



# Rituximab experience in children with nephrotic syndrome: what have we observed differently

Nefrotik sendromlu çocuklarda rituximab deneyimi, farklı ne gözlemledik?

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## The known about this topic

Studies relating to rituximab treatment and outcomes in children with various nephrotic syndromes have recently increased. Some studies have shown that peripheral blood B cell depletion is strongly correlated with remission. Administration of rituximab is generally recommended in a protein-free period via steroids in children with frequent relapses and steroid-dependent nephrotic syndrome. There is no consensus regarding the optimal number of rituximab doses in the treatment of pediatric nephrotic syndrome.

## Contribution of the study

Rituximab appears to be an effective treatment for steroid-dependent nephrotic syndrome whereas this treatment confers benefit in approximately one-third of the patients with steroid resistant nephrotic syndrome. The present study showed that remission was not observed in some patients despite B cell depletion. Rituximab could be given in the nephrotic period in children who do not respond to other immunosuppressive therapies or experience adverse effects with steroid therapy. We think that four weekly doses of rituximab may increase the likelihood of response by compensating for the amount of drug lost in the urine in children with nephrotic proteinuria. However, our findings must be confirmed with dose-comparison studies conducted with larger populations and an evaluation of long-term adverse effects.

## Abstract

**Aim:** We aimed to evaluate the efficacy of rituximab therapy in children with nephrotic syndromes and to share our experiences.

**Material and Methods:** Twelve children with nephrotic syndrome (four with steroid-dependent, eight with steroid-resistant nephrotic syndrome) who were treated with rituximab were retrospectively evaluated in terms of clinical and laboratory data and CD19-20 levels. All patients received rituximab (375 mg/m<sup>2</sup>) once weekly for 4 weeks. A proteinuria-free period under steroid therapy was not sought prior to initiating rituximab therapy.

**Results:** The overall remission rates in patients with steroid-dependent and steroid-resistant nephrotic syndrome were 100% and 27%. Focal segmental glomerulosclerosis was diagnosed in six patients and the remission rate was 33% in this population. CD19 cell depletion was observed in 10 of the 12 children. Seven of the 10 patients with CD19 depletion achieved remission, whereas the other three had persistent nephrotic proteinuria despite CD19 depletion. Two patients without CD19 depletion never achieved remission. Relapse occurred in three of the seven patients associated with increased CD19.

## Öz

**Amaç:** Amacımız nefrotik sendromlu çocuklarda rituksimab tedavisinin etkinliğini değerlendirmek ve kendi deneyimlerimizi paylaşmaktır.

**Gereç ve Yöntemler:** Rituksimab tedavisi verilen 12 nefrotik sendromlu (dördü steroid bağımlı, sekizi steroid dirençli nefrotik sendrom) çocuğun klinik, laboratuvar sonuçları ve CD19-CD20 seviyeleri geriye dönük olarak değerlendirildi. Tüm hastalara dört hafta süre ile haftada bir rituksimab 375mg/m<sup>2</sup> tedavisi uygulandı. Hastalara rituksimab tedavisi vermek için steroid tedavisi ile proteinürisiz döneme girmeleri beklenmedi.

**Bulgular:** Remisyon oranları; steroid bağımlı ve steroid dirençli nefrotik sendromlu hastalarda sırası ile %100 ve %27 idi. Fokal segmental glomeruloskleroz tanılı 6 hastanın %33'ünde remisyon gözlemlendi. CD19 depleasyonu 12 hastanın 10'unda gözlemlendi. Bu 10 hastanın yedisinde parsiyel ya da komplet remisyon gözlenirken, üç hastada CD19 depleasyonu na rağmen nefrotik proteinüri sebat etti. CD 19 depleasyonu sağlanmayan iki hasta remisyona girmedi. İzlemde yedi hastanın üçünde görülen relaps CD19 artışı ile birlikte idi.

**Çıkarımlar:** Rituksimab tedavisinin, hastaların steroid ile proteinürisiz

Cont. ⇒

**Cite this article as:** Girişgen İ, Yüksel S, Pekal Y. Rituximab experience in children with nephrotic syndrome: what have we observed differently. Turk Pediatri Ars 2020; 55(1): 60–6.

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**Received/Geliş Tarihi:** 17.05.2019 **Accepted/Kabul Tarihi:** 28.11.2019

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DOI: 10.14744/TurkPediatriArs.2019.76148

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**Conclusion:** We observed that rituximab could be given without waiting for a proteinuria-free period under steroid therapy. Our result suggest that administering four weekly doses of rituximab increases the likelihood of remission, considering the amount of drug lost in the urine of children with nephrotic proteinuria. However, our findings must be confirmed with dose-comparison studies conducted with larger populations and an evaluation of long-term adverse effects. Some patients did not achieve remission despite B cell depletion, which suggests that B cell depletion is necessary but insufficient for remission in nephrotic syndromes.

