Long-Term Efficacy and Safety of Rituximab Versus Tacrolimus in Children With Steroid Dependent Nephrotic Syndrome

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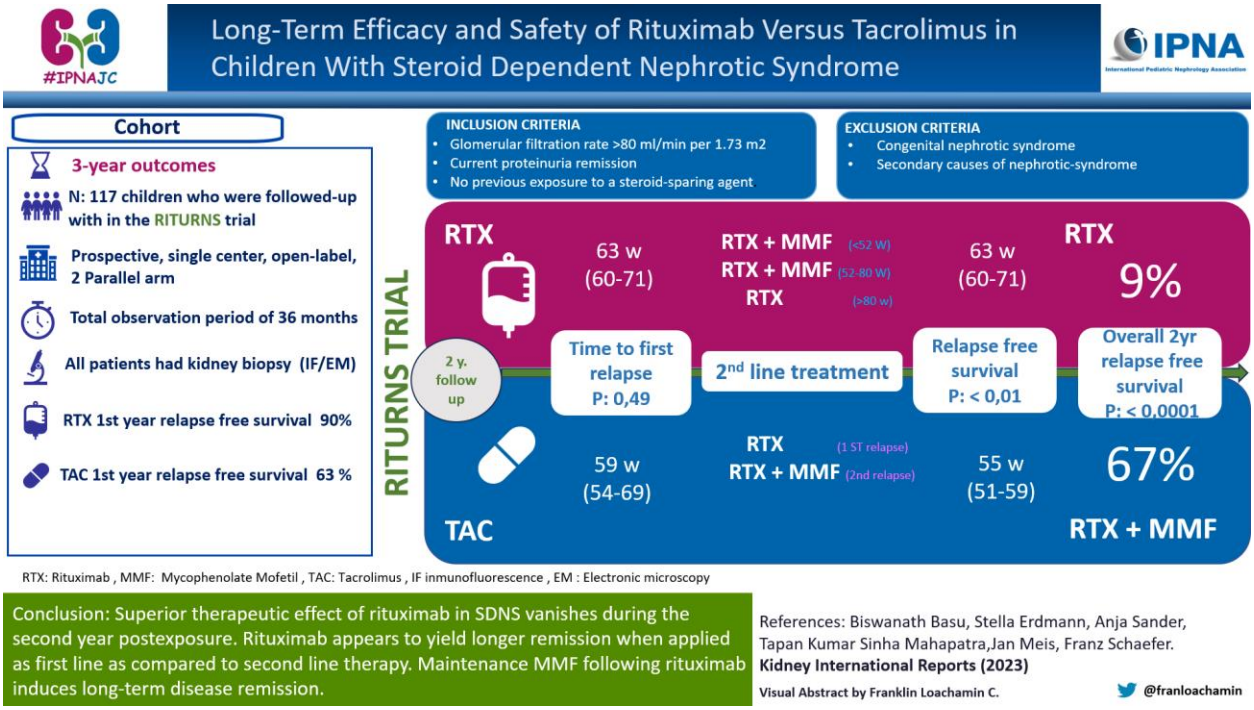

