Original Article

http://journals.sbmu.ac.ir/jpn
https://doi.org/10.22037/jpn.v9i2.33354

Safety and Efficacy of Rituximab in Children with Steroid-Dependent or Resistant Nephrotic Syndrome

Golshid Nourihosseini[1], Mehrdad Gazanchian[1], Yalda Ravanshad[2], Sahar Ravanshad[3], Anoush Azarfar[1*], Mohammad Esmaeeli[4], Gholamreza Sarvari[4]

[1]Kidney Transplantation Complications Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.
[2]Department of Community Medicine, Mashhad Branch, Islamic Azad University, Mashhad, Iran.
[3]Department of internal medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[4]Department of Pediatric Nephrology, Mashhad University of Medical Sciences, Mashhad, Iran.

[*]**Corresponding Author**
Dr. Anoush Azarfar,
Email: AzarfarA@mums.ac.ir

Received: December, 2020
Revised: January, 2021
Accepted: February, 2021

Abstract

Background and Aim: Rituximab is a novel therapy that can help patients with steroid-dependent or resistant nephrotic syndrome. The aim of this study was to evaluate the efficacy of rituximab in children with corticosteroid-dependent and resistant nephrotic syndrome and to determine the factors associated with its efficacy.

Methods: In this study, 40 children with corticosteroid-dependent or resistant nephrotic syndrome who were treated with rituximab in Dr. Sheikh Hospital, Mashhad, between 2014 and 2018 were enrolled. Patients with a history of hematuria, severe urinary tract infection, or secondary nephrotic syndrome were excluded.

Results: The mean age of patients was 11.9 ± 5.04 years, and 55% were female. The most common underlying pathology of nephrotic syndrome was focal segmental glomerulonephritis (FSGS) (42.5%) followed by membranoproliferative glomerulonephritis (MPGN) and minimal change disease (MCD). Most of the participants (62.5%) were steroid-dependent and the rest (27.5%) were steroid resistant. Only 10% of the patients showed complications following rituximab administration and 57.5% went into complete remission. A negative family history and steroid-dependent nephrotic syndrome were significantly associated with a better treatment response. Moreover, patients with steroid-resistant nephrotic syndrome were more likely to have a positive family history, while factors associated with steroid response included underlying pathology, gender, and family history.

Conclusion: Rituximab can cause remission in more than half of the patients with steroid-resistant or dependent nephrotic syndrome. Moreover, the only factors that reduce response to rituximab are a history of corticosteroid resistance and a positive family history of nephrotic syndrome.

Keywords: Nephrotic Syndrome; Rituximab; Corticosteroid Resistant; FSGS; MPGN.

Conflict of interest: The authors declare no conflict of interest.
Please cite this article as: Nourihosseini G, Gazanchian M, Ravanshad Y, Ravanshad S, Azarfar A, Esmaeeli M, Sarvari G. Safety and Efficacy of Rituximab in Children with Steroid-Dependent or Resistant Nephrotic Syndrome. J Ped Nephrol 2021;9(2):1-7. https://doi.org/10.22037/jpn.v9i2.33354

Introduction

Idiopathic nephrotic syndrome is the most prevalent chronic glomerular disease among children affecting 2 in 100,000 children in western countries annually (1). The most common underlying causes of nephrotic syndrome in children include minimal change disease (MCD), membranoproliferative glomerulonephritis (MPGN), focal segmental glomerulonephritis (FSGS), and systemic lupus erythematous (SLE). About 80% of the patients with nephrotic syndrome respond well to steroids (Steroid Sensitive Nephrotic Syndrome (SSNS)). However, another form of nephrotic syndrome is steroid-dependent nephrotic syndrome (SDNS) defined as two consecutive relapses during tapering of steroids or within 14 days after the end of steroid

treatment. Nonetheless, 10-20 % of the patients with nephrotic syndrome have steroid-resistant nephrotic syndrome (SRNS) characterized by persistent proteinuria after a period of 4 to 8 weeks of treatment with oral prednisone (2).

