Single Dose of Rituximab in Children with Steroid-Dependent / Frequently Relapsing Nephrotic Syndrome, Clinical Efficacy and Evaluation of Health-Related Quality of Life

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Introduction. Steroid-dependent (SD)/frequently relapsing (FR) nephrotic syndrome (NS) follows a relapsing and remitting course. It is also characterized by proteinuria and edema, which can significantly affect health-related quality of life (HRQOL) in children. This study evaluated the effectiveness and safety of a single dose of rituximab (RTX) as well as the impact of RTX on HRQOL in children with SDFRNS.
Methods. Sixteen children with SDFRNS were enrolled in the study. Each patient was administered a single intravenous dose of RTX (375 mg/m^2). Effectiveness was defined as remission of proteinuria. The side effects of RTX were monitored. HRQOL was assessed using PedsQL™ 4.0 Generic Core Scales.
Results. All the patients completed the study. Three SDNS patients and three FRNS patients discontinued treatment over 1 to 3.25 years of follow-up. Additionally, three SDNS patients and three FRNS patients experienced 1 to 2 relapses. The mean relapse-free period was 79.0 ± 77.6 days. The mean dosages of prednisolone and other immunosuppressants required were significantly lower ($P < .05$, $< .001$) six months after treatment with RTX compared with six months before treatment. Relapse rate was significantly reduced ($P < .001$) after treatment with RTX. Skin rash, hypotension, and fever were observed in one child. Total health score and physical, emotional, and school functioning were significantly higher six months after treatment with RTX ($P < .001$).
Conclusion. A single dose of RTX is effective and safe for children with SDFRNS and can improve HRQOL, especially physical, emotional, and school functioning.

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INTRODUCTION

Steroid-sensitive (SS) nephrotic syndrome (NS) is a severe kidney disease characterized by proteinuria, hyperlipidemia, hypoalbuminemia, and edema.[1-3] Few studies have looked at the detrimental effects of NS on health-related quality of life (HRQOL) among children.[4-6] HRQOL is low among children with NS because of edema and worsening disease severity.[7] Furthermore, there is a significant temporal association between stressful days and proteinuria, which suggests that psychological stress may trigger proteinuria in children with SSNS.[8] Approximately 80% of SSNS patients suffer a relapse after the first treatment with steroids, and approximately one-half of them suffer a relapsing and remitting course that may

result in steroid-dependent NS (SDNS) or frequently relapsing NS (FRNS).[1,3]

Relapses in patients with steroid-dependent/frequently relapsing nephrotic syndrome (SDFRNS) are associated with complications such as sepsis, thrombosis, and dyslipidemia.[1,3] Immunosuppressive (IS) drugs such as cyclosporine A (CyA), mycophenolate mofetil (MMF), cyclophosphamide (CYC), and tacrolimus (Tac) are efficacious in SDFRNS management.[3,9,10] Rituximab (RTX) is a chimeric anti-CD20 monoclonal antibody used as a rescue therapy for children with SDFRNS.[1,2] The median time for the first relapse in children with SDFRNS is seven months after treatment with CYC and 14 months after one or two dose of RTX.[11] Furthermore, a 12-month study revealed that, among children with SDNS, treatment with RTX is associated with a higher 12-month relapse-free survival rate and a lower cumulative corticosteroid dose than treatment with Tac.[12]

Presently, there are no standard RTX doses or dosages for children with SDFRNS.[1,2,4] Additionally, MMF has relatively few side effects; it does not cause nephrotoxicity or systemic toxicity. However, it is less effective than CyA or Tac is. Moreover, CyA is associated with high relapse rates with short-term use and nephrotoxicity with long-term use.[10,13] There are limited data on HRQOL in children with NS who are treated with RTX.[14] Therefore, the present study assessed response to treatment with a single dose of RTX in children with SDFRNS. HRQOL was also evaluated following the treatment.

MATERIALS AND METHODS

The study population was children aged < 16 years with SDFRNS, who were candidates for treatment with RTX at the First Affiliated Hospital of Anhui Medical University in Hefei between 2017 and 2020. The ethics committee of the hospital approved the study protocol.