**Keywords:** Children, nephrotic syndrome, rituximab

## Introduction

Nephrotic syndrome (NS) is a common glomerular disease in children. Idiopathic NS is defined by the four signs of proteinuria, hypoalbuminemia, hyperlipidemia, and edema (1). Approximately 80% of affected children have minimal change disease and most respond well to steroid therapy, which is termed steroid-sensitive nephrotic syndrome (SSNS) (2). About 40% of children with SSNS have frequent relapses (FRNS) or are steroid-dependent (SDNS) (3). Corticosteroid therapy is the primary treatment for childhood NS. However, patients with both SDNS and FRNS are at increased risk of excessive side effects of corticosteroids. Therefore, other immunosuppressive agents including alkylating agents, calcineurin inhibitors (CNIs), and mycophenolate mofetil (MMF) are used to induce remission in such children (4). In addition, 10–20% of patients with idiopathic NS have steroid-resistant nephrotic syndrome (SRNS). The most common lesion in SRNS is focal segmental glomerulosclerosis (FSGS). These patients are at significantly higher risk of complications as well as progression to chronic kidney disease or end-stage kidney disease (5). Calcineurin inhibitors are the main immunosuppressive agents used to treat SRNS. For children who do not respond to CNIs, additional alternative agents such as MMF are often used (6). However, management of SRNS remains a challenge in pediatric nephrology. The lack of optimal treatment strategy for SRNS has led researchers to seek new therapeutic options in the last decade.

Rituximab is a chimeric anti-CD20 monoclonal antibody that inhibits CD20-mediated B-cell proliferation and differentiation and has been increasingly used for the treatment of renal disorders, including NS, lupus nephritis, and vasculitis (6). Studies have demonstrated quite variable response rates to rituximab in children with FRNS, SDNS, and SRNS (6). Rituximab is recommended in the Kidney Disease: Improving Global Outcomes (KDIGO) guideline for children with SDNS and FRNS who have persistent frequent relapses despite optimal combinations of steroids associated with corticosteroid-sparing agents (4). The KDIGO guideline does not recommend

döneme girmelerini beklemeden verilebileceğini gözlemledik. Nefrotik proteinürlü çocukların idrarında kaybedilen ilaç miktarı göz önüne alındığında, haftada dört doz rituximab uygulamasının remisyona olasılığını artırdığına inanıyoruz. Bununla birlikte, bulgularımız daha büyük popülasyonlarla yapılan doz karşılaştırmalı ve uzun vadeli yan etkilerin değerlendirildiği çalışmalar ile doğrulanmalıdır. Bazı hastalarda B hücre depleksiyonuna rağmen remisyona sağlanmadığını saptamak, B hücre depleksiyonunun remisyona için gerekli ancak yetersiz olduğunu düşündürdü.

**Anahtar sözcükler:** Çocuk, nefrotik sendrom, rituksimab

rituximab as a treatment for SRNS due to both the lack of randomized clinical trials supporting its use and the risks of serious adverse effects (4). There is no consensus regarding rituximab dose amount or frequency in the treatment of pediatric NS. Studies related to rituximab therapy and outcomes in children with various NSs have recently increased.

The aim of this study was to evaluate the efficacy of rituximab therapy in children with NS and to share our experiences.

## Materials and Methods

### Study population

This retrospective study included 12 children with NS (four with SDNS, eight with SRNS) who were treated with rituximab and followed up in our center.

### Definitions

Steroid-dependent nephrotic syndrome was defined as two consecutive relapses during corticosteroid therapy or within 14 days of discontinuing therapy; SRNS was defined as no urinary remission after eight weeks of corticosteroid treatment (7). Complete remission was defined as proteinuria less than 4 mg/m<sup>2</sup>/hour, absolute urine protein to creatinine ratio <200 mg/g, and <1+ of protein on urine dipstick. Partial remission was defined as having absolute urine protein to creatinine ratio between 200–2000 mg/g and proteinuria reduction of 50% or greater from initial value (5, 7, 8). B-cell depletion was defined as <1% of CD19+ lymphocytes (6).

### Rituximab treatment and follow-up

All patients received rituximab (375 mg/m<sup>2</sup>) once weekly for 4 weeks. Methylprednisolone, paracetamol, and chlorphenamine were administered 1 hour before each rituximab infusion (2, 3). A proteinuria-free period under steroid therapy was not sought prior to initiating rituximab therapy.

