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Calcineurin inhibitor versus mycophenolate mofetil along with rituximab in non-genetic calcineurin inhibitor resistant steroid resistant nephrotic syndrome: retrospective observation from western India

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Abstract

Background: In 25-35% children with non-genetic calcineurin inhibitor (CNI) -resistant- steroid resistant nephrotic syndrome (SRNS), rituximab has been effective as rescue therapy. Use of add-on immunosuppression to maintain remission has not been studied well.

Methods and materials: Recorded demographic details, response and relapse rate, infections, hospitalizations, progression to chronic kidney disease and death were compared between two groups: mycophenolate mofetil (MMF) with rituximab, CNI with rituximab.

Results: Of 95 children with SRNS, 24 children received 32 rituximab treatment-events, including 18 in the MMF group and 14 in the CNI group. Baseline demographic, clinical, and histopathological characteristics were comparable. Minimal change disease was the commonest histopathological diagnosis (57.6%). Following the first rituximab cycle, complete or partial remission was achieved in 33.3% of treatment events in the MMF group and 28.6% in the CNI group. Relapse rates were similar between groups (38.9% vs. 35.7%; p=0.854). Median relapse-free survival was longer in CNI with rituximab group (mean 18.2 months +/-6.5 months) as compared to MMF with rituximab group (mean 12.17 +/- 11.56 months)(p,0.07). Hospitalizations for edema and infections decreased following rituximab therapy in both groups. Among first-cycle non-responders, 23.5% progressed to chronic kidney disease (CKD) stage ≥3. CKD progression (46.2% vs. 18.2%) and mortality (23.1% vs. 9.1%) were more frequent in the MMF group. At 36 months, overall survival was 70.5% in the MMF group and 90.0% in the CNI group.

Conclusion: In CNI-resistant-SRNS, proportionately higher remission, fewer hospitalizations and fewer progression to CKD is seen in CNI with rituximab compared to MMF with rituximab. Small sample size requires longitudinal prospective studies for validation.

Background and Rationale

Steroid-resistant nephrotic syndrome (SRNS) accounts for 10–15% of nephrotic syndrome cases in children [1]. Amongst 10–30% of children with SRNS, mutations in podocyte-associated genes can be detected [2]. Calcineurin inhibitors (CNI) are recommended as first-line immunosuppression therapy for non-genetic SRNS. Out of these, approximately 25–35% of patients with non-genetic forms of SRNS do not show a complete or partial response to CNI [3]. This substantial group of SRNS is associated with unfavourable prognosis, with 36–50% of patients progressing to chronic kidney disease and chronic kidney failure within 10 years [4–6]. The risk is particularly high among those who fail to achieve remission with second-line immunosuppressive therapies.

The role of rituximab as monotherapy has been studied extensively for SDNS, FRNS, and also in refractory SRNS [2, 8–14]. Response to rituximab in SRNS is heterogenous and predictors of sustained remission as monotherapy remain poorly defined. Observational studies showed complete remission in 30% of patients treated with rituximab as a rescue therapy for CNI-resistant SRNS [15]. Possible factors related to 30% remission in previous studies could be the genetic cause of SRNS. In clinical practice, add-on

immunosuppression in combination with rituximab for maintaining remission is often used; evidence for the choice of add-on immunosuppression is scarce.

Given the increasing use of rituximab in refractory SRNS, defining the optimal add-on immunosuppressant has clinical relevance. There is limited data comparing the role of CNI versus Mycophenolate Mofetil (MMF) for maintaining remission in children with refractory SRNS after rituximab. The current study was conducted to compare the effectiveness of add-on immunosuppression after rituximab, using CNI versus mycophenolate mofetil, for maintaining remission in non-genetic, CNI-resistant SRNS.

Methods

Study Design and Study Period

A single-center, retrospective cohort study conducted at the pediatric nephrology department in western India between March 2021 and October 2024.

Study Participants

Children aged ≤18 years with CNI-resistant SRNS or CNI-intolerant SRNS were included. Exclusion criteria were genetic forms of SRNS -children who had likely pathogenic/pathogenic variants according to ACMG criteria (16); secondary nephrotic syndrome; eGFR less than 60 ml/min/1.73 m2 by modified Swartz method (17); and kidney biopsy showing chronicity with IFTA more than 50%.