The standard treatment for patients with SRNS and SDNS is immunosuppressive agents such as cyclosporine and tacrolimus (3). These treatments are effective in the majority of the patients. However, some patients go through a complicated clinical stage. About 10 to 20% of the children who have SDNS and 30% of the children with SRNS that receive cyclosporine experience several relapses (4-6). In spite of lack of efficiency in some patients, cyclosporine may cause side effects, especially chronic nephrotoxicity (7), which suggests that cyclosporine should not be used for long durations. However, discontinuation of cyclosporine generally leads to recurrence requiring long-term steroid treatment, which in turn causes additional serious adverse effects.

Rituximab, a chimeric monoclonal antibody against CD20 first designed for treatment of patients with Non-Hodgkin B cell lymphoma, is now used for the treatment of various diseases such as Wegner's granulomatosis, rheumatoid arthritis, and microscopic polyangiitis. Interestingly, many studies since ten years ago have shown the efficacy of rituximab for treatment of SDNS and SRNS (8, 9).

However, this drug does not cure the disease, because a study found that all of the patients that used rituximab as a treatment experienced relapse 19 months after the end of treatment (9).

Re-administration of rituximab immediately after relapse or within 3 months may be effective (10, 11). A systematic review study by Azarfar et al concluded that rituximab could be effective in treating refractory nephrotic syndrome and reduce the need for immunosuppressive drugs and corticosteroids (12). Nonetheless, further studies are warranted to prove the efficacy of rituximab.

To the best of our knowledge, only one study evaluated the efficacy and side effects of rituximab in children with SRNS and SDNS in Iran (13). Therefore, this study was conducted to assess the safety and efficacy of this drug in patients with nephrotic syndrome admitted to Dr. Sheikh Hospital, Mashhad, Iran during 2014-2018 and to determine the factors associated with its efficacy.

Methods

This cross-sectional study was carried out on children with nephrotic syndrome that received rituximab treatment in Dr. Sheikh Hospital, Mashhad, Iran from April 2014 to March 2018. The study population included children aged 2 to 19 years with a diagnosis of steroid-resistant or dependent nephrotic syndrome that underwent treatment with four weekly standard doses of rituximab (375mg/m^2). The patients with a history of severe hematuria, urinary tract infection, or secondary nephrotic syndrome, except for SLE patients with pure kidney involvement and no systemic symptoms, were excluded from the study.

Demographic data including age, sex, and age at disease onset as well as clinical data including a family history of nephrotic syndrome, disease pathology, steroid resistance or dependence, response to rituximab, and rituximab-induced side effects were extracted from the patients' medical records.

Remission was defined as the absence of proteinuria in patients for 3 consecutive days. Relative remission was defined as a decrease in protein excretion and edema in the patients despite proteinuria. Corticosteroid resistance was defined as no remission or relative remission within 8 weeks of an adequate dose of systemic corticosteroid therapy. Corticosteroid dependence was defined as reversible proteinuria and edema immediately after dose reduction or systemic corticosteroid discontinuation. A positive family history was defined as the presence of nephrotic syndrome in first-degree relatives.

Statistical analysis:

The data were analyzed using the SPSS software version 23. To investigate the relationship between different variables between patients, the normal distribution of the data was analyzed using the Kolmogorov-Smirnoff test. Then, based on the distribution, chi-square or Fisher's exact test was used for qualitative data and Independent T-test or Mann-Whitney U test was used for quantitative data. In all analyses, p-values <0.05 were considered significant.

The Bonferroni method was adopted for post-hoc analysis of the Fisher's exact test. In other words, after the results of the Fisher's exact test turned out to be statistically significant, the variables were compared in pairs. In order to prevent analysis bias, the p-value of 0.05 was divided by the number of

comparisons and the resulting value was considered as the threshold for statistical significance.

Ethical considerations:

Written informed consent was obtained from all patients participating in this study. The patients were free to leave the study at any time upon their request. This study was approved by the Ethics Committee of Mashhad University of Medical Sciences. The data were obtained from thesis number 9238P.

Results

A total of 40 patients were included in our study as shown in Table 1. The mean age of the participants and the mean age at disease onset was 11.9 ± 5.04 and 7 ± 4.27 years, respectively. Most of the patients (57.5%) went into complete remission and 20% went into relative remission following completion of rituximab treatment. Moreover, only 4 patients showed significant side effects to rituximab. One patient had an anaphylactic shock, two patients experienced oral ulcers and alopecia and one patient developed progressive encephalopathy.