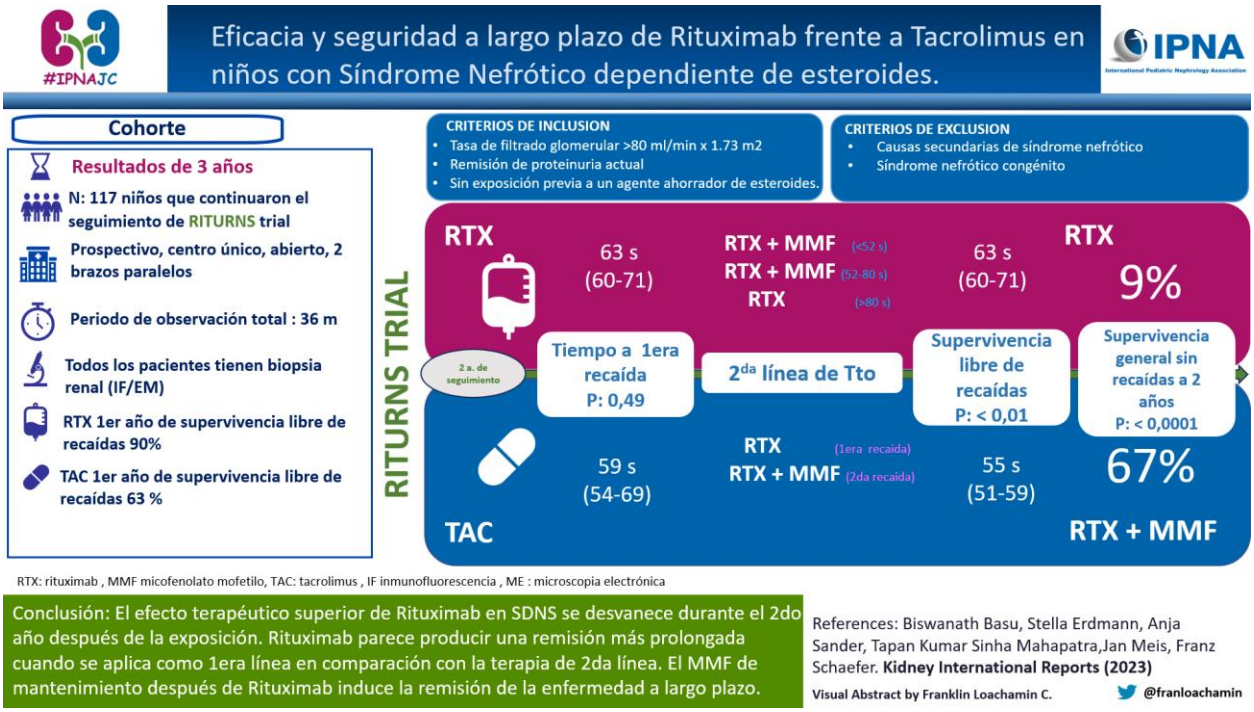

BACKGROUND:

The landmark publication of ISKDC established steroids as the first-line treatment for childhood nephrotic syndrome. Most children respond well to steroids, but one-third of them develop a frequently relapsing or steroid dependent pattern effecting in a prolonged and frequent steroid dosing and hence accrual of significant side effects and long-term complications. Resultantly, a search for an alternative drug or a steroid-sparing regimen is perhaps one of the top items on a pediatric nephrologist's career bucket list.

Currently, calcineurin inhibitors and mycophenolate mofetil are on the top of the list of steroid sparing agents. In the early 2000's, experimental studies with the B-lymphocyte-depleting monoclonal antibody, rituximab (RTX) showed promising results. An Italian multicentre case series showed encouraging results when used in SDNS/calcineurin dependent SDNS children. This set the stage for a non-inferiority randomized controlled trial by Raviani et al in 2015 that compared RTX with steroids in SDNS and found positive outcomes. A head-to-head comparison of the calcineurin inhibitor tacrolimus (TAC) with RTX was conducted by Basu et al in the RITURNS trial (Rituximab for Relapse Prevention in Nephrotic Syndrome).

The RITURNS trial demonstrated that a single course of RTX was associated with a significantly higher 12-month relapse-free survival rate than daily TAC therapy (90.0% vs 63.3%) during 12 months of follow-up.

The present study being discussed looked at the long-term efficacy and safety of both the drugs over a period of further 24 months.

METHODS

The study cohort in the RITURNS continuation study was divided **into two arms**

1. **RTX arm**: Relapsing patients received a second course of RTX either with or without Mycophenolate Mofetil (MMF) co-treatment.
2. **TAC arm:** RTX monotherapy was used as a second line agent after relapse or electively. A second course of RTX was administered and MMF maintenance therapy was added in case of re-relapse after RTX monotherapy.

