

ORIGINAL ARTICLE

RITUXIMAB USE IN CHILDREN WITH COMPLICATED IDIOPATHIC NEPHROTIC SYNDROME - A SINGLE CENTRE EXPERIENCE

USO DE RITUXIMAB EM CRIANÇAS COM SINDROMA NEFRÓTICA IDIOPÁTICA COMPLICADA

Carla Leal Moreira¹, Rita Baptista¹, Pedro Maneira Sousa¹, Juliana Maciel¹, Liane Costa¹, Ana Teixeira¹, Teresa Costa¹, Paula Matos¹, Líliliana Rocha¹, Maria Sameiro Faria¹, Conceição Mota¹

ABSTRACT

Background: In children with idiopathic nephrotic syndrome, rituximab can maintain short-term remission allowing steroids and calcineurin inhibitors taper.

Methods: We retrospectively reviewed all children receiving rituximab for idiopathic nephrotic syndrome at a tertiary hospital. All patients, except one who received a single dose, had four infusions of 375mg/m² of rituximab at a one-week interval, minimum follow-up duration of four and maximum 118 months.

Results: Eleven patients were included, three patients with steroid resistant nephrotic syndrome and eight steroid dependent or frequently relapsing nephrotic syndrome. Male:female ratio was 8:3 and median age at onset was 2.7 (minimum 1.7-maximum 9.9) years-old.

All patients received a trial of calcineurin inhibitors, eight received cyclophosphamide and seven mycophenolate mofetil. Remission of proteinuria was observed in nine patients. Two patients were non-responders evolving to end-stage renal disease. Patients experienced in median three relapses during the six months preceding rituximab. Responders did not relapse in the following six months ($p=0.013$) and daily dose of prednisolone was significantly reduced ($p=0.001$). Two patients relapsed at 9 and 12 months after rituximab. Another patient experienced relapse immediately after kidney transplant, successfully treated with our protocol for focal and segmental glomerulosclerosis relapse. Recovery of CD19 cells counting was observed in six patients including two relapsing patients. No severe infection or neoplasia were reported.

Conclusions: Rituximab successfully reduced relapsing in complicated idiopathic nephrotic syndrome, steroid dose and enabled other immunosuppressants weaning off in most patients. Recovery of CD19 cells did not anticipate relapse, but may herald the need for additional rituximab infusions.

Keywords: nephrotic syndrome; steroid-dependent; steroid-resistant; rituximab

RESUMO

Introdução: O rituximab pode ser uma arma terapêutica útil no tratamento da síndrome nefrótica complicada, permitindo a redução de inibidores da calcineurina e de corticóides.

Métodos: Estudo retrospectivo de todas as crianças que receberam rituximab no tratamento de síndrome nefrótica num hospital terciário. Todos os doentes, exceto um (dose única), receberam quatro infusões de rituximab 375mg/m² com intervalo de uma semana, tendo um seguimento mínimo de quatro meses e máximo de 118 meses.

Resultados: Foram incluídos 11 doentes, três com síndrome nefrótica corticorresistente e oito com síndrome nefrótica corticodependente

I. Pediatric Nephrology Unit, Centro Materno-Infantil do Norte, Centro Hospitalar Universitário do Porto. 4099-001 Porto, Portugal.
moreira.l.s.carla@gmail.com; ritagbatista@gmail.com; pedromaneirasousa@gmail.com; julianamaciel@live.com; lianexcosta@gmail.com; anafeteixeira@gmail.com; teresa.v.c.tavares@gmail.com; ppiresmatos@hotmail.com; liliana.oli.rocha@gmail.com; mariasameirofaria@gmail.com; conceicaoocmota@gmail.com

ou multirrecidivante. A relação masculino:feminino foi de 8:3, com idade mediana no quadro inaugural de 2,7 anos (mínimo 1,7 - máximo 9,9). Todos os doentes foram tratados previamente com inibidores da calcineurina, oito com ciclofosfamida e sete com micofenolato de mofetil. Dois doentes não responderam, evoluindo para a doença renal crónica estágio 5. Registou-se uma mediana de três episódios de recidiva nos seis meses pré-rituximab e nenhuma recidiva nos seis meses pós-rituximab ($p=0.013$). Foi possível reduzir significativamente a dose de corticóides ($p=0.001$). Dois doentes recidivaram aos 9 e 12 meses pós-rituximab. Um outro doente recidivou imediatamente após transplante renal. Verificou-se recuperação da contagem de células CD19 em seis doentes, incluindo dois recidivantes. Não se reportou nenhum caso de infeção severa ou neoplasia.