The association between rituximab response and different variables was analyzed, and the results showed that only corticosteroid response and family history were significantly associated with rituximab response (P= 0.001 and 0.026, respectively). Post hoc analysis showed that remission with rituximab was significantly associated with SDNS, while most of the patients with SRNS showed no response to rituximab (data not shown).

Factors associated with corticosteroid response were sought and our results showed that gender, pathology and family history were significantly related to the corticosteroid response (Table 2). Our post hoc analysis revealed that patients with the underlying FSGS pathology were more likely to have SRNS (data not shown). Finally, factors associated with family history were sought and the results showed that family history was only significantly related to the corticosteroid response, and patients with a positive family history of the nephrotic syndrome were more likely to have SRNS (Table 3).

Discussion

This study was conducted on 40 patients with nephrotic syndrome who received rituximab between 2014 and 2019 in Dr. Sheikh Hospital, Mashhad, Iran. FSGS was the most common underlying pathology of nephrotic syndrome. Most of the participants (62.5%) had SDNS and the rest (27.5%) had SRNS. Only 10% of the patients showed complications following rituximab administration and more than half of the subjects went into complete remission following rituximab treatment. The only factors associated with a better response to rituximab were a negative family history and steroid-dependent nephrotic syndrome. Moreover, the results showed that patients with SRNS were more likely to have a positive family history, while factors associated with steroid response included underlying pathology, gender, and family history.

The patients with FSGS were more likely to have SRNS, indicating a poorer prognosis for these patients compared to others. Although the percentage of people who did not respond to treatment was higher in patients with FSGS, this difference was not statistically significant, indicating that the type of pathology causing nephrotic syndrome is not an effective factor in response to rituximab treatment.

A guideline released in 2012 by KDIGO (Kidney Disease: Improving Global Outcomes) recommended the use of rituximab in children with nephrotic syndrome who failed to respond to a combination of prednisone and corticosteroid-reducing agents such as cyclosporine, cyclophosphamide, mycophenolate or tacrolimus (14).

It seems that rituximab, a monoclonal anti-CD20 antibody that acts against B-lymphocytes, is effective in prolonging the duration of remission in patients with steroid-dependent nephrotic syndrome (SDNS) (9, 10, 15-17). The results of observational studies also showed that rituximab administration could reduce the dose of one or more immunosuppressive drugs in these patients (18, 19). However, a striking proportion of patients experience relapse after administration of rituximab due to B-lymphocyte remodeling (20).

Moreover, this drug should be limited to children who have recurrent relapses and those who have experienced serious side effects of immunosuppressant medications, because the long-term effects and safety of rituximab are unknown in children (21-23).

Table-1. Association of different factors with Rituximab Response

		Total	Rituximab response			P-value
			Remission (n=23)	Relative remission (n=8)	No response (n=9)	
Mean Age (years)		11.9 ± 5.04	13.7 ± 4.1	8.6 ± 4.2	10.2 ± 6.3	0.334
Mean Age at disease onset (years)		7 ± 4.27	8.1 ± 4.5	5.6 ± 3.2	5.3 ± 4.1	0.606
	Male	18 (45%)	11 (47.8%)	2 (25%)	5 (55.6%)	
	Female	22 (55%)	12 (52.2%)	6 (75%)	4 (44.4%)	
	FSGS	17 (42.5%)	6 (26.1%)	4 (50%)	7 (77.8%)	
	MCD	5 (12.5%)	4 (17.4%)	1 (12.5%)	0 (0%)	
	MPGN	12 (30%)	10 (43.5%)	2 (25%)	0 (0%)	
	Lupus	6 (15%)	3 (13%)	1 (12.5%)	2 (22.2%)	
	Steroid dependent	25 (62.5%)	19 (82.6%)	5 (62.5%)	1 (11.1%)	
	Steroid resistant	15 (37.5%)	4 (17.4%)	3 (37.5%)	8 (88.9%)	
	Positive	4 (10%)	0 (0%)	2 (25%)	2 (22.2%)	
	Negative	36 (90%)	23 (100%)	6 (75%)	7 (77.8%)	

Table-2. Association of different factors with Corticosteroid Response

		Corticosteroid response		P-value
		Steroid Dependent (n=25)	Steroid Resistant (n=15)	
Mean Age (years)		12.7 ± 4.5	10.6 ± 5.7	0.192
Mean Age at disease onset (years)		7.6 ± 4.2	6.1 ± 4.4	0.267
	Male	8 (32%)	10 (66.7%)	
	Female	17 (68%)	5 (33.3%)	
	FSGS	4 (16%)	13 (86.7%)	
	MCD	5 (20%)	0 (0%)	
	MPGN	11 (44%)	1 (6.7%)	
	Lupus	5 (20%)	1 (6.7%)	
	Positive	0 (0%)	4 (26.7%)	
	Negative	25 (100%)	11 (73.3%)	

In the present study, patients who did not respond to routine treatments were treated with rituximab and more than half of them went into complete remission.