RTX arm was further divided into **three sub groups** according to the time to first relapse after receiving the initial RTX dose:

a. Early relapsers (<52 weeks)
b. Intermediate relapsers (52-80 weeks)
c. Late relapsers (>80 weeks).

The early and intermediate relapsers were given RTX+MMF and the late relapsers received RTX monotherapy as 2nd line treatment.

The initial and subsequent RTX treatment courses consisted of two infusions (375 mg/m2, maximum 500mg) administered within a 7-day interval after attainment of remission. The MMF dose was 1200 mg/m^2 per day orally in 2 divided doses.

RESULTS

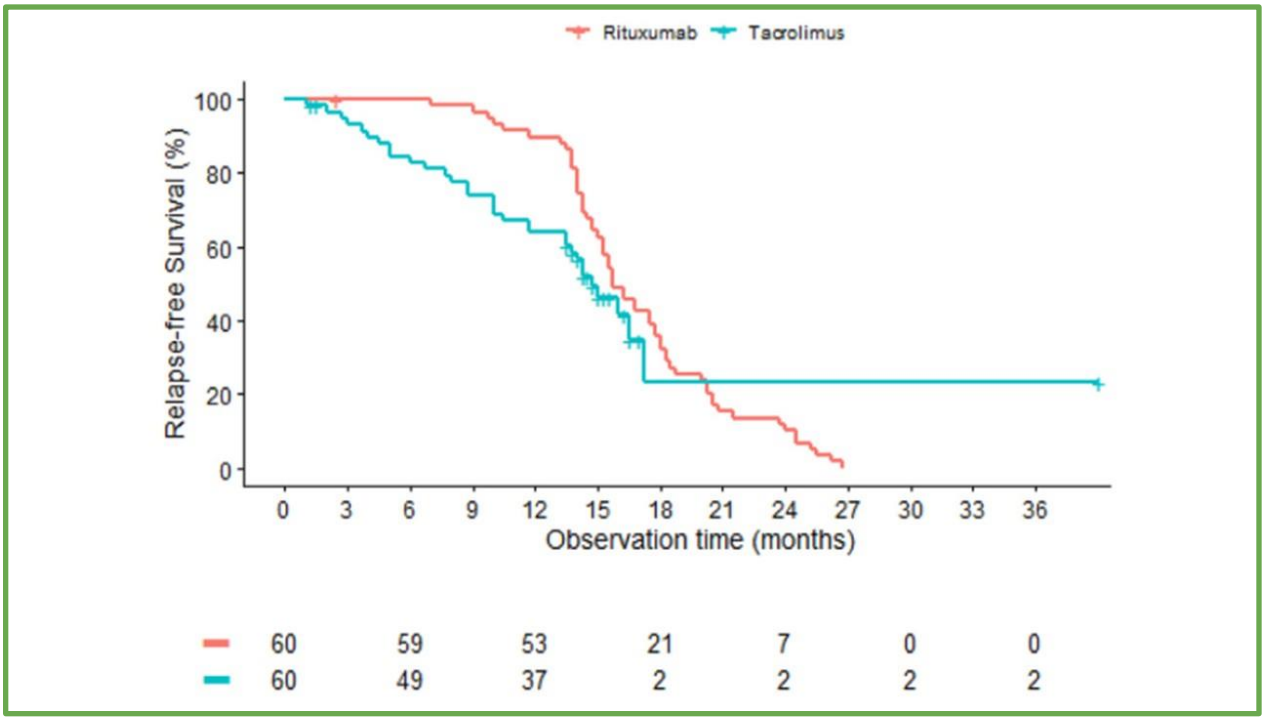

Figure 1: KM curve demonstrating long-term relapse-free survival of patients in the RTX and TAC arms. The table below the graph indicates the number of patients still at risk at the respective points in time.