Clinical and laboratory data (leukocyte count, kidney function and liver function tests, serum albumin, and proteinuria in monthly 24-hour urine collection) were evaluated

**Table 1. The list of drugs used before rituximab**

Patient	Corticosteroids	Cyclosporine	Tacrolimus	MMF	Cyclophosphamide	Adalimumab
#1	+	+	–	–	–	–
#2	+	+	+	+	–	–
#3	+	+	+	+	+	–
#4	+	+	–	+	–	–
#5	+	–	–	–	+	–
#6	+	–	+	+	–	–
#7	+	+	–	+	+	–
#8	+	+	–	–	–	–
#9	+	+	–	–	–	a
#10	+	+	+	–	–	–
#11	+	+	–	+	–	–
#12	+	+	–	–	–	–

a: The patient with chronic recurrent multifocal osteomyelitis plus SRNS

weekly for up to 4 weeks (during rituximab therapy) and monthly after completing the rituximab therapy. CD19-20 levels were evaluated weekly during the 4-week rituximab treatment period. All patients were monitored during follow-up for previously reported adverse effects, and all outcomes and adverse events were recorded.

The study protocol was approved by the Institutional Review Board of Pamukkale University Medical Faculty (60116787-020/44410/20.06.2018/13), and the study was conducted in accordance with the Declaration of Helsinki.

### Statistical Analyses

All statistical analyses were performed using the SPSS version 24.0 statistics software. Continuous variables are expressed as mean±standard deviation and median values, and categorical variables as number (n) and percentage (%).

### Results

The mean age of 12 patients with NS (7 boys) was 13.08±4.8 years. Eight of the patients had SRNS and the remaining four were diagnosed as SDNS. Kidney biopsy performed in 10 patients revealed FSGS in six patients and normal findings (minor glomerular abnormalities) in four patients. Biopsy could not be performed in two patients; one had a solitary kidney and was diagnosed as having SRNS, and the other was diagnosed as having SDNS.

The medications used before rituximab are shown in Table 1. The baseline characteristics of the patients are given in Table 2. The median duration of the pre-rituximab period was 5.6±5.2 years (Table 2). At the beginning

of rituximab therapy, the mean protein excretion of all patients was 121 mg/m<sup>2</sup>/hour. The initial mean proteinuria level was 122 mg/m<sup>2</sup>/hour among patients who achieved remission with rituximab, and 120 mg/m<sup>2</sup>/hour among those who did not.

All four of the children diagnosed as having SDNS achieved complete remission. In the SRNS group, only one patient achieved complete remission and two patients achieved partial remission (Table 2). The overall remission rates in patients with SDNS and SRNS were 100% and 27%, respectively. Among the patients with FSGS, complete remission was observed in 1/6, partial remission in 1/6, and no remission in 4/6.

CD19 cell depletion (≤1%) was observed in 10 of the 12 children. Seven of the 10 patients with CD19 depletion achieved partial or complete remission, whereas the other three patients had persistent nephrotic proteinuria despite CD19 depletion. Depletion of CD19 occurred after the first dose of rituximab in nine of the 10 patients and after the second dose in the other patient. Patients who did not exhibit CD19 depletion with rituximab were unable to achieve clinical and laboratory remission. After rituximab therapy, the patients were followed up for at least 12 (mean: 16±4) months. Relapse occurred in three of the seven patients in remission; one patient relapsed at one month and the other two patients relapsed at six months. CD19 levels were elevated in these patients at time of relapse, ranging from 10% to 17%, respectively.

Drug-related adverse effects were observed in four patients (throat itching in three children and facial redness in one child).

Table 2. Characteristics of patients receiving rituximab (RTX) treatment

Patients	Sex	Actual age (years)	Age at diagnosis	Follow-up years	Kidney biopsy	Type	CD 19–20 levels (%)	B cell depletion	Pre-treatment albumin (g/dL)	Post-treatment albumin (g/dL)	Pre-treatment urine protein (mg/m <sup>2</sup> /h)	Post-treatment urine protein (mg/m <sup>2</sup> /h)	Remission with RTX
#1	M	16	14	2	Normal	SDNS	7–7	+	1.78	4.24	136	3.3	Complete
#2	M	17	13	4	Normal	SDNS	8–9	+	1.7	4.94	242	1.6	Complete
#3	M	13	3	11	Normal	SRNS	3–3	+	3.3	4.77	104	4	Complete
#4	M	19	2	17	FSGS	SDNS	5–6	+	2.1	4.5	169	2.2	Complete
#5	M	7	5.5	1.5	No done	SDNS	19–20	+	3.3	4.3	50	3.5	Complete
#6	F	12	5	7	FSGS	SRNS	12–13	+	4	4.1	72	19	Partial
#7	F	14	4	10	Unable	SRNS	10–11	+	3.6	3.9	83	28	Partial
#8	M	6	5	1.5	FSGS	SRNS	1–1	+	1.98	1.28	120	96	–
#9	M	19	17	1.5	FSGS	SRNS	31–30	–	2.00	2.42	210	300	–
#10	F	15	13	8	FSGS	SRNS	12–13	–	3.46	3.62	46	73	–
#11	F	15	13	3	FSGS	SRNS	22–22	+	2.4	2.3	130	186	–
#12	F	4	3	1.5	Normal	SRNS	18–17	+	1.77	1.6	97	63	–