Children with congenital NS were not included in the study. FRNS was defined as the recurrence of proteinuria at least twice within six months or at least thrice within a year. Children were classified as having SDNS when they suffered relapse while on a weaning course of prednisolone (PSL) or within 14 days of discontinuing steroids. The interval between NS diagnosis and being prescribed RTX was different among the patients but found to be at least one year.

The treatment plan was explained to all patients and their parents. Written informed consent was obtained from caregivers before treatment was administered. Each patient was administered a single intravenous dose of RTX (375 mg/m^2 body surface area; maximum dose, 500 mg). The premedication consisted of dexamethasone (0.2 mg/kg, intravenous injection) and promethazine (0.125 mg/kg, intramuscular injection), which were administered 5 and 30 min; respectively, before the RTX infusion. Patients were excluded from the study if they showed adverse reactions to RTX or did not cooperate to achieve study goals.

The doses of PSL and IS agents were tapered off after treatment with RTX. Relapses were managed with MMF twice daily (1000 to 1200 mg·m^{-2}·d^{-1}, maximum; 2 g/d) or PSL once daily (2 mg/kg; maximum, 60 mg/d). B-cell depletion was defined as peripheral CD19$^+$ B-cell count < 1% and 5 cells/mm^3, whereas B-cell recovery was defined as peripheral CD19$^+$ B-cell count > 3% and 15 cells/mm^3. Patients were told to have enough rest and monitor their blood pressure. Urine protein was examined daily at home with self-test Albustix® paper. Routine urinalysis and visits for side effects monitoring were scheduled once per month for six months and then every three months thereafter.

HRQOL was evaluated before and six months after treatment with RTX using the Chinese version of the parent-proxy report format of the Pediatric Quality of Life Inventory (PedsQL™) 4.0 Generic Core Scales.[6] The 23-item instrument for children aged 5 to 18 years consists of measurements based on physical (8 items), emotional (5 items), social (5 items), and school (5 items) functioning. School functioning was simplified to three items to facilitate use for children aged 2 to 4 years. Responses were based on a 5-point Likert scale with "0" denoting "never a problem" and "5" denoting "almost always a problem".[6,7] All responses were reversely transformed using a 0 to 100 scale with higher scores representing better HRQOL.

Trained nurses and doctors measured height and weight. Bone mineral density Z-scores (97% of peers) (BMZs) were measured using an ultrasonic bone densitometer (CM-200; Furuno Electric Co., Ltd., Hyogo, Japan). Body mass index (BMI) was also calculated as weight (kg) / height (m)^2. The

WHO AnthroPlus software was used to calculate height for age Z-score (HAZ), weight for age Z-score (WAZ), and BMI for age Z-score (BAZ).[15,16]

The primary study endpoint was testing negative for proteinuria for at least three consecutive days, a 24-h urine protein level of < 150 mg/kg, and normal renal function and blood pressure for complete response.[3] The secondary endpoint was relapse of proteinuria (positive urinary protein in routine urinalysis for ≥ 3 consecutive days) in those who achieved remission after treatment and safety of the drug based on side effects. Leukopenia, serum sickness, leukoencephalopathy, and related infections were the side effects monitored in this study. The tertiary endpoint was HRQOL at 6 months after therapy with RTX.

Results have been expressed as mean ± standard deviation for quantitative variables. Pearson's test was used to assess the correlation between HRQOL before treatment with RTX and the period between NS diagnosis and RTX administration. Paired *t*-test was used to compare quantitative variables at different time points. Statistical analyses were performed using IBM SPSS. *P* values < .05 were considered statistically significant.

RESULTS

Twenty children with SDFRNS were recruited for the study; however, eight SDNS patients and eight FRNS patients continued the study. Three FRNS patients discontinued all treatments for 2 months to 6 years; however, they had suffered relapse in the recent 1 to 2 years. All 16 patients were receiving IS agents such as CYC, CyA, Tac, and MMF with obvious side effects. The patients received their first RTX treatment after having NS for 3.34 ± 2.12 (range: 1 to 7) years. The average age of the participants was 7.25 ± 3.09 (range: 3 to 15) years. The male-to-female ratio was 13:3. Thirteen patients had minimal change disease. The parents of three patients refused renal biopsy.

Only one patient (6.2%) tested negative for proteinuria. Edema (n = 8, 50%), hypoproteinemia (n = 10, 62.5%), and hyperlipidemia (n = 8, 50%) were observed in some patients. Two patients (12.5%) produced little urine.