Standard definitions were used for nephrotic syndrome, steroid resistance, complete remission, partial remission, and relapse as per the latest International Pediatric Nephrology Association and Indian Society of Pediatric Nephrology consensus, as described in Table 1.

Table 1: Definitions for Nephrotic Syndrome and treatment response

SRNS [2]	Lack of complete remission within 6 weeks of treatment with 6-weeks daily treatment with prednisolone
CNI-resistant SRNS [7]	Lack of at least partial remission after at least 6 months of CNI treatment administered at adequate doses and blood levels
CNi intolerance	At least two AKI episodes with rise in serum creatinine by >=0.3 mg/dl or >30 % rise from baseline.
Complete remission (CR) [7]	UPCR (based on first morning void or 24 h urine sample) ≤ 20 mg/mmol (0.2 mg/mg) or negative or trace dipstick on three or more consecutive occasions.
Partial remission (PR) [7]	UPCR (based on first morning void or 24 h urine sample) 0.2-2.0, or +1/+2 (dipstick) and, if available, serum albumin ≥ 30 g/l and absence of edema

Data Collection

Data related to children who were included in the study were retrieved retrospectively from hospital medical records , including 1)baseline characteristics -demographic details -age , at onset of nephrotic syndrome, at SRNS onset and at rituximab administration; sex; baseline renal function; kidney biopsy; prior

immunosuppressive therapy; duration of disease ; 2)treatment details: rituximab regimen (dose, frequency), add-on immunosuppressive therapy(CNI or MMF), pre- and post-rituximab ; 3) Outcome: achievement of complete or partial remission, time to remission, and relapse episodes, progression to chronic kidney failure and mortality, infection frequency, hospitalizations related to disease activity or complications.

Treatment protocol

As summarized in Fig 1; after establishing a diagnosis of SRNS, children were offered a kidney biopsy and genetic analysis. Children were offered CNI as 1st line immunosuppression with tapering doses of steroids over 4-6 weeks. CNI levels monitoring and optimisation of doses were done accordingly. Response to CNI was assessed at 6 months. ACEi or ARBs were also added with CNI for optimal reduction in proteinuria before assessing the response to CNI. Dual blockade with ACEi and ARBs was not used in any patient. Those who did not achieve response (partial/ complete) and those who developed at least 2 AKI episodes requiring stoppage of CNI in the first 6 months were labelled as CNI-resistant and CNI-intolerant SRNS, respectively[1]. Rituximab was administered to such patients along with add-on immunosuppression – CNI or MMF. Monitoring of IgG levels pre-rituximab was not done routinely[2]. However, children who developed infection requiring hospitalisation pre-rituximab were checked for serum IgG levels; those with low IgG levels, received 2 g/kg intravenous immunoglobulin (IVIg) in 5 divided doses. Rituximab was given after ruling out active bacterial, fungal, and viral infection. Two doses of 375 mg/m^2/dose were given intravenously at least 2 weeks apart. CD19 suppression was monitored 2 weeks after administration of 2nd dose in each cycle. Additional dosing of rituximab was administered in children with peripheral blood CD19 levels > 1.0% of lymphocytes or >5 cells/mm^3. Maximum number of rituximab was limited to 4 doses per cycle with CD-19 suppression monitoring. Anti-bacterial and anti-viral prophylaxis were given for 3 months, starting from the first dose of rituximab. Choice of CNI versus MMF as an add-on immunosuppression to rituximab was based on clinical characteristics of patients and prior tolerance. Children with CNI intolerance or biopsy-proven CNI toxicity received MMF.

Post Rituximab: Children who received rituximab with add-on immunosuppression were monitored monthly. Response to therapy was assessed at 6 months, 12 months, and 24 months after last dose of rituximab in each cycle in the form of complete remission, partial remission, edema-free state, or no response. The number of hospitalizations pre- and post-rituximab with an add-on immunosuppressive agent was recorded. Each hospitalisation was reviewed for the reason of admission-for edema management or infection management.

