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Preventing Relapses in Childhood Nephrotic Syndrome

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The majority of children with steroid-sensitive idiopathic nephrotic syndrome (SSNS) will eventually attain complete remission. Treatment balances side effects of different immunosuppressants while we await disease resolution. Rituximab decreases the risk of relapses in children with frequently relapsing nephrotic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS), who still have difficulty controlling the disease and other steroid-sparing agents.[1–3] More recently, rituximab has been trialed with good effect as a first-line steroid-sparing agent in children with FRNS or SDNS.[4–6]

In this issue, Liu *et al.*[7] ask if using rituximab in conjunction with prednisone for the presenting episode of SSNS can decrease the risk of developing FRNS or SDNS. They undertook a single-arm, open label, prospective study in China of a single 375 mg/m^2 dose of rituximab after remission of the initial presentation. Forty-four children were enrolled, with median age of 4 years, 77% male, and all had B cell depletion after the single dose of rituximab. One child was lost to follow-up. At 12 months, 32 of 43 children (74%) remained in remission and 5 of 43 (12%) had FRNS or SDNS. At 24 months, 27 of 43 children (63%) remained relapse-free with rates of FRNS or SDNS not reported. Significant neutropenia occurred in 9% of children and infusion-related reactions occurred in 3%.

Relapse rates in Liu *et al.*[7] were markedly better than other much larger trials and cohort studies, but marked heterogeneity between the studies makes it difficult to compare outcomes. Over the last 50 years, various prednisone courses induced slightly different short-term remission rates; however, by 2 years, most children had relapsed.[8,9] In 3200 children, the relapse-free rate at about 2 years was 26%, compared to 63% in Liu *et al.*[7] (Figure 1).[S1–S5] In 2600 children, the rate of SDNS or FRNS by 12 months post-presentation was 43% compared to 12% in Liu *et al.*[7,S3–S8] The relapse rates in the study by Liu *et al.*[7] are also superior to other trials of rituximab in children previously only treated with prednisone (Table 1). The largest study randomized Indian children with SDNS and no previous steroid-sparing agent to receive either rituximab or tacrolimus.[4,S9] The rituximab group had a 90% sustained remission rate by 12 months, which dramatically dropped to 0% by 24 months, compared to 63% remission rate at 24 months in the study by Liu *et al.*[7,S9] A large retrospective study of children who had varying steroid-sparing agents before rituximab found that 1-year remission rates ranged from 20% to 50% in children with severe disease (2–3 immunosuppressive drugs before rituximab) and 60% to 90% in children with milder disease.[S10] Comparisons between studies are difficult. The aforementioned studies all capture different populations, with different severity of disease, at different times in the disease course and at differing risks of future relapse. The work by Liu *et al.*[7] involves an unselected cohort at first presentation of disease and thus at much lower risk of relapse. Ethnic differences and the inherent uncertainty in small sample sizes may also account for the differing relapse rates. In addition, the Liu *et al.*[7] study involves no randomized control arm of standard care for comparison.

In contrast, an intriguing explanation for the apparent dramatic decrease in the risk of relapse could be that rituximab, when given at disease onset, may change the natural course of the disease. The physiopathology of SSNS is still unclear; however, recent studies suggest a role for antinephrin antibodies that cause disruption of the glomerular filtration barrier.[S11] Hypothetically, early rituximab therapy could prevent the formation of long-lived plasma cells that cause relapsing disease. To date, no disease-modifying drugs have been identified in SSNS. However, trials

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Table 1. Relapse rates in children treated with rituximab with no prior steroid-sparing agent

Study	Population	1-year relapse, *n/N* (%)	2-year relapse, *n/N* (%)	Rituximab dose (mg/m^2)
Liu *et al.*[7]	First presentation	11/43 (26)	16/43 (37)	1 × 375
Basu *et al.*[4], Basu 2023[4,S9]	SDNS	6/59 (10)	59/59 (100)	2–4 × 375
Kari *et al.* 2020[5]	FRNS or SDNS	3/19 (16)	NA	2 × 375
Ravani *et al.* 2021[6]	SDNS	2/15 (13)	NA	1 × 375

FRNS, frequently relapsing nephrotic syndrome; NA, not available; SDNS, steroid-dependent nephrotic syndrome. Some children in Ravani *et al.* had previously had other steroid-sparing agents >6 months before recruitment.

testing rituximab in SSNS suggest that a limited number of patients do not relapse after rituximab therapy, which could indicate permanent effects of rituximab on the immune system.