Conclusão: O rituximab reduziu significativamente o número de recidivas e a dose de corticóides na síndrome nefrótica complicada. A recuperação da contagem de células CD19 não previu a recidiva, mas pode indicar a necessidade de doses adicionais de rituximab.

Palavras-chave: corticodependente; corticorresistente; síndrome nefrótica; rituximab

INTRODUCTION

Idiopathic nephrotic syndrome (INS) affects 2–10 children per 100,000 per year in Western countries, with a prevalence of 16 cases per 100,000.¹ Oral steroids are the cornerstone of therapy for INS, inducing remission within 4–6 weeks in approximately 90% of cases, while approximately 10% – 15% of children with INS are steroid resistant.^{2,3} Moreover, up to 85% of these patients experience relapse within five years, and many will develop steroid dependence.⁴ For those with a frequently relapsing (FRNS) course or steroid-dependent nephrotic syndrome (SDNS), second-line treatment with cyclophosphamide, calcineurin inhibitors (CNI), and mycophenolate mofetil (MMF) is indicated to maintain remission and reduce the dose of steroids.⁵ To suppress or control proteinuria in steroid-resistant nephrotic syndrome (SRNS), treatment strategy also includes second-line drugs such as CNI, MMF, cyclophosphamide, and others.⁶ Given the toxicity of these agents, alternative treatment options were pursued.

The primary injury in nephrotic syndrome is at the level of the glomerular podocyte. Systemic factors, immune mediated or a circulating permeability factor, as described in focal and segmental sclerosis (FSGS), can alter the glomerular filtration barrier. Alternatively, inherited structural abnormalities of the podocyte can result from mutations in genes that encode slit diaphragm proteins in the genetic forms of FSGS.^{7–9} Traditionally, the underlying pathogenic mechanism for nephrotic syndrome has focused on dysregulation of T cells, but there is increasing evidence of a role for B cells.¹⁰

Rituximab (RTX) is a monoclonal antibody that acts directly against CD20 expressed on B lymphocytes, resulting in rapid and sustained B

cell depletion. The exact mechanism by which RTX would be effective in the treatment of nephrotic syndrome is unclear, but it has been proposed that induction of regulatory T cells may lead to a late effect on decreasing proteinuria.^{11,12} RTX experience in difficult-to-treat INS has been mainly supported by anecdotal reports, case series and observational studies.^{13–17} Seven randomized controlled trials (RCT) involving children assessed RTX efficacy in SRNS and SDNS, two and five, respectively.^{18–23} Whereas for SRNS, RTX therapy has conflicting results, in SDNS, RTX successfully reduced steroids dose exposure and increased relapse-free survival.

We aimed to describe our single-center experience using RTX for the treatment of difficult-to-treat INS.

METHODS

We performed a retrospective study of all patients managed with RTX for INS involving native kidneys between 2014 and 2018 in the Department of Pediatrics at Centro Materno Infantil do Norte, Centro Hospitalar do Porto, Portugal. Their clinical courses in the six months preceding RTX infusion and afterwards were retrospectively reviewed. SDNS was defined as two or more relapses of nephrotic syndrome during the reduction of steroid treatment or within two weeks of discontinuation of steroid treatment. FRNS was defined as two or more relapses of nephrotic syndrome within six months after initial remission, or more than four relapses within any 12-month period. INS unresponsive to prednisone for a minimum period of eight weeks fulfilled the criteria for SRNS.²⁴ Our protocol for RTX infusion included an intravenous dose of 375mg/m² once weekly during four weeks. One patient received a single dose of RTX infusion 375mg/m², following another institution protocol. We used pretreatments with clemastine, methylprednisolone and acetaminophen to prevent infusion reaction. CD19-positive cell count was measured before RTX treatment, at the end of RTX treatment, and at last follow up or relapsing time. Relapse was defined by three or four positive results on albuminuria dipstick testing for three consecutive early-morning specimens.