However, unfortunately, the patients' follow-up data were not available to determine the recurrence rate.

There is limited information on the efficacy of rituximab in nephrotic syndrome due to the small number of patients. Azarfar et al. investigated the safety and efficacy of rituximab in children with severe nephrotic syndrome in a systematic review of 17 studies (12). Most of the studies demonstrated that rituximab was effective in treating nephrotic syndrome. However, only two of the 17 studies were clinical trials, and the rest were retrospective studies without a control group, similar to present study. In a clinical trial, 48 children with recurrent or steroid-dependent nephrotic syndrome were randomly assigned to receive weekly doses of rituximab (375 mg/m^2) or placebo for four weeks (9).

Table-3. Association of different factors with Family history of Nephrotic Syndrome

		Family history		P-value
		Positive (n=4)	Negative (n=36)	
Mean Age (years)		7.7 ± 4.3	12.4 ± 4.9	0.831
Mean Age at disease onset (years)		4.5 ± 3.3	7.3 ± 4.3	0.598
	Male	2 (50%)	16 (44.4%)	
	Female	2 (50%)	20 (55.6%)	
	FSGS	3 (75%)	14 (38.9%)	
	MCD	0 (0%)	5 (13.9%)	
	MPGN	0 (0%)	12 (33.3%)	
	Lupus	1 (25%)	5 (13.9%)	
	Steroid dependent	4 (100%)	11 (30.6%)	
	Steroid resistant	0 (0%)	25 (69.4%)	

At one-year follow-up, the recurrence-free duration was longer in the rituximab group compared to the control group (267 vs. 101 days).

Moreover, the rate of recurrence (1.54 versus 4.17 recurrences per year) and the daily dose of prednisolone were lower in the rituximab group (4.4 versus 21 mg/m^2). However, within one year, 17 of the 24 patients receiving rituximab and 23 of the 24 patients receiving placebo experienced at least one recurrence (71 vs. 96%) and all of the patients had a recurrence by the end of 19 months. Another clinical trial in children with steroid-dependent nephrotic syndrome compared the efficacy of prednisone alone and prednisolone combined with a single dose of rituximab (24). Prednisone was gradually discontinued in both groups after 15 months of treatment. Proteinuria was 42% lower in the combination therapy group at the three-month follow-up. In addition, all but one patient in the prednisone alone group experienced recurrence within only six months, while the median time to relapse was 18 months in the combination group. The results of these studies indicate that the disease will eventually relapse in most patients after using rituximab; however, the use of rituximab may increase the duration of recurrence-free period in patients with recurrent relapses.

Kamei et al retrospectively examined the risk factors of relapse in steroid-dependent nephrotic syndrome patients who were treated with rituximab. The results showed that only a history of steroid resistance was a statistically major risk factor for relapse in these patients, and underlying pathology was not a risk factor for relapse (19). Similarly, Sinha et al. found that the remission period was significantly shorter in patients with steroid-resistant nephrotic syndrome compared to patients with steroid-dependent nephrotic syndrome (17). The results of these studies are consistent with our study, as we also demonstrated that response to rituximab was significantly associated with corticosteroid resistance or dependence. Furthermore, the present study found that response to rituximab was not significantly correlated with the underlying pathology of nephrotic syndrome, while patients with a positive family history for nephrotic syndrome were less likely to respond satisfactorily to rituximab.