Outcome Measures

The primary outcome was to compare between the rituximab with MMF group and the rituximab with CNI group for attainment of complete or partial response at 6 months. Incidences of relapses, time to relapse, hospitalizations, infections episodes, progression to chronic kidney failure, and death in each group were also compared.

Statistical Analysis

Data was compiled and analysed using SPSS version IBM. Categorical variables were reported as frequencies and percentages, and continuous variables as mean ± standard deviation (SD) or median (interquartile range), as per distribution. Chi-square or Fisher's exact test was applied for categorical comparisons, and Student's t-test or Mann–Whitney U test was used for continuous variables. Since several categorical variables contained expected cell counts less than five, Fisher's exact test was used wherever appropriate, whereas chi-square testing was applied to variables fulfilling assumptions for contingency testing. Statistical significance was reported at p value of < 0.05. Baseline characteristics between groups were compared to assess potential confounding in view of observational study-design. Analyses were conducted at two levels. Response to a rituximab with add-on immunosuppression therapy and hospitalisation were analysed at treatment-event-level. Outcomes reflecting overall clinical condition of a child (relapse-free survival, progression to CKD, mortality and overall survival) were noted at patient-level. Relapse-free survival and overall survival were measured with Kaplan-Meier method. Univariate Cox regression used to compare MMF and CNI groups as post-rituximab immunosuppression. Small sample size and small event numbers limited usage of multivariate logistic regression. Some children had received more than one rituximab treatment event, treatment -event outcome observations are not independent to patient outcome observations. Small patient population size and small number of treatment events were interpreted as an exploratory rather than confirmatory results.

Ethical Considerations

Ethics approval was obtained from the institutional Ethics Committee (Guts/Ec-06/Paed Nephro-12, on 20/6/2023). Requirement for individual patient consent was waived off as this was a retrospective study with anonymized data.

Results

Out of 95 children with SRNS, thirty-four children met the inclusion criteria and received Rituximab along with add-on immunosuppression. Ten children were excluded from the study: rapid progression to chronic kidney failure within a month of rituximab therapy (4 children), poor medication compliance (2 children), and less than 6 months of follow-up (2 children, Fig. 2). A total of 32 treatment events were analysed in 24 children, eighteen treatment events observed in MMF group comprising of 13 children, and fourteen treatment events in CNI group having 11 children. Baseline demographic and disease characteristics were comparable in two groups (Table 2). From these 24 children, 8 were female, and 14 children had primary SRNS. Children had the onset of nephrotic syndrome at an early age (mean 3.39 ± 2.73 years). Atypical features were noted in a total of five children (5/24 ,20.8%), such as age at onset (3/24, 12.5%), microscopic haematuria (2/24,8.33%), and persistent hypertension (1/24,4.16%). Extra-renal involvement in the form of imperforated hymen, along with right thumb postaxial polydactyly was seen in 1/24 children. Thirty-two kidney biopsies were done, with MCD (57.6%) being the commonest histopathology, FSGS being 2nd most common.

Table 2
Baseline demographic and disease characteristics of children

Variables	**MMF group (N = 13) (n, %) / Median (IQR)**	**CNI group (N = 11) (n, %) / Median (IQR)**	
Gender			p = 0.597
Male	7 (53.8)	8 (72.7)	
Female	6 (46.2)	3 (27.3)	
SRNS Type			p = 0.231
Primary	4 (30.8)	7 (63.6)	
Late	9 (69.2)	4 (36.4)	
Biopsy findings			p = 0.223
FSGS	4 (30.8)	4 (36.4)	
MCD	9 (69.2)	5 (45.5)	
MCD → FSGS	0 (0.0)	2 (18.2)	
History of infections pre-rituximab			p = 0.597
Yes	6 (46.2)	3 (27.3)	
No	7 (53.8)	8 (72.7)	
Age at onset of nephrotic syndrome (years)	2.0 (1.5–4.5)	3.0 (2.0–5.0)	p = 0.255
Age at onset of steroid resistance (years)	3.0 (1.9–7.0)	2.9 (2.38–5.63)	p = 0.839
Age at rituximab therapy (months)	57.0 (45.0–117.0)	78.0 (52.5–111.5)	p = 0.451