Patients were followed up for a minimum of four months and a maximum of 118 months after RTX. Data regarding serum albumin, serum creatinine, lipid profile, anthropometric features, immunosuppressive strategy, hypertension and adverse outcomes were collected. Estimated glomerular filtration rate (eGFR) was calculated using creatinine-based “Bedside Schwartz” equation (2009). Height and weight z-scores calculation follows that used by the National Health and Nutrition Examination Survey (NHANES).

Our main outcomes were the change in relapse rate and steroid dose at six months before and after RTX infusion.

Data are expressed as either relative frequency or median and interquartile range (IQR), where applicable. Wilcoxon matched-pairs signed-rank test was used when appropriate. P values < 0.05 were considered statistically significant. Stata software, version 14.2 software (Texas, USA) was used for the statistical analysis.

RESULTS

Patient characteristics

A total of 11 children (male to female ratio, 8:3) were included, three patients with SRNS and eight patients with SDNS or FRNS. The median age of patients at the onset of nephrotic syndrome and at the initial cycle of RTX treatment were 2.7 years-old (2.0, 3.2) and 8.2 years-old (6.2, 11.3), respectively. The median duration of the disease before the initial cycle of RTX treatment was 54 months (31, 95). Renal biopsy was performed in all patients; minimal change disease was found in nine patients, four of them with mesangial deposits of IgM, while FSGS was the histologic finding in two patients.

History of the disease

Eight patients (73%) experienced two or more relapses in the six months preceding RTX infusion, while two patients (18%) had refractory nephrotic syndrome and only one patient was relapse-free in the six months before RTX infusion.

RTX significantly reduced the number of relapses in the six months following RTX (before vs after RTX, median 3 vs 0, $p=0.013$). Nine patients were successfully treated with RTX and no relapse was

documented in this period. Two patients with SRNS were non-responders maintaining nephrotic range proteinuria, however one patient had $eGFR < 25 \text{ mL/min/1.73m}^2$ at the time of RTX infusion. Both progressed to end-stage renal disease in nine months and two months, respectively, after last RTX infusion. Three patients experienced four relapses until the end of the follow up: one at nine months, steroids were titrated, however a second relapse led to CNI start; one at 12 months, responded well to steroid titration; the last patient, with SRNS, initially non-responder, experienced relapse after kidney transplantation at nine months after RTX infusion (one month post-kidney transplantation). The patient was successfully treated for FSGS relapse (FSGS was documented in the native kidney biopsy) using plasmapheresis, intravenous immunoglobulin and two additional infusions of RTX 375 mg/m² were given, remaining relapse-free for further 35 months. Among relapsing patients, two relapsing patients experienced recovery of CD19-positive B-cells, one patient had missing data regarding CD19 cells count before relapse (Figure 1). Median serum albumin levels significantly improved from 3.9 g/dL (3.3, 4.2) to 4.5 g/dL (4.0, 4.8) ($p=0.002$) and prednisolone dose was reduced from 20 mg (7.5, 30) to 2.5 mg (1.2, 5) per day ($p=0.001$). Although not statistically significant, lipidic profile, weight and height z-scores slightly improved after RTX, table 1.