The twelve- month relapse free survival period in the original RTX arm was 54 weeks vs. 38 weeks in the original TAC arm (P<0.001); (odds ratio, 5.21; 95% CI, 1.93-14.07) and hence statistically significant.However, there was no significant difference in relapse free survival for the original trial arms for the entire period of observation 63 weeks vs. 59 weeks (p=0.49) as illustrated in **figure1**

Relapses occurred later in the RTX arm than in the TAC arm in the first year but more patients in RTX developed their first relapse in the second year.The pre-trial disease duration (p<0.001) and patient age (p=0.016) significantly impacted the relapse risk.

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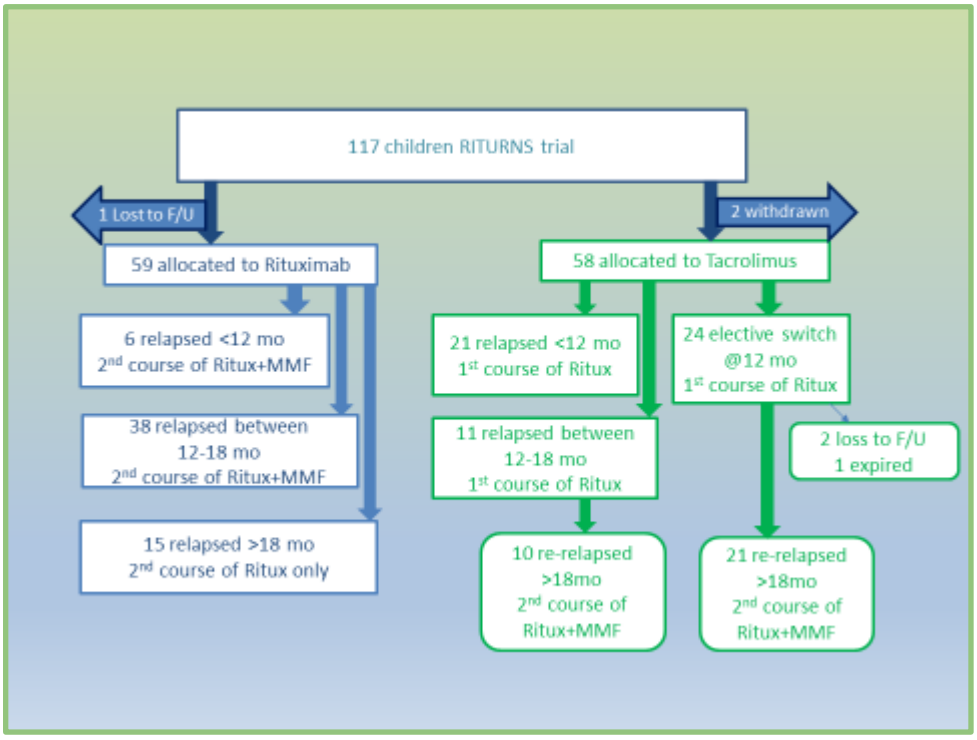
A flowchart of patient allocation and follow-up interventions is seen in **Figure 2**



Relapsing patients in the RTX arm received a second course of RTX, either with (*n*= 44) or without MMF co-treatment (*n*=15). In the TAC arm, second line RTX monotherapy was initiated after relapses (*n*=32) or electively (*n*=24). The median (95% CI) time to first relapse when RTX was used as 2nd line agent in patients with prior maintenance tacrolimus therapy was 55 (51–59) weeks, as compared to 63 (60–71) weeks after first-line rituximab therapy (P=0.0055).