All patients (100%) showed complete response. Depletion of peripheral $CD19^+$ B-cells was observed in all patients within 2 weeks; however, B-cell count increased at an average of 4.42 months after treatment with RTX. Significant decreases in 24-h urine protein levels and total cholesterol were observed 6 months after treatment with RTX ($P < .0001$, $P < .05$). Additionally, serum albumin level significantly increased, whereas urinary protein level decreased ($P < .05$). Serum creatinine, blood urea nitrogen, and neutrophil percentage were always within normal levels in all patients and did not change significantly 6 months after the RTX treatment (Table 1).

During the 6 months before treatment with RTX, patients experienced 1 to 4 (2.13 ± 0.96) relapses; however, these reduced significantly during the 6 months after treatment (0.38 ± 0.62, $t = 5.916$,

HRQOL Scores and Laboratory Indexes for Patients with SDFRNS (n = 16) Before and 6 Months After Treatment with RTX

	Before treatment (mean ± SD)	Six Months After Treatment (mean ± SD)	*t*	*P*
Total Health Score	74.58 ± 18.62	81.63 ± 16.42	6.51	< .0001
Physical Functioning Score	69.06 ± 15.58	76.18 ± 14.09	4.96	< .0001
Emotional Functioning Score	71.87 ± 15.26	80.94 ± 14.59	5.62	< .0001
Social Functioning Score	87.81 ± 16.05	89.69 ± 14.99	1.19	> .05
School Functioning Score	80.63 ± 21.95	90.63 ± 24.03	3.87	< .001
WAZ Score	1.98 ± 0.53	1.16 ± 0.51	2.98	< .05
HAZ Score	0.30 ± 0.15	0.52 ± 0.24	0.88	> .05
BAZ Score	1.27 ± 0.58	1.12 ± 0.52	0.84	> .05
BMZ Score (97% peers)	-0.61 ± 0.15	-0.28 ± 0.15	5.49	< .05
Urine Protein 24 h, mg/kg	36.75 ± 20.96	4.07 ± 2.89	5.94	< .0001
Serum Albumin, g/L	33.24 ± 7.87	39.31 ± 8.61	3.58	< .05
Serum Creatinine, μmol/L	41.43 ± 10.54	40.31 ± 14.32	0.43	> .05
Blood Urea Nitrogen, mmol/L	3.84 ± 1.14	4.10 ± 1.66	0.41	> .05
Total Cholesterol, mmol/L	4.96 ± 1.24	3.85 ± 0.82	3.28	< .05
Neutrophils (%)	44.13 ± 15.09	47.89 ± 12.90	1.61	> .05

$P < .0001$; Figure 1). Over a follow-up period of 1 to 3.25 years (16.31 ± 7.09 months), only 3 SDNS patients and 3 FRNS patients experienced 1 to 2 relapses. The first relapse-free period was 79.00 ± 77.64 days. Relapse of NS occurred at 1 month in 3 patients, and at 3, 4, 5, 7, and 13 months in 1 patient each.

Furthermore, at 6 months after treatment with RTX, PSL was discontinued in 4 SDNS patients (25%) and 3 FRNS patients (18.75%). PSL dosage was reduced by more than 50% in 9 patients and by less than 50% in 7 patients. The rate of PSL dosage reduction was 81.3%. One SDNS patient and one FRNS patient were treated with a single daily dose of PSL (2 mg/kg; maximum, 60 mg/d) for relapse; however, they needed higher dosages at 6 months after the RTX therapy compared to 6 months before the treatment. Nevertheless, the average PSL dosage at 6 months after treatment with RTX was significantly lower than that at 6 months before treatment with RTX (0.58 mg/kg vs. 0.15 mg/kg, $t = 3.075$, $P < .05$; Figure 2). Additionally, 1 SDNS patient continued to receive a reduced dosage of FK506, whereas 2 SDNS patients and 4 FRNS patients discontinued treatment with IS drugs 6 months after the RTX therapy ($P < .001$). At the end of the observational period, 3 SDNS patients and 3 FRNS patients had discontinued all