SDNS: Steroid-dependent nephrotic syndrome; SRNS: Steroid-resistant nephrotic syndrome; FSGS: Focal segmental glomerulosclerosis

### Discussion

In this study, 12 patients with NS were treated with rituximab and seven exhibited partial or complete remission. The most notable findings of our study were that some patients did not achieve remission despite B cell depletion, and that rituximab could be given in the nephrotic period in children who did not respond to other immunosuppressive therapies or experienced adverse effects with steroid therapy.

There is no consensus regarding the optimal number of rituximab doses in the treatment of pediatric NS. The use of rituximab in children with NS was first reported in 2004, using 375 mg/m<sup>2</sup> weekly for four weeks, as in non-Hodgkin lymphoma (9). Several studies have compared the response rate in children treated with 1–2 doses vs. 3–4 doses (10, 11). A study published in 2017 suggested that four weekly doses of rituximab might increase the likelihood of response by compensating for the amount of drug lost in the urine in some children with NS (10). Another study revealed no significant difference in outcomes between 2-dose and 4-dose rituximab protocols in children with NS (11). Some centers use protocols in which rituximab is administered according to CD19 levels. However, Takahashi et al. (12) suggested that the number of circulating B cells was not necessarily helpful in predicting relapse. Some concerns were expressed related to basing rituximab re-treatment protocols on CD19 elevation in children with NS. A potential problem with their protocol is that repeated rituximab dosing might have been excessive for some patients. Considering evidence that CD19 recovery is not always associated with relapse, we chose not to use a rituximab protocol based on CD19 levels. In our center, we used a rituximab regimen of 375 mg/m<sup>2</sup> weekly for 4 weeks. Considering the amount of drug lost in the urine of children with nephrotic proteinuria, we believe administering four weekly doses of rituximab increases the likelihood of remission. However, our findings must be confirmed with dose-comparison studies conducted with larger populations and an evaluation of long-term adverse effects.

Some studies reported the effectiveness of rituximab for FRNS and SDNS (2, 3). It is believed that rituximab is more effective in children with FRNS and SDNS, as treated patients have exhib-

ited long remission periods without the need for corticosteroid therapy (13, 14). In our study, complete remission was achieved in all patients with SDNS (100%).

Unlike with FRNS and SDNS, the KDIGO guideline does not recommend rituximab as a treatment choice for SRNS due to the lack of randomized controlled trials (4). The response to rituximab in patients in SRNS is variable; some authors have reported benefits, and other series have reported that it is less effective (15, 16). An international multicenter report showed the rituximab response rate in patients with SRNS as 22–48.5% (17–19). In our study, complete remission was observed in one patient and partial remission in two patients with SRNS, with an overall remission rate of 27%. These findings suggest that rituximab may also assist in the treatment of patients with SRNS.

The influence of histologic subtype on the response to rituximab is unclear. Chan et al. (19) reported that rituximab was effective in about half of their patients with FSGS, whereas Sinha et al. (20) observed that FSGS was associated with a higher probability of nonresponse. In our study, the remission rate was 33% in patients with FSGS. As definitive data on this issue are lacking, we hope our findings may contribute to a future meta-analysis.

Some studies have shown that peripheral blood B cell depletion is strongly correlated with remission (6, 21). However, Sato et al. (22) reported that some of their patients experienced relapse during B cell depletion after rituximab therapy. In another study, it was observed that bone marrow B cells were more resistant to depletion than circulating CD19 B cells (23). Sellier et al. (24) concluded that children with NS treated with rituximab might experience relapse after B cell recovery, whereas some treated children maintain long-term remission even after total B cell recovery. Colucci et al. (25) found that although mature B cells and CD19 levels returned to initial levels 12 months after rituximab therapy and levels of memory B cells were still low while patients were in remission. They suggested that B cell subtypes such as memory B cells might be a useful indicator of NS relapse and could replace CD19 as a marker used to determine rituximab dosing schedules. We observed CD19 depletion in 10 of 12 patients. Overall remission was achieved in seven of 10 patients, and the other three patients did not achieve CD19 depletion. Three of seven patients who achieved remission developed relapse after one month (in one patient) or six months (in two patients), and all relapses were associated with a rise in CD19 cell count. Therefore, B cell depletion seems to be necessary but not sufficient for rituximab to be effective