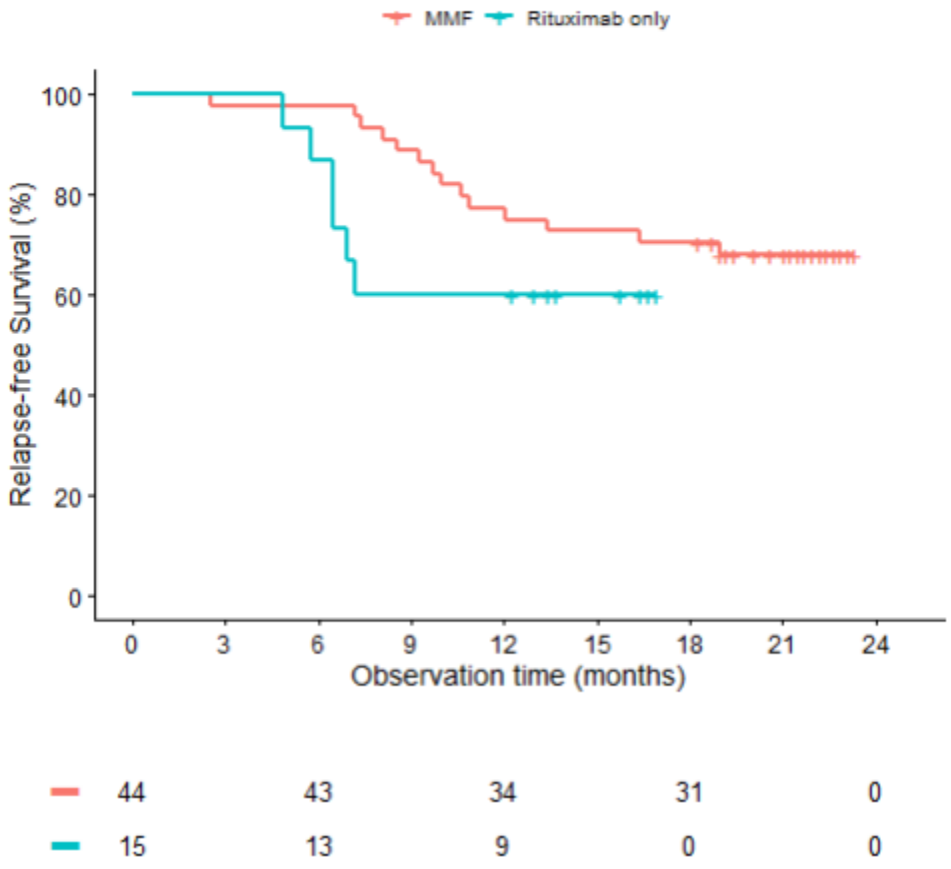
Interestingly,the 24 TAC patients switched to RTX electively had a longer and statistically significant time to relapse (p=0.07) than those switched post-relapse while on TAC.

MMF maintenance therapy was associated with a lower relapse rate after RTX dosing. While no difference in re-relapse rates, after 2nd dosing of RTX in both arms, was apparent in the first year of observation, the 2-year relapse-free survival was 67% with maintenance MMF therapy as compared to 9% for the periods without post-rituximab maintenance immunosuppression (P < 0.0001; difference of proportions: 58%; 95% CI 45%–71%).