Limited other data exist for rituximab use at first presentation of nephrotic syndrome, because of concerns about the risk-benefit profile. Three Chinese children treated with 4 doses of rituximab attained remission within 2 weeks and were relapse-free at 4 months.[S12] In adults, case reports of 24 Chinese and Italian adults with first presentation of minimal change disease revealed that most gained remission after rituximab.[S13–S15] Reluctance to perform these studies stems from concerns of overtreating patients with mild disease using a drug with rare but significant side effects. Rare, but potentially serious adverse events include rituximab-associated lung injury, anaphylactic reactions, fulminant myocarditis, hepatitis B virus reactivation, severe colitis, and possibly, multifocal leukoencephalopathy.[S16] In addition, post-rituximab hypogammaglobulinemia is of concern, occurring in 14% to 58% of children.[S17] In a French multicenter study including 107 children with SDNS, 43% of patients experienced at least 1 episode of hypogammaglobulinemia that persisted for more than 1 year in 12% of cases.[S18] Similar rates were reported in an Italian study including 27 patients with SDNS, 4 of whom developed severe persisting hypogammaglobulinemia requiring long-term periodic immunoglobulin substitution.[S19] Importantly, younger children were at a higher risk of developing hypogammaglobulinemia in both studies, which corresponds to the age of patients that present with a first episode of SSNS, such as those that were included in the study by Liu *et al.*[7]

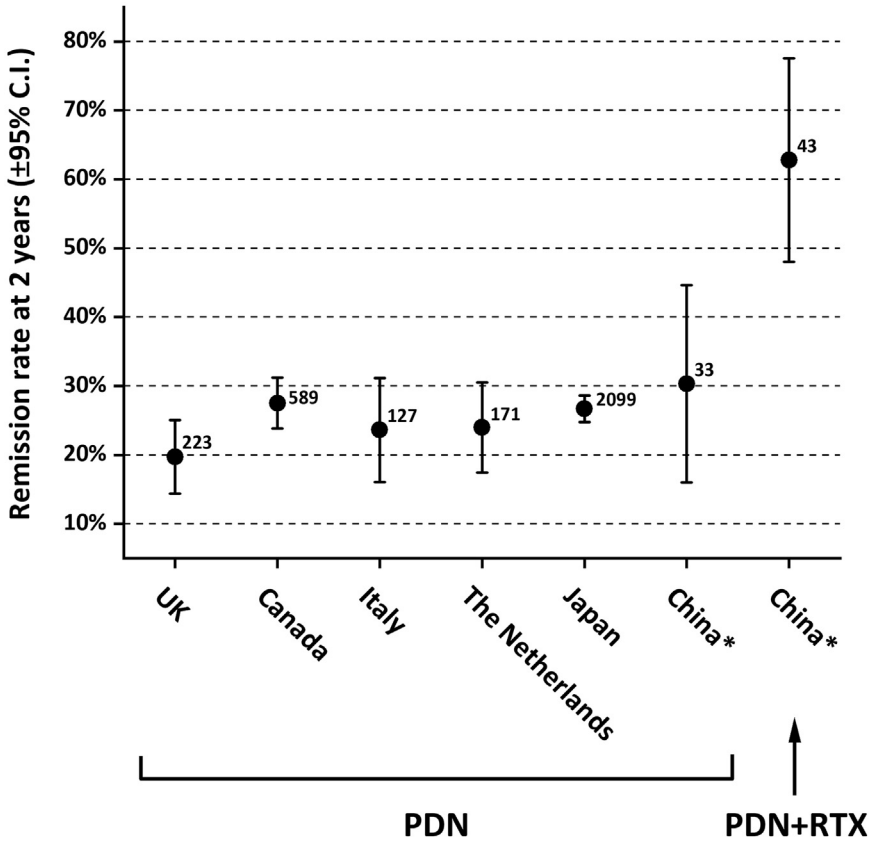

Figure 1. Relapse-free survival at 2 years from presentation of childhood steroid-sensitive nephrotic syndrome. Data from (7,S1,S3–S5,S20). The numbers in the figure are the number of children in each cohort. *The rates for the 2 Chinese datasets are a historical cohort with prednisone induction and for a prospective cohort with rituximab after prednisone induction. CI, confidence interval; PDN, prednisone; RTX, rituximab.

Should we envision treating all children with rituximab at disease onset? First, the authors should continue monitoring their cohort to inform the scientific community about the outcome of their patients in the long-term. If a significant proportion of patients remain in remission after 4 to 5 years, the risk-benefit ratio of treating children with rituximab at disease onset would favor testing this more aggressive approach. Any future studies should include a randomized control group treated with standard prednisone-based protocols, in order to compare benefits and side effects of therapy. Given that 50% of children are likely to have no relapses to infrequent relapses, rituximab administration in the initial presentation poses risks without benefits to about half of the children. Potential factors associated with developing FRNS or SDNS include younger age at first presentation, longer time until remission and shorter time to first relapse.[S7,S18,S20–S23] Any potential

future trials could target these subgroups to further maximize risk-benefit balances.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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