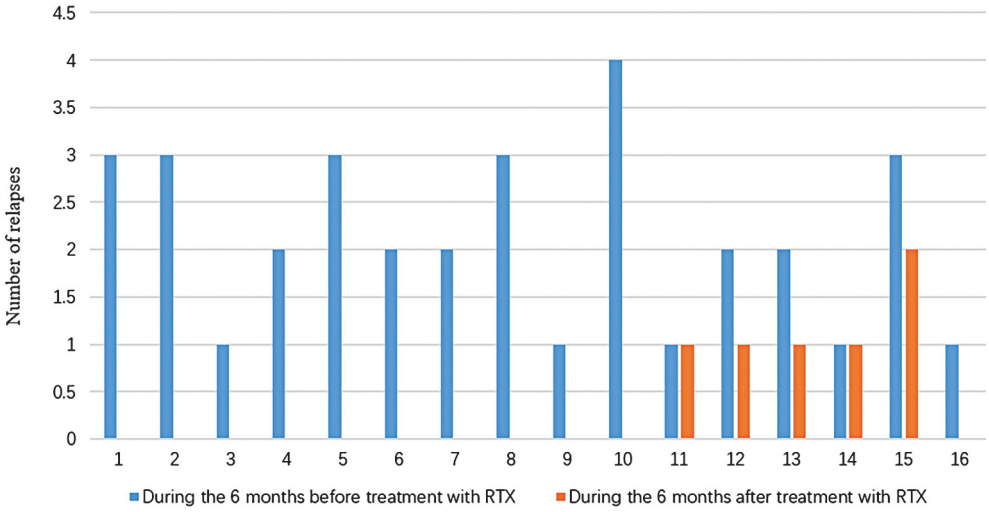

Figure 1. Relapse Frequency During the 6 Months Before and 6 Months After Treatment with RTX in 16 Children with SDFRNS

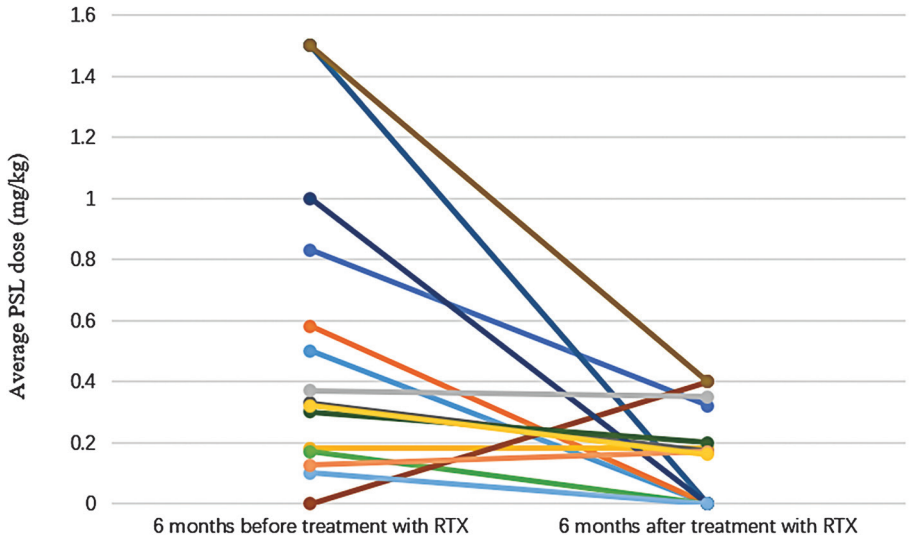

Figure 2. Average PSL Doses for 16 Children with SDFRNS at 6 Months Before and 6 Months After Treatment with RTX

treatments. However, 1 FRNS patient continued treatment with only MMF, 2 SDNS patients and 3 FRNS patients continued with single-dose PSL at a reduced dosage, whereas 2 SDNS patients and 1 FRNS patient continued treatment with PSL and MMF with relapse.

The side effects observed were skin rash (1 child), hypotension (1 child), and fever (1 child).

Patients completed the PedsQL™ questionnaire based on the following age groups: 2 to 4 years (n = 1), 5 to 7 years (n = 5), 8 to 12 years (n = 7), and 13 to 18 years (n = 3). The duration between NS diagnosis and RTX administration was negatively correlated with total health score before treatment with RTX ($P > .05$).