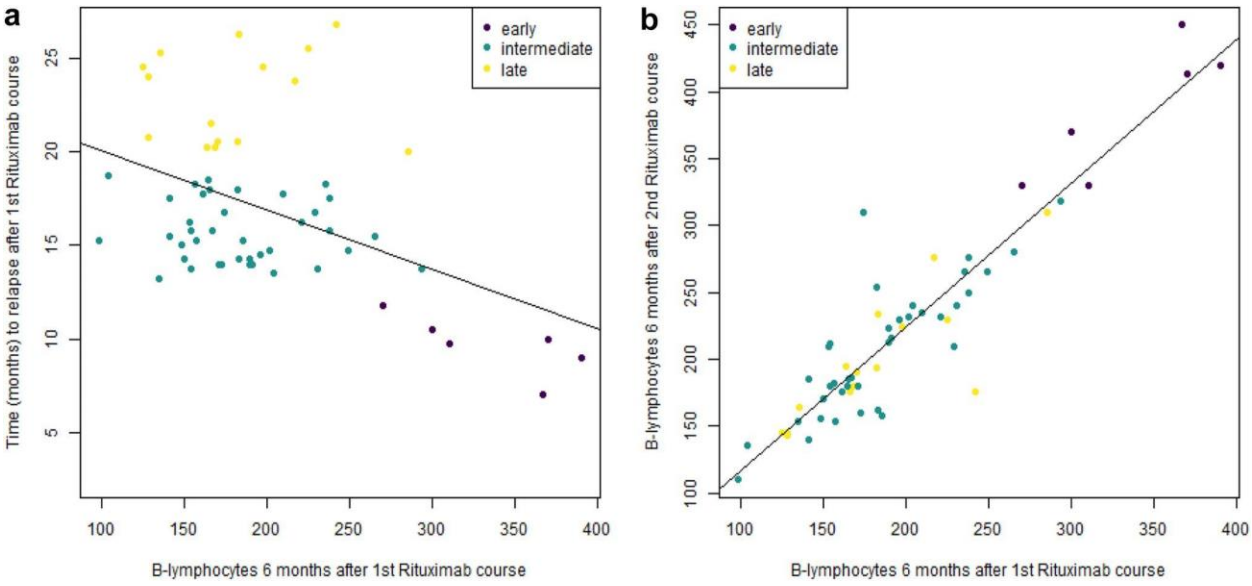
When only the RTX arm was analyzed, multivariable Cox regression analysis revelaed a nearly 4-fold increased risk of developing a re-relapse in patients who received a

second course of rituximab **without** MMF maintenance versus patients who those who **received** MMF (HR 3.95; 95% CI 1.25–12.39; P=0.019) as seen in the figure below.

Figure S-1: Time from second course of Rituximab to second relapse in patients of previous Rituximab trial arm with (44 patients, red curve) and without MMF maintenance therapy (15 patients, blue curve).



The B-lymphocytes count six-month post dosing was inversely correlated with the time to first relapse (p=0.001). A 6-month B-cell count >270/ul was predictive of a relapse within 12 months of dosing at a sensitivity of 100% and a specificity of 96%. A relapse beyond 12 month period could not be predicted from the 6-month B-cell count. Degree of initial depletion and recovery within 6 months was similar for all intervention groups as noted in the figure below.



Grade 1 adverse events i.e. acute infusion reactions were highest with RTX monotherapy; while grade 2 adverse events i.e. infection was more frequent in the tacrolimus group.

With RTX therapy, cumulative dose of steroid was significantly decreased and patients had a more favorable BMI z-score whether used as 1st line or 2nd therapy.

Discussion:

In the initial RITURNS trial, RTX appeared to be the more efficient drug in maintaining remission when compared to TAC in the first 12 months. However, the superior therapeutic effect of RTX in children with SDNS disappeared during the second year post-exposure. Longer duration of disease before RTX administration and older patient age are the only two significant variables that affect the risk of relapse and perhaps reflect a population that is inherently difficult to treat.

RTX appears to yield longer remission when given as the 1st line as compared to the 2nd line. However, patients who were electively switched while being in remission on TAC fared similarly to those given RTX as first line. Probably a sustained state of remission of proteinuria, individual to each patient, is a better predictor of outcome than any drug regime as can be seen when the effect of RTX eventually wears off.

Similarly, the recovery of B cell count at 6-month post dosing of RTX in both groups was predictive of earlier time to relapse and points to a possible need of individualized dosing with more frequent monitoring of B cell count rather than a standardized protocol.

Overall the RTX regime was well tolerated with a minimally reported side effect profile. Immunoglobulin levels, however, were not monitored in this study. Specific monitoring of B-lymphocyte counts appears to be sufficient to monitor its effect. This is relevant to low-resource settings where investigations have to be ordered very judiciously.

In summary, this extension of the RITURNS trial has answered some pertinent questions as we treat children with various regimes of RTX; both, as first or second line drugs; but, at the same time raises some relevant queries that require further probing.

The requirement of MMF as an add-on therapy for maintenance of remission to induce long term remission following RTX will be further tested in the RITURNS 2 RCT https://pubmed.ncbi.nlm.nih.gov/33256621/

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