Overall, the treatment outcome is reported per treatment outcome and is summarised in Table 3. Complete remission was achieved in 2 (11.1%) and 2(14.3%); partial response was achieved in 4 (22.2%) and 2 (14.3%) children in MMF group and in CNI group, respectively. 11 out of 24 children relapsed in 14.9 +/- 9.42 months. There was no significant difference in relapse rate in both groups (38.9% vs 35.7%, p = 0.854). However, relapse-free survival was longer in CNI group (mean 18.2 +/-6.5 months) as compared to MMF group (mean 12.17+/-11.56 months) p,0.07). Univariable hazard analysis showed no significant association between immunosuppressive regimen and relapse-free survival [HR: 1.16; 95% CI: 0.33–4.05; p = 0.813].

Table 3
Treatment outcomes* at 12 months after each cycle of rituximab

Outcome	**MMF group (N = 18) (n, %)**	**CNI group (N = 14) (n, %)**	
Complete Response	2 (11.1)	2 (14.3)	p = 0.873
Partial Response	4 (22.2)	2 (14.3)	
No Response	12 (66.7)	10 (71.4)	
*Response according to rituximab treatment-event level			

Seventeen Children who failed to respond to 1st cycle of rituximab were monitored closely. Among these non-responders (17 /24) to 1st cycle, 23.5% (4 / 17) progressed to CKD stage > = 3, 2 children from each group. Seven children received 2nd cycle of rituximab; 2 of 7 children (28.6%) were responders. Amongst non-responder (5/7 children) to the second cycle, CKD progression was observed in 4 children, all four were from MMF with rituximab group.

Hospitalization rates before and after rituximab therapy are presented in Table 4. Hospitalization rates for both edema and infections decreased following rituximab therapy in both groups.

Table 4
Comparison of number of hospitalizations* before and after rituximab therapy

Number of Hospitalizations	**MMF group(n = 18)** **Median (IQR)**	**CNI group (n = 14)** **Median (IQR)**	
Total number of Hospitalizations (Pre-rituximab)	2.5 (2–3.75)	5.5 (1.25–7)	p = 0.347
Total number of Hospitalizations (Post-rituximab)	2.5 (0.25–3)	0.5 (0–2.75)	p = 0.299
Hospitalization for edema (Pre-rituximab)	2 (1.25–3)	4.5 (1–5.75)	p = 0.318
Hospitalization for infection (Pre-rituximab)	0 (0–1)	1 (0–2)	p = 0.230
Hospitalization for edema (Post-rituximab)	0 (0–3)	0 (0–2.5)	p = 0.950
Hospitalization for infection (Post-rituximab)	0 (0–1.75)	0 (0–0.75)	p = 0.292

*Hospitalizations are recorded at rituximab treatment-event- level with repeated contribution of some patients who had received more than one rituximab cycles.

Table 5
Comparative summary

Study design	**Basu et al.** (18)	**Sinha et al** (19)	**Kandai et al.** (20)	**Assadi et al.** (21)	**Our study**
	retrospective	**retrospective, multicenter**	**multi-center, single-arm clinical trial**	**Multi-center non-blinded RCT**	**Single center** **retrospective cohort study**
Number of participants	twenty-four children	thirty-one children	six children	sixty-six children	twenty-four children
Add-on immunosuppression	MMF after achieving partial response to rituximab	Tacrolimus (n = 20) or mycophenolate mofetil (n = 11)	Pulse steroids in combination with CNI	32 children received MMF, 34 children received cyclosporine after RTX induction (1:1 randomized by means of an interactive response technology)	13 children received MMF and 11 children received CNI after rituximab
Comparison of add-on immunosuppression	No	No	No	Rituximab and MMF group versus Rituximab and cyclosporine group	Rituximab with MMF group versus Rituximab with CNI group