Total health, physical functioning, emotional functioning, and school functioning scores were significantly higher at 6 months after the RTX treatment than before the treatment (81.63 vs. 74.58, $P < .0001$; 76.18 vs. 69.06, $P < .0001$; 80.94 vs. 71.87, $P < .0001$; 90.63 vs. 80.63, $P < .001$). Social functioning scores were similar before and after the RTX therapy (89.69 vs. 87.81, $P > .05$). Furthermore, BMZ was significantly better 6 months after the RTX therapy than before the treatment (-0.61 vs. -0.28, $P < .05$), whereas WAZ was significantly lower 6 months after the treatment (1.98 vs. 1.16, $P < .05$) (Table 1).

DISCUSSION

We report a case series of 16 children with SDFRNS who had complicated clinical courses (i.e., SDFRNS was difficult to control despite treatment with PSL and IS agents) and were each administered a single dose of RTX.[2] The total response rate was 100%. Our data confirmed that RTX alleviated proteinuria in the patients.[1,2,11,12] Furthermore, relapse rate reduced approximately fivefold during the 6 months after treatment with RTX, although the doses of PSL and IS were tapered off. Nevertheless, over 1 to 3.25 years of follow-up, only 3 SDNS patients and 3 FRNS patients experienced 1 to 2 relapses. The mean relapse-free period was 79.0 ± 77.6 days. Childhood NS can be managed with one or two doses of RTX during the remission period at 3.05 to 9.06 months,[17] which is consistent with our findings. Similarly, some recently published studies (RCTs) have shown favorable outcomes with the use of RTX in both pediatric and adult patients with SDFRNS.[2,11,12,17]

Side effects of RTX in this study were skin rash, hypotension, and fever. In a previous study in Korea, 40 children with calcineurin inhibitor (CNI)-dependent SDNS were administered a single dose of RTX at 375 mg/m^2 (a second dose was administered if CD19$^+$ B-cell depletion was not achieved with the first dose). The results were then compared to those obtained for controls with SDNS who were not treated with RTX.[18] The findings showed remission rates of 74 and 31% in the RTX-treated and control groups ($P < .05$), respectively, with a longer duration of remission (9 months vs. 2.9 months; $P < .05$) in the RTX-treated group. Additionally, some participants treated with RTX experienced infusion reactions such as chest discomfort, fever, vomiting, and skin rash.[18] In a previous study, these reactions disappeared rapidly after timely treatment, as observed in the present study, without life-threatening reactions in the cohorts.[12,18,19] In another study, 10 children with steroid and CYC dependence treated with 4 doses of RTX showed complete response to the treatment but experienced adverse effects such as leukopenia, alopecia, and eosinophilia.[19] However, the only side effect observed in a previous study was allergic reaction to RTX.[11]

The exact mechanism underlying the effects of RTX in SDFRNS is unclear.[1-3] It was initially hypothesized that NS is primarily a disorder of T-cell function. B-cells induce and maintain T-cell activation, mediate antibody-independent autoimmune damage, express co-stimulatory molecules, and produce cytokines. Furthermore, RTX-induced B-cell depletion caused by apoptosis, antibody-dependent cellular cytotoxicity, or phagocytosis is associated with reduced numbers of Th17 and Th2 lymphocytes and increase in the number of regulatory T cells.[20] RTX may have a direct and non-immunological effect on podocytes by stabilizing actin remodeling and binding to CD20 and sphingomyelin phosphodiesterase acid-like 3B.[2] Recovery of B-cells and memory B-cells may predict the occurrence of a relapse.[20] T-cells and blood gamma globulin were not assessed in the present study; therefore, the precise interactions between B-cells and T-cells after treatment with RTX must be investigated.[2,20]

MMF selectively blocks de novo purine synthesis, which is a crucial for the function of B-cells and T-cells. Maintenance therapy with MMF,

corticosteroids, or CNIs after treatment with RTX at a low (375 mg/m^2), medium (750 mg/m^2), or high (1125 to 1500 mg/m^2) dose results in similar relapse-free periods for SDFRNS;[21] however, without maintenance therapy, low-dose RTX is associated with a shorter relapse-free period and a higher relapse risk. In the present study, we used MMF or a single daily dose of PSL for maintenance therapy. Six patients discontinued all treatments, whereas the other patients were always in remission and continued to receive MMF or a reduced dose of PSL. The efficacy and safety of MMF have been evaluated in children with complicated SDFRNS who are treated with RTX.[22] Therefore, RTX and maintenance therapy may lead to better outcomes in these patients.

