Comparison of rituximab, cyclophosphamide, and tacrolimus as first steroid-sparing agents for complicated relapsing/steroid-dependent nephrotic syndrome in children: an evaluation of the health-related quality of life

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Abstract

Introduction: Frequently-relapsing/steroid-dependent nephrotic syndrome (FRSDNS) leads to steroid toxicity impairing quality of life (QOL), thus prompting the use of steroid-sparing drugs.

Methods: 51 FRSDNS children not previously treated with steroid-sparing agents were randomized to receive rituximab, cyclophosphamide, or tacrolimus. Clinical findings and QOL were evaluated before and after treatment.

Results: The mean relapse rate in all groups declined six months after treatment, however, 1-year relapse-free survival rate, number of relapses, and cumulative prednisolone dosage were lower with rituximab than with tacrolimus and cyclophosphamide. Cyclophosphamide group had twice frequency of infections compared to the other groups. At 1 year after treatment, total scores showed greater improvement with rituximab.

Conclusions: As first-line steroid-sparing agent, rituximab is more effective and safer than cyclophosphamide and tacrolimus in FRSDNS, and improve QOL.

Key words: rituximab, tacrolimus, cyclophosphamide, frequently relapsing/steroid-dependent nephrotic syndrome, quality of life.

Frequently relapsing (FR) nephrotic syndrome (NS)/steroid-dependent (SD) NS (FRSDNS) has frequent relapses and require repeated or ongoing use of glucocorticoids. Children who had a relapse at least twice within a half year or three times within 1 year were defined as FRNS. Patients who had a relapse on a reducing course of prednisolone or within 2 weeks of stopping steroids were diagnosed with SDNS. Relapses in patients with FRSDNS are closely related to infections, thrombosis, and dyslipidemia [1, 2]. Immunosuppressive drugs, e.g., cyclosporine A (CyA), mycophenolate mofetil (MMF), cyclophosphamide, and tacrolimus are efficacious in FRSDNS [1–3]. A meta-analysis of randomized controlled trials (RCTs) reported cyclophosphamide to be more effective than CyA and preferred initially in children with FRSDNS [2]. Although tacrolimus is often associated with nephrotoxicity, it could induce remission in CyA and MMF resistant pediatric onset of NS [4].
Since 2004, several studies [5–7] have reported that rituximab, a chimeric anti-CD20 monoclonal antibody, maintains remission in complicated FRSDNS. Sinha et al. [5] showed that the median time to first relapse with single-dose of rituximab (375 mg/m²) in children with SDNS and 2–4 times to first relapse with single-dose of rituximab (375 mg/m²) in children with SDNS and 2–4 weeks. More FRSDNS children achieved complete withdrawal of steroids within 3 months with rituximab as the first steroid-sparing agent than cyclophosphamide [7]. A comprehensive search of PubMed for relevant papers published before July 2021 found only three RCTs that documented a higher 1-year relapse-free survival rate and lower cumulative corticosteroid dose with rituximab than conventional drugs, MMF, and tacrolimus as the first steroid-sparing agent in children with SDNS [3, 8, 9].

Materials. A prospective randomized study of 51 children with FRSDNS not previously treated with steroid-sparing agents were randomized to cyclophosphamide, tacrolimus, or rituximab. Patients completed 6–8 doses of IV cyclophosphamide (10 mg/kg/day for 2 days, biweekly; maximum cumulative dose: 168 mg/kg), along with intravenous saline hydration and bicarbonate (2–3 ml/kg) alkalization. Children received tacrolimus, 0.1–0.15 mg/kg area; maximum dose, 500 mg). They also received a prophylactic dose of trimethoprim (3 mg/kg per time, QOD) for 3 months, which was continued for 6 months in cases where the CD4+ T-cell counts were below 410 cells/µl. At 5 and 30 min before rituximab infusion, children were administered dexamethasone (0.2 mg/kg, intravenous injection) and promethazine (0.125 mg/kg, intramuscular injection). Rituximab was re-administered (375 mg/m²; if CD19+ B-cell counts < 90 cells/µl, half-dose of 375 mg/m²) at 6 months’ intervals. Prednisolone was stopped by 3 months for all groups. Patients who experienced a relapse following their allocated treatment received remission-induction steroids again. Prednisolone was re-administered at a dose of 2 mg/kg/day for 1–2 weeks, then 2 mg/kg/day every other day for 2–3 weeks, then tapered by 0.25 mg/kg every 2 weeks, and stopped within 3 months.