Study design	Basu et al. (18)	Sinha et al (19)	Kandai et al. (20)	Assadi et al. (21)	Our study
	retrospective	**retrospective, multicenter**	**multi-center, single-arm clinical trial**	**Multi-center non-blinded RCT**	**Single center** **retrospective cohort study**
Response to therapy	After 6 months, 67% (10/15) of children on MMF achieved complete remission and 33% (5/15) were in partial remission.	58% patients achieved remission with rituximab	On day 169, five patients (83.3%) achieved primary end-point, two patients showed partial remission, and two patients showed complete remission	26 patients (83.1%) in MMF group and 21 patients (61.7%) in cyclosporine group achieved complete remission.	at 12 months after 1st cycle rituximab therapy, Complete remission was achieved in 2 (11.1%) and 2(14.3%); partial response was achieved in 4 (22.2%) and 2 (14.3%) children in MMF group and in CNI group, respectively.
Limitation of study	small patient number in each subgroup, no direct comparison of efficacy of rituximab versus rituximab-MMF among children with SRNS	small cohort size, No comparison between CNI and MMF as add-on IS to rituximab, lack of genetic data	small sample size and lack of an internal control group	Non-blinded RCT and only 12-month follow- up	small sample size and retrospective study design

Patient-level outcomes i.e., CKD progression, mortality, overall survival and disease-free survival are reported using the number of patients per group as denominator. Although CKD progression (eGFR < 60 mL/min/1.73m²) was more frequently observed in MMF group (6/13 children, 46.2%) as compared to CNI group (2/11 children,18.2%), there was no statistically significant difference (p = 0.211). Similarly, mortality was higher in MMF group (3/13, 23.1%) than in CNI group (1/11, 9.1%), but no statistically significant difference in overall survival status was seen (p = 0.596). Disease-free survival was observed in 5/11 (45.5%) children receiving CNI compared to 1/11(7.7%) children in MMF group(p = 0.061).

Univariate logistic regression analysis evaluating predictors of CKD progression demonstrated no statistically significant associations. Patients receiving MMF had 3.86 times higher odds of CKD progression compared to those receiving CNI (OR:3.857; 95% CI: 0.59–25.29; p = 0.159).

At 36 months, when stratified by post-rituximab immunosuppressive therapy, survival probability remained 90.0% in CNI group compared to 70.5% in MMF group. Univariable survival analysis (**Fig. 3**: Group-specific overall survival) revealed no statistically significant association between post-rituximab immunosuppressive regimen and overall survival (HR: 2.90; 95% CI: 0.30–27.92; p = 0.357).

Discussion

In this retrospective single center study of 24 children with non-genetic CNI-resistant or CNI-intolerant SRNS receiving rituximab, add-on CNI was associated with higher remission rates, less CKD progression and lower mortality in comparison to MMF. Existing literature is limited for add-on immunosuppression with rituximab, in children having CNI-resistant SRNS. To our knowledge, this is the largest single-center experience from Asia comparing CNI and MMF as add-on immunosuppression in children having CNI-resistant SRNS after rituximab. The exclusion of monogenic SRNS also strengthens internal validity of the study, ensuring that the observed treatment responses were attributable to immunosuppressive agents rather than underlying podocytopathies. Basu et al. retrospectively analysed the efficacy of mycophenolate mofetil (MMF) as maintenance therapy after rituximab in children with refractory SRNS [18]. After 6 months of MMF, 67% (10/15) children attained complete remission, and 33% (5/15) attained partial remission. About one third (5/15 children, 33%) remained in sustained remission at 24 months, considerably higher than rituximab monotherapy (p < .001). MMF-treated children in our study achieved complete or partial remission at lesser rate reflecting differences in baseline disease severity, treatment exposure. Sinha et al. [19] reported on early use of rituximab in calcineurin inhibitor (CNI) refractory and steroid-resistant nephrotic syndrome, demonstrating 58% patients achieved remission with rituximab. Following rituximab infusion, either CNI or mycophenolate was continued with tapering doses of steroid. However, a direct comparison between MMF and CNI was not performed in that study. Nozu et al. [20] Published a multi-center, single-arm clinical trial of the role of rituximab in combination with cyclosporine and steroid pulse therapy for childhood-onset multi-drug-resistant nephrotic syndrome in six children. There were no pathogenic variants of podocyte-related genes in these children. The primary endpoint of study was to achieve > 50% reduction in proteinuria from baseline after 6 months of rituximab. On day 169, five patients (83.3%) achieved the primary endpoint, two patients were in partial remission, and two patients in complete remission. In our study, 1(4.16%), 3 (12.5%), 6 (25%) children received with CNI with rituximab achieved complete remission, partial remission, and no response respectively at 6 months. In a multicentre nonblinded randomized controlled trial by Assadi et al. [21] comparing MMF versus cyclosporine following rituximab in 66 children with SRNS, the authors demonstrated higher complete remission rates in the MMF group compared with the cyclosporine group (83.1% vs. 61.7%), along with longer relapse-free survival and fewer adverse events. In contrast, our study demonstrated a trend toward better renal outcomes and lower CKD progression in children receiving CNI-based therapy after rituximab. This difference may be explained by variation in study populations, as our cohort specifically included children with difficult-to-treat non-genetic CNI-resistant or CNI-intolerant SRNS with prior prolonged CNI exposure.