in children with NS. In addition, although relapse was consistent with B cell increase, remission was not always consistent with B cell depletion. In addition, some authors described patients who could not achieve B cell depletion and proposed that this was related to nephrotic level proteinuria, and especially increased rituximab loss through the urine due to nonselective proteinuria (9, 26). Two of our patients who did not show B cell depletion were diagnosed as having FSGS, and we believe that they may not have entered remission due to the presence of nonselective proteinuria.

Many studies have reported that rituximab was most effective in patients when administered during a proteinuria-free period induced by other immunosuppressive drugs (10, 27). It is known that massive proteinuria may cause rituximab loss through the urine, reducing its therapeutic effectiveness (27). These patients need a recurrent or higher dose. In another study, however, seven patients were infused with rituximab during the nephrotic period and unexpectedly, three of them achieved remission (28). Similarly, the majority of our patients had SRNS and were not in remission with other treatments. Patients with SDNS were not given steroids again due to the development of steroid-related adverse effects (weight gain and signs of Cushing's syndrome). Although we think that rituximab is more effective in the proteinuria-free period, we believe that rituximab can be used in the proteinuria period for resistant patients who did not respond to other therapies and have steroid-related adverse effects.

Mild as well as serious adverse events have been reported in association with rituximab therapy, including anaphylactic reactions, fatal hepatitis induced by rituximab reactivation of hepatitis B virus, progressive multifocal leukoencephalopathy, lung fibrosis, hypotension, leukopenia, and serum sickness (18, 29, 30). In our study, only mild drug-related adverse effects occurred in the form of throat itching in three patients and redness of the face in one patient.

A weakness of our study is the low number of patients from a single center. Another limitation was that the CD19 levels of patients in remission after rituximab therapy were not monitored.

## Conclusion

Our study demonstrated that rituximab was an effective therapy for SDNS and conferred benefit approximately one-third of the patients with SRNS and FSGS. The results also suggest that rituximab can be given in the proteinuria period to patients who do not respond to other



therapies or encounter adverse effects with steroid therapy. Some patients in our study did not achieve remission despite B cell depletion after rituximab treatment, which suggests that complete B cell depletion is necessary but insufficient for remission in NS. Markers other than CD19 are needed to predict relapse after rituximab therapy and to determine a repeat dosing schedule.

**Ethics Committee Approval:** The study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the local ethics committee of Pamukkale University Faculty of Medicine (26.06.2018/13).

**Informed Consent:** Written consent was obtained from the parents of all patients.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept - İ.G., S.Y.; Design - İ.G., S.Y.; Supervision - S.Y.; Funding - İ.G., Y.P.; Materials - İ.G., Y.P.; Data Collection and/or Processing - İ.G., Y.P.; Analysis and/or Interpretation - İ.G., S.Y.; Literature Review - İ.G., S.Y.; Writing - İ.G., S.Y., Y.P.; Critical Review - S.Y.; Other - İ.G., S.Y., Y.P.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Etik Kurul Onayı:** Çalışma Helsinki deklarasyon prensiplerine uygun olarak gerçekleştirildi. Bu çalışma için etik kurul onayı Pamukkale Üniversitesi Tıp Fakültesi Lokal Etik Kurulu'ndan alınmıştır (26.06.2018/13).

**Hasta Onamı:** Yazılı hasta onamı hastaların ebeveynlerinden alınmıştır.

**Hakem Değerlendirmesi:** Dış bağımsız.

**Yazar Katkıları:** Fikir - İ.G., S.Y.; Tasarım - İ.G., S.Y.; Denetleme - S.Y.; Kaynaklar - İ.G., Y.P.; Malzemeler - İ.G., Y.P.; Veri Toplanması ve/veya İşlemesi - İ.G., Y.P.; Analiz ve/veya Yorum - İ.G., S.Y.; Literatür Taraması - İ.G., S.Y.; Yazıyı Yazan - İ.G., S.Y., Y.P.; Eleştirel İnceleme - S.Y.

**Çıkar Çatışması:** Yazarlar çıkar çatışması bildirmemişlerdir.

**Mali Destek:** Yazarlar bu çalışma için mali destek almadıklarını beyan etmişlerdir.

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