Statistical analysis. Statistical analyses were carried out using SPSS 19.0. Continuous data are expressed as mean (standard deviation). Data at different time-points or among three groups were analyzed using paired t-test or one-way ANOVA. Adverse events were compared using the χ² test. Kaplan-Meier analysis and Cox regression model were used to analyze and compare relapse-free survival. Pearson’s test was used to assess pre-treatment HRQL and NS duration. Statistical significance was set at p < 0.05. Results. The baseline demographic and clinical characteristics were well balanced among the treatment groups. Our study demonstrated a significant and clinically relevant reduction in the mean relapse rate during the 6 months after treatment with rituximab, tacrolimus, and cyclophosphamide compared to 6 months before treatment. The mean prednisolone dosage was significantly lower in all groups, confirming that these drugs are effective in minimizing relapse frequency in children with FRSDNS [1, 2, 7, 8].

The 1-year relapse-free survival rate was significantly higher in patients treated with rituximab (82.4%) than in those treated with tacrolimus (64.7%, p = 0.043) and cyclophosphamide (11.8%, p < 0.001) (Figure 1). In patients who relapsed in the first year, the mean time to first relapse was longest with rituximab (8.3 months), followed by tacrolimus (4.6 months) and cyclophosphamide (3.3 months) (p < 0.001). An RCT by Basu et al. [8] reported a longer median time to first relapse with rituximab (40 weeks) than with tacrolimus (29 weeks). Another non-RCT showed a higher 1-year relapse-free survival with rituximab (84.2%) than cyclophosphamide (58.6%) [7]. Therefore, rituximab was more effective than cyclophosphamide and tacrolimus in prolonging the remission time.

A key aim of steroid-sparing agents is to minimize the use of glucocorticoids [7, 8]. Concurring with previous observations, within 1 year af-
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Table I. Relapses, infections, and the cumulative prednisolone dosage in FRSDNS patients after 1 year of treatment with cyclophosphamide, tacrolimus, or rituximab

| Treatment      | N   | Relapse | Infection | Cumulative prednisolone dosage [mg/kg] |
|----------------|-----|---------|-----------|---------------------------------------|
| Cyclophosphamide | 17  | 1.2 (0.6) | 2.6 (1.3) | 119.2 (58.4)                        |
| Tacrolimus      | 17  | 1.1 (0.9) | 1.6 (1.0)* | 101.7 (72.5)                        |
| Rituximab       | 17  | 0.5 (0.6)* | 1.1 (0.7)* | 53.2 (33.2)*                        |
| F              |     | 3.780   | 8.420     | 4.611                                |
| P-value         |     | 0.030   | 0.001     | 0.016                                |

Data shown are the mean (Standard Deviation) number of relapses, infections, and the cumulative prednisolone dosage 1 year after treatment with cyclophosphamide, tacrolimus, or rituximab. *In comparison with the cyclophosphamide group, p < 0.05; †In comparison with the tacrolimus group, p < 0.05. FRSDNS – frequently relapsing/steroid-dependent nephrotic syndrome.

In conclusion, our study showed improved psychological health summary and social and school functioning scores 1 year after rituximab treatment, compared to pre-treatment. Better total HRQOL.
scores, especially related to social and school functioning, have been reported for patients with incident NS than prevalent NS [14]. Another study on 21 NS patients found that the total HRQOL scores improved by 10 points or more over a 2-year rituximab treatment, administered four times at 6-month intervals [15].

At 1 year after treatment, the rituximab group had higher total, psychological health summary, and social and school functioning scores than the cyclophosphamide and tacrolimus groups, indicating a higher HRQOL with rituximab. In contrast, compared to children with NS who received no medication, those on other steroid-sparing agents (tacrolimus, CyA, oral cyclophosphamide, MMF) for 6 months showed lower overall HRQOL scores [14]. Additionally, no association was seen between the HRQOL scores and functioning domains (physical, emotional, social, and educational), consistent with our findings that cyclophosphamide and tacrolimus did not affect the functioning domain scores [14].

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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