This study adds to existing data on the role of post-rituximab maintenance immunosuppression in children with refractory SRNS, an area with limited evidence. The inclusion of a well-characterized cohort with exclusion of genetic SRNS and the evaluation of relapse, CKD progression, and survival, strengthen the

study. However, treatment allocation to CNI or MMF as add-on therapy was influenced by prior CNI intolerance or biopsy proven CNI toxicity, introducing potential confounding by indication. Heterogeneity in prior immunosuppressive exposure and the inability to clearly attribute response to rituximab in children with persistent partial remission on CNI may have further affected outcome interpretation. In this study ,32 treatment events are observed in 24 children which cannot be assumed to be fully independent, which has been analyzed at treatment-level outcome and patient-level outcome. Outcome and comparisons were tested retrospectively in a cohort of 24 children, large prospective randomized multi center studies are needed to confirm our findings.

Conclusion

In this analysis of CNI-resistant-non-genetic SRNS, CNI with rituximab showed proportionately higher remission rates, fewer hospitalizations, and fewer progression to CKD, while MMF demonstrated a safer profile in CNI-intolerant patients. These findings should not be interpreted as supportive evidence of superiority of add-on immunosuppression over other and needs large prospective study for validation.

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Figures

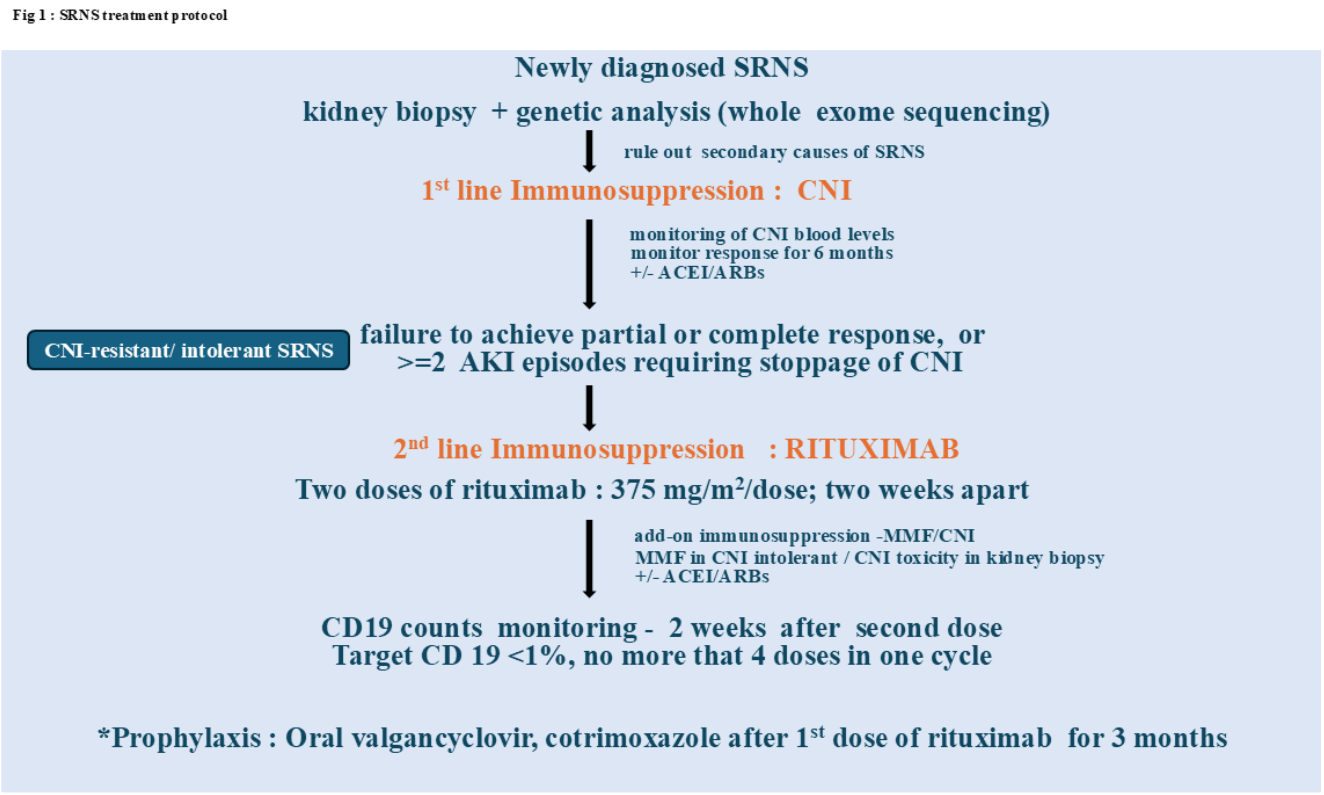


Figure 1

See image above for figure legend

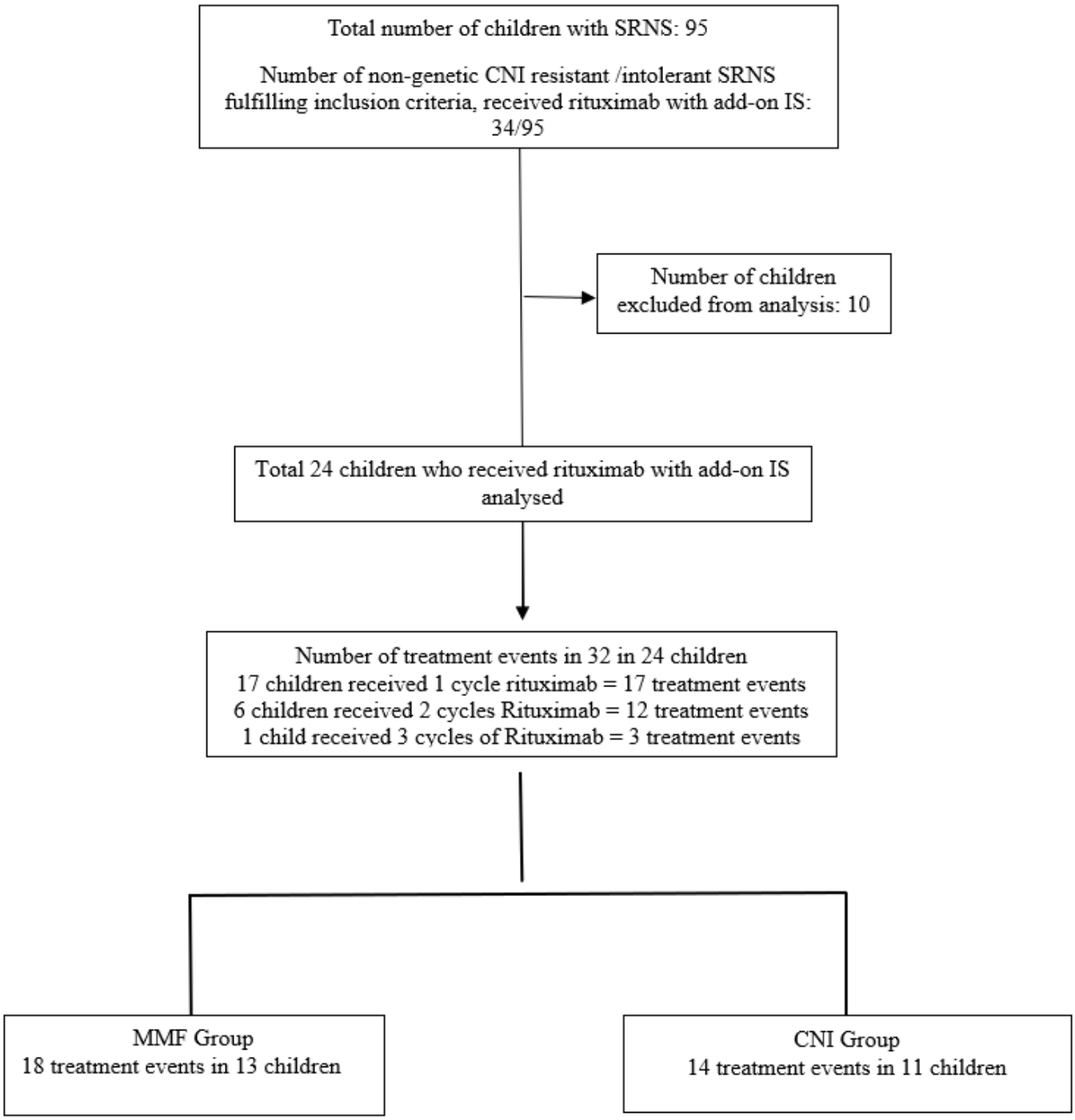


Figure 2

See image above for figure legend

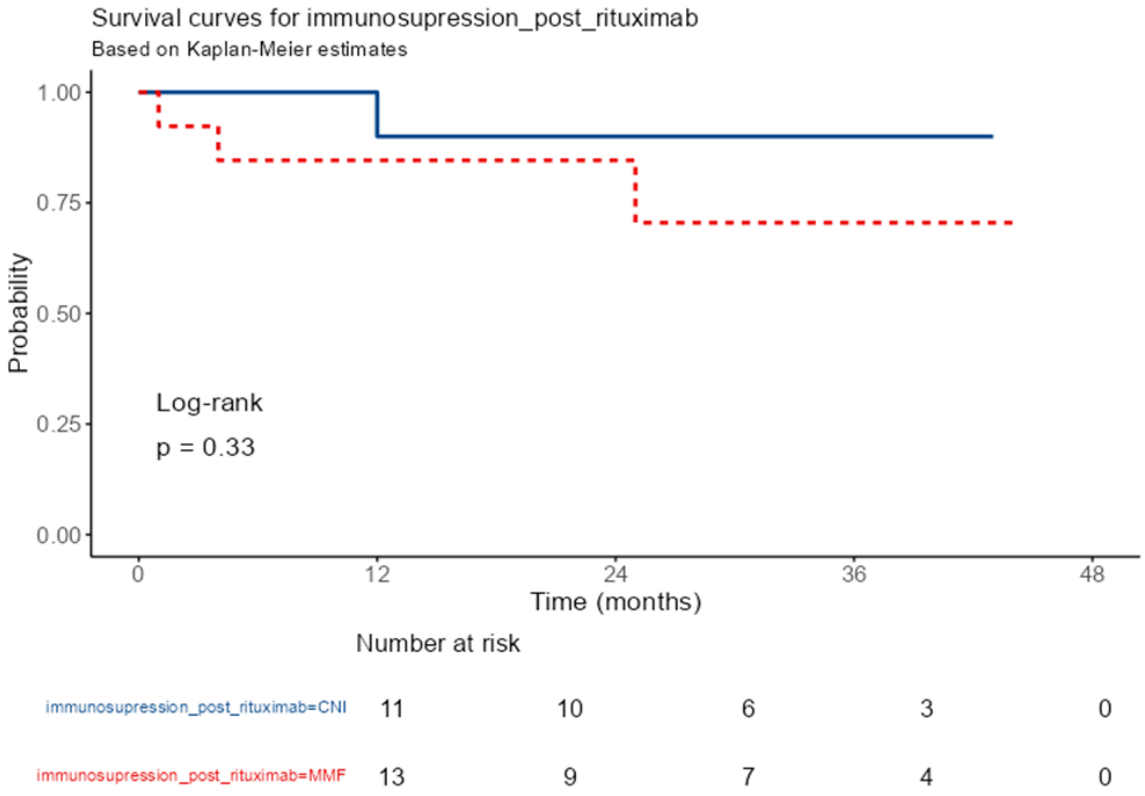


Figure 3

See image above for figure legend