Our results are encouraging because patients with long-standing NS suffer side effects and relapse and usually need high cumulative steroid doses and several medications.[1-3] In a previous study in children with SSNS, significantly higher scores were obtained for each domain in the PedsQL™ questionnaire with low-dose PSL than with high-dose PSL.[23] Children with NS have an impaired quality of life.[6] In the present study, physical functioning significantly improved 6 months after treatment with RTX. Importantly, the decreases in 24-h urine protein level and total cholesterol, increase in serum albumin level, disappearance of edema, and low frequency of relapses observed confirm that a single dose of RTX is effective for managing SDFRNS.[1,2]

Long-term use of medications, particularly steroids, for NS treatment is associated with side effects that affect normal growth and decrease bone mineralization. It was found in a previous study that the growth and spine bone mineral density of 30 children with NS were negatively associated with the cumulative dose of glucocorticosteroids they received. HAZ was also significantly lower in patients receiving > 0.2 mg·kg^{-1}·d^{-1} of glucocorticosteroids.[15] In another study, the median HAZ for pediatric SSNS patients was found to be -1.2 at treatment initiation with RTX and -0.6 at the last follow-up visit ($P < .05$). However, median BAZ decreased from 1.6 at the time of treatment initiation to 1.1 at the last follow-up visit. [16] In the present study, physical functioning improved 6 months after treatment with RTX with a mean PSL dose of 0.15 mg/kg. Additionally, WAZ significantly decreased, whereas BMZ increased. Therefore, we believe that RTX might improve disease outcome and growth in children with SDFRNS.[2,15,16]

In the current study, emotional and school functioning were significantly higher 6 months after the RTX therapy; however, social functioning was slightly impaired after the RTX treatment. In a previous study conducted in children with NS, the social and school functioning scores for patients with incident disease were better than those for patients with prevalent disease, which are inconsistent with our results.[24] Improved social functioning might be related to better research on NS, emphasis on psychosocial problems, and better communication. Nevertheless, 6 months after the RTX infusion, PSL was needed in lower doses or discontinued in SDNS patients, whereas FRNS patients had a decrease in relapse frequency. These resulted in higher total health scores, which indicated better HRQOL. In a previous study, global quality of life score was found to be 74.7 for 78 "difficult-to-treat" NS patients in stable remission, 72.6 for RTX-treated patients, and 76.2 for patients treated with oral drugs ($P > .05$). Moreover, results for the sub-dimension "school" during stable remission were significantly low in patients treated with RTX.[14] Therefore, a continuing longitudinal study is required to confirm these findings and further explore HRQOL in children with SDFRNS using different IS drugs.

CONCLUSION

A single dose of RTX was successful in achieving remission in all patients with minor side effects. PSL dose was maintained for SDNS patients. Relapse frequency decreased in the FRNS patients. Total health score was significantly higher for questionnaires completed by parents. Finally, physical, emotional, and school functioning scores at 6 months after treatment with RTX indicated better HRQOL.

DECLARATION OF INTEREST

The authors report no conflict of interest.

