Letters

RESEARCH LETTER

Rituximab vs Low-Dose Mycophenolate Mofetil In Recurrence of Steroid-Dependent Nephrotic Syndrome in Children and Young Adults: A Randomized Clinical Trial

Children and young adults with steroid-dependent nephrotic syndrome (SDNS) are exposed to the toxic effects of both steroids and common steroid-sparing agents, such as calcineurin inhibitors, reporting an increased risk of kidney failure.[1] Alternative low-toxicity, long-acting therapies are needed to treat SDNS.[1]

Supplemental content

Methods | This randomized clinical trial was designed to test the superiority of a single dose of rituximab (375 mg/m^2) vs low-dose mycophenolate mofetil (MMF) (350 mg/m^2 twice daily) in preventing the recurrence of SDNS. Eligibility criteria were age 3 to 24 years and SDNS requiring prednisone 0.3 mg/kg/d to 1 mg/kg/d during at least 6 months before enrollment.

Eligible White patients were randomly assigned in a 1:1 ratio to receive either rituximab (intervention) or oral MMF (active comparator) (**Figure 1**). Sex and age were equally distributed. The trial protocol (Supplement 1) and study were approved by the regional review board (Liguria, IT) and Italian Drugs Agency (AIFA) and the trial protocol was registered at ClinicalTrials.gov (NCT04402580). Written consent was obtained by patients or by their parents.

The primary outcome was the occurrence of a relapse of SDNS within 12 months of randomization; the secondary outcome was the probability of remaining relapse-free up to 24 months from randomization. Relapse was defined by a urine protein/creatinine ratio (uPCR) of 2000 mg/g or more. Logistic regression was used to compare the risk of relapse at 1 year with a 2-sided *P* value of <.05 as statistical significance.

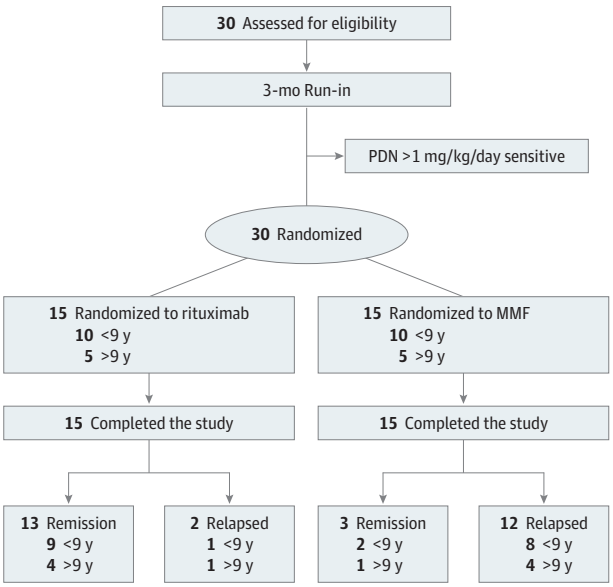
Results | The monitoring board recommended stopping the trial after the randomization of only 30 study participants owing to unexpectedly high rates of relapse in the MMF arm (Figure 1). Of note, no relapses occurred in the intervention arm in the first 6 months. After rituximab, CD19$^+$ B cells immediately decreased to 0%, maintaining low values until 6 to 9 months after infusion, with no differences between relapse or not.

The risk of relapse was 0.8 (12/15) in the comparator arm and 0.13 (2/15; *P* = .008) in the intervention arm, with a significantly higher odds among children in the MMF arm (odds ratio [OR], 26; 95% CI, 2.9-311.0). The median time to the relapse in the active comparator arm was 3.15 months (95% CI, 2.5-9.9 months; **Figure 2**). No adverse effects were observed in either group and none related to rituximab infusion.

Discussion | Approximately 90% of children with idiopathic nephrotic syndrome develop steroid dependence.[1] Considering the toxic effects of calcineurin inhibitors, alternative interventions or low-dose approaches are needed for long-term treatments.

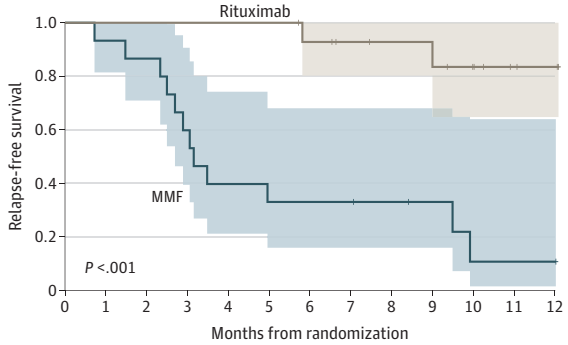
The anti-CD20 monoclonal antibody rituximab emerged as a promising steroid-sparing drug in patients with SDNS.[1,2] In the present study, single-dose rituximab, withdrawing

Figure 1. Schematic View of Trial Design



MMF indicates mycophenolate mofetil; PDN, prednisone.

Figure 2. One-Year Relapse-Free Survival in the Rituximab and Mycophenolate Mofetil (MMF) Arms



No. at risk

MMF	15	14	13	9	6	5	5	5	4	3	1	1	1
Rituximab	15	15	15	15	15	15	13	11	10	10	7	4	3

The risk of relapse was 0.8 (12/15) in the MMF and 0.13 (2/15; *P* = .008 in the rituximab arm, with higher odds in the MMF arm (odds ratio, 26; 95% CI, 2.9-311.0).

steroids, resulted in effective control of SDNS. Given the limited adverse effects, rituximab should be considered as the main steroid-sparing drug in patients with SDNS.

Previous reports indicate that MMF can maintain steroid-free remission in children with SDNS.[2] However, existing small and uncontrolled studies on MMF generated conflicting data[2,3]: the minimum dose of MMF sufficient to maintain remission of SDNS is unknown, and variable doses (ranging from 700 mg/m^2-1200 mg/m^2 daily) are reported.[4]

This study aimed to address the efficacy of low-dose MMF, and the inefficacy provides useful evidence for designing future trials. The adherence to MMF, monitored with monthly reports, was complete in all patients. The strategy of monitoring may represent a weakness and better strategies to estimate MMF exposure are to be defined.

Conclusions | Rituximab was effective in maintaining long-term remission of SDNS; MMF given at low dose (350 mg/m^2 twice daily) was, instead, inadequate. The effect of higher doses (1200 mg/m^2) deserve testing in randomized clinical trials. Lack of efficacy of low-dose MMF may have implications in clinical practice or research of other immune-mediated conditions.[5,6]

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Concept and design: Ravani, Ghiggeri.
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