In a similar study by Hosseini et al., the safety and efficacy of rituximab were investigated in 40 children with steroid-dependent or cyclosporine-dependent nephrotic syndrome in Ali Asghar Hospital, Tehran, Iran (13). The results of this study are in line with our study. The rate of complete remission was 60% in the above study and 57.5% in the present study. Moreover, 40% of the patients with steroid resistance and 85% of the patients with steroid dependence had complete remission in the above study whereas 17.4% of the patients with steroid resistant nephrotic syndrome and 82% of the patients with steroid dependent nephrotic syndrome had complete remission following rituximab administration in the present study. Similar to our analysis, this study also showed that response to rituximab was significantly higher in steroid-dependent patients compared to steroid-resistant subjects, and age, sex, and the underlying pathology of the disease were not significantly correlated with response to rituximab. Hosseini et al followed their patients for two years and reported that no

recurrence was observed during the first 6 months after rituximab treatment. However, 20% of the patients developed recurrence at 2 years eventually. The most important limitation of the present study was the absence of a control group. Moreover, due to the lack of appropriate data in patients' medical records, it was not possible to calculate the recurrence rate. Another limitation was lack of the laboratory data of the patients, including creatinine, urea, proteinuria, and CD20 levels, which was due to the timeframe in which patients were studied, lack of laboratory facilities in the first years of the study, and the failure to collect data. Another limitation of this study was its cross-sectional design, which does not allow establishing a causal relationship and only shows the presence or absence of association between different variables.

It is recommended that future studies evaluate the efficacy of rituximab using controlled clinical trials that offer more valid results. Moreover, long-term follow-up of patients is of great importance for investigating the relapse rate and long-term complications of rituximab.

Conclusion

The use of rituximab may result in remission in more than half of the patients with SDNS or SRNS in whom other treatments have failed. Short-term side effects of rituximab are rare but dangerous, so this agent should be used in patients who have not responded well to other treatments. The results of the present study demonstrated that the only factor affecting the patients' response to rituximab was steroid-resistant nephrotic syndrome and a positive family history of nephrotic syndrome. Interestingly, the underlying pathology of nephrotic syndrome was not significantly associated with response to rituximab; however, it should be noted that patients with FSGS are more likely to have steroid-resistant nephrotic syndrome.

Conflict of Interest

The author declares no conflicts of interest.

Financial Support

The author declares no financial support.

References

1. Niaudet P, Boyer O. Idiopathic nephrotic syndrome in children: clinical aspects. Pediatric nephrology 2009.
2. Gipson DS, Massengill SF, Yao L, Nagaraj S, Smoyer WE, Mahan JD, Wigfall D, Miles P, Powell L, Lin J-J. Management of childhood onset nephrotic syndrome. Pediatrics. 2009;124(2):747-57.
3. Hodson EM, Wong SC, Willis NS, Craig JC. Interventions for idiopathic steroid- resistant nephrotic syndrome in children. Cochrane database of systematic reviews. 2016(10).
4. Ishikura K, Ikeda M, Hattori S, Yoshikawa N, Sasaki S, Iijima K, Nakanishi K, Yata N, Honda M, Children JSgoRDi. Effective and safe treatment with cyclosporine in nephrotic children: a prospective, randomized multicenter trial. Kidney international. 2008;73(10):1167-73.
5. Ishikura K, Yoshikawa N, Hattori S, Sasaki S, Iijima K, Nakanishi K, Matsuyama T, Yata N, Ando T, Honda M. Treatment with microemulsified cyclosporine in children with frequently relapsing nephrotic syndrome. Nephrology Dialysis Transplantation. 2010;25(12):3956-62.
6. Hamasaki Y, Yoshikawa N, Hattori S, Sasaki S, Iijima K, Nakanishi K, Matsuyama T, Ishikura K, Yata N, Kaneko T. Cyclosporine and steroid therapy in children with steroid-resistant nephrotic syndrome. Pediatric nephrology. 2009;24(11):2177-85.
7. Iijima K, Hamahira K, Tanaka R, Kobayashi A, Nozu K, Nakamura H, Yoshikawa N. Risk factors for cyclosporine-induced tubulointerstitial lesions in children with minimal change nephrotic syndrome. Kidney international. 2002;61(5):1801-5.
8. Kamei K, Okada M, Sato M, Fujimaru T, Ogura M, Nakayama M, Kaito H, Iijima K, Ito S. Rituximab treatment combined with methylprednisolone pulse therapy and immunosuppressants for childhood steroid-resistant nephrotic syndrome. Pediatric nephrology. 2014;29(7):1181-7.
9. Iijima K, Sako M, Nozu K, Mori R, Tuchida N, Kamei K, Miura K, Aya K, Nakanishi K, Ohtomo Y. Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial. The Lancet. 2014;384(9950):1273-81.
10. Sellier-Leclerc A-L, Macher M-A, Loirat C, Guérin V, Watier H, Peuchmaur M, Baudouin V, Deschênes G. Rituximab efficiency in children with steroid-dependent nephrotic syndrome. Pediatric Nephrology. 2010;25(6):1109-15.
11. Kimata T, Hasui M, Kino J, Kitao T, Yamanouchi S, Tsuji S, Kaneko K. Novel use of rituximab for steroid-dependent nephrotic syndrome in children. American journal of nephrology. 2013;38(6):483-8.

