed no relevant abnormalities in three patients. All five had treatment intervals exceeding one year, with one as long as 8.1 years.

LIMITATIONS:

The study on rituximab treatment for steroid-resistant nephrotic syndrome (SRNS) acknowledges several limitations, including variability in treatment protocols, gaps in genetic testing, and challenges in interpreting the effectiveness of immunosuppressive therapies.

CONCLUSION

Despite these limitations, the study concludes that early administration of rituximab, in conjunction with Cyclosporine A and multi-agent therapy, may improve long-term outcomes for patients. However, further prospective research is necessary to validate these findings.

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