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REFERENCES

1. Iijima K, Sako M, Kamei K, Nozu K. Rituximab in steroid-sensitive nephrotic syndrome: lessons from clinical trials. Pediatr Nephrol. 2018;33(9):1449-55.
2. Kallash M, Smoyer WE, Mahan JD. Rituximab use in the management of childhood nephrotic syndrome. Front Pediatr. 2019;7:178.
3. KDIGO Clinical Practice Guideline for Glomerulonephritis Work Group. Chapter 3: Steroid-sensitive nephrotic syndrome in children. Kidney Int Suppl. 2012;2(2):163-71.
4. Khullar S, Banh T, Vasilevska-Ristovska J, et al. Impact of steroids and steroid-sparing agents on quality of life in children with nephrotic syndrome. Pediatr Nephrol. 2020 Jul 15.
5. Agrawal S, Krishnamurthy S, Naik BN. Assessment of quality of life in children with nephrotic syndrome at a teaching hospital in South India. Saudi J Kidney Dis Transpl. 2017;28(3):593-8.
6. Eid R, Fathy AA, Hamdy N. Health-related quality of life in Egyptian children with nephrotic syndrome. Qual Life Res. 2020;29(8):2185-96.
7. Mbanefo NR, Odetunde OI, Okafor HU, et al. The clinical parameters affecting the health-related quality of life of children with nephrotic syndrome. Archives of Nephrology. 2018;1(1):11-8.
8. Bakkum L, Willemen AM, Zoetebier L, Bouts AH. A longitudinal study on the effects of psychological stress on proteinuria in childhood steroid-sensitive nephrotic syndrome. J Psychosom Res. 2019;121:8-13.
9. Ahmed HM. Tacrolimus can induce remission in cyclosporine and mycophenolate mofetil resistant pediatric onset nephrotic syndrome. Iran J Kidney Dis. 2019;13(5):322-7.
10. Arslansoyu Camlar S, Soylu A, Kavukçu S. Cyclosporine in pediatric nephrology. Iran J Kidney Dis. 2018;12(6):319-30.
11. Webb H, Jaureguiberry G, Dufek S, Tullus K, Bockenhauer D. Cyclophosphamide and rituximab in frequently relapsing/steroid-dependent nephrotic syndrome. Pediatr Nephrol. 2016;31(4):589-94.
12. Basu B, Sander A, Roy B, et al. Efficacy of rituximab vs tacrolimus in pediatric corticosteroid-dependent nephrotic syndrome: a randomized clinical trial. JAMA Pediatr. 2018;172(8):757-64.
13. Querfeld U, Weber LT. Mycophenolate mofetil for sustained remission in nephrotic syndrome. Pediatr Nephrol. 2018;33(12):2253-65.
14. Roussel A, Delbet JD, Micheland L, Deschênes G, Decramer S, Ulinski T. Quality of life in children with severe forms of idiopathic nephrotic syndrome in stable remission-A cross-sectional study. Acta Paediatr. 2019;108(12):2267-73.
15. Ribeiro D, Zawadynski S, Pittet LF, Chevalley T, Girardin E, Parvex P. Effect of glucocorticoids on growth and bone mineral density in children with nephrotic syndrome. Eur J Pediatr. 2015;174(7):911-7.
16. Topaloğlu R, Gülhan B, Çelegen K, et al. Rituximab for children with difficult-to-treat nephrotic syndrome: Its effects on disease progression and growth. Front Pediatr. 2019;7:313.
17. Maratea D, Bettio M, Corti MG, Montini G, Venturini F. The efficacy and safety of rituximab in treating childhood nephrotic syndrome: an Italian perspective. Ital J Pediatr. 2016;42(1):63.
18. Ahn YH, Kim SH, Han KH, et al. Efficacy and safety of rituximab in childhood-onset, difficult-to-treat nephrotic syndrome: A multicenter open-label trial in Korea. Medicine (Baltimore). 2018;97(46):e13157.
19. Hoseini R, Sabzian K, Otukesh H, et al. Efficacy and safety of rituximab in children with steroid- and cyclosporine-resistant and steroid- and cyclosporine-dependent nephrotic syndrome. Iran J Kidney Dis. 2018;12(1):27-32.
20. Bhatia D, Sinha A, Hari P, et al. Rituximab modulates T- and B-lymphocyte subsets and urinary CD80 excretion in patients with steroid-dependent nephrotic syndrome. Pediatr Res. 2018;84(4):520-6.
21. Chan EY, Webb H, Yu E, et al. Both the rituximab dose and maintenance immunosuppression in steroid-dependent/frequently-relapsing nephrotic syndrome have important effects on outcomes. Kidney Int. 2020;97(2):393-401.
22. Horinouchi T, Sako M, Nakanishi K, et al. Study protocol: mycophenolate mofetil as maintenance therapy after rituximab treatment for childhood-onset, complicated, frequently-relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicenter double-blind, randomized, placebo-controlled trial (JSKDC07). BMC Nephrol. 2018;19(1):302.
23. Raja K, Parikh A, Webb H, Hothi D. Use of a low-dose prednisolone regimen to treat a relapse of steroid-sensitive nephrotic syndrome in children. Pediatr Nephrol. 2017;32(1):99-105.
24. Selewski DT, Troost JP, Massengill SF, et al. The impact of disease duration on quality of life in children with nephrotic syndrome: a midwest pediatric nephrology consortium study. Pediatr Nephrol. 2015;30(9):1467-76.

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