12. Azarfar A, Ravanshad Y, Mehrad-Majd H, Aval SB, Nastarani S, Emadzadeh M, Khazaei MR, Fazel M, Azimi B. Efficacy and Safety of rituximab in children with difficult-to-treat nephrotic syndrome; a systematic review. Journal of Renal Injury Prevention. 2018;7(4).
13. Hoseini R, Sabzian K, Otukesh H, Zafaranloo N, Panahi P, Rahimzadeh N, Nakhaie S, Sepehi MA. Efficacy and safety of rituximab in children with steroid-and cyclosporine-resistant and steroid-and cyclosporine-dependent nephrotic syndrome. Iranian journal of kidney diseases. 2018;12(1):27.
14. Lombel RM, Gipson DS, Hodson EM. Treatment of steroid-sensitive nephrotic syndrome: new guidelines from KDIGO. Pediatric nephrology. 2013;28(3):415-26.
15. Fujinaga S, Hirano D, Nishizaki N, Kamei K, Ito S, Ohtomo Y, Shimizu T, Kaneko K. Single infusion of rituximab for persistent steroid-dependent minimal-change nephrotic syndrome after long-term cyclosporine. Pediatric Nephrology. 2010;25(3):539-44.
16. Guigonis V, Dallocchio A, Baudouin V, Dehennault M, Hachon-Le Camus C, Afanetti M, Groothoff J, Llanas B, Niaudet P, Nivet H. Rituximab treatment for severe steroid-or cyclosporine-dependent nephrotic syndrome: a multicentric series of 22 cases. Pediatric Nephrology. 2008;23(8):1269.
17. Sinha A, Bhatia D, Gulati A, Rawat M, Dinda AK, Hari P, Bagga A. Efficacy and safety of rituximab in children with difficult-to-treat nephrotic syndrome. Nephrology Dialysis Transplantation. 2014;30(1):96-106.
18. Ravani P, Magnasco A, Edefonti A, Murer L, Rossi R, Ghio L, Benetti E, Scozzola F, Pasini A, Dallera N. Short-term effects of rituximab in children with steroid-and calcineurin-dependent nephrotic syndrome: a randomized controlled trial. Clinical Journal of the American Society of Nephrology. 2011;6(6):1308-15.
19. Kamei K, Ogura M, Sato M, Sako M, Iijima K, Ito S. Risk factors for relapse and long-term outcome in steroid-dependent nephrotic syndrome treated with rituximab. Pediatric Nephrology. 2016;31(1):89-95.
20. Kamei K, Ito S, Nozu K, Fujinaga S, Nakayama M, Sako M, Saito M, Yoneko M, Iijima K. Single dose of rituximab for refractory steroid-dependent nephrotic syndrome in children. Pediatric nephrology. 2009;24(7):1321-8.
21. Boyer O, Niaudet P. Nephrotic syndrome: Rituximab in childhood steroid-dependent nephrotic syndrome. Nature Reviews Nephrology. 2013;9(10):562.
22. Haffner D, Fischer D-C. Nephrotic syndrome and rituximab: facts and perspectives. Pediatric Nephrology. 2009;24(8):1433-8.
23. Hodson EM, Craig JC. Rituximab for childhood-onset nephrotic syndrome. The Lancet. 2014;384(9950):1242-3.
24. Ravani P, Rossi R, Bonanni A, Quinn RR, Sica F, Bodria M, Pasini A, Montini G, Edefonti A, Belingheri M. Rituximab in children with steroid-dependent nephrotic syndrome: a multicenter, open-label, noninferiority, randomized controlled trial. Journal of the American Society of Nephrology. 2015;26(9):2259-66.