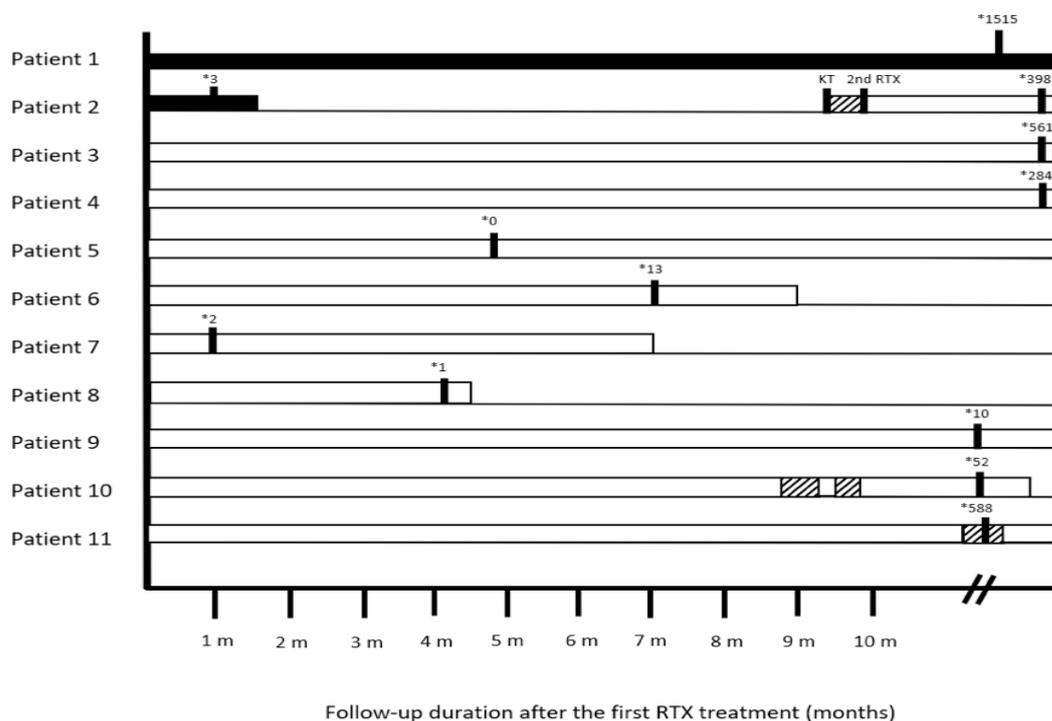


Figure 1 - Patient's clinical course.

▨ Relapse □ Relapsing-free time ■ Non-responder

Seven patients showed sustained remission after last rituximab cycle, and three patients had one or more episodes of relapses after the last cycle of rituximab treatment. Two patients were initially non-responders.

KT: kidney transplant; 2nd RTX: Second rituximab cycle.

* Peripheral CD19 + Cell, No. per mm³

Table 1 - Demographic characteristics six-months before and six-months after last rituximab infusion.

Characteristics	Pre-RTX	Post-RTX	P value
N		11	
Demographics			
Male:female ratio		8:3	.
Age of INS onset, yo		2.7 (2.0, 3.2)	.
Age at RTX start, yo		8.2 (6.2, 11.4)	.
Anthropometry			
Height, cm	124.5 (107.9, 145)	126.8 (116.5, 163)	0.001
Height z score*	-0.3 (-0.7, -0.0)	-0.5 (-1.5, 0.0)	0.54
Weight, kg	40.8 (27.9, 55.6)	47.2 (26.9, 63)	0.22
Weight z score*	1.2 (0.9, 2.2)	0.9 (0.3, 2.3)	0.06
Disease history			
Hypertension, No. (%)		2(18)	.
Disease duration, months		54 (31, 95)	.
Previous immunosuppressive treatments, No. (%)			
Steroids		11 (100)	.
Cyclosporine		11 (100)	.
Cyclophosphamide		8 (73)	.
Mycophenolate mofetil		7 (64)	.
Tacrolimus		1 (9)	.
No. of relapses [§] , No. (%)			.
0	1 (11)	0 (0)	0.013
2	3 (33)	0 (0)	
3	4 (44)	0 (0)	
4	1(11)	0 (0)	
Daily prednisolone dose, mg	20 (7.5, 30)	2.5 (1.25, 5)	0.001
Renal histologic status			
MCD, No. (%)		9 (82)	.
No deposits		5 (55)	.
IgM deposits		4 (44)	.
FSGS, No. (%)		2 (18)	.
Serum biochemistry			
Albumin, g/dL	3.9 (3.3, 4.2)	4.5 (4.03, 4.8)	0.002
Cholesterol, mg/dL	211.5 (172, 252)	191 (155, 222)	0.18
Triglycerides, mg/dL	186.5 (94, 416)	117 (107, 170)	1.0
eGFR [§] , mL/min/1.73m ²	131 (108, 166)	126 (120, 154)	0.51
Follow up time, months		69 (54, 110)	.

Data is presented as n (percentage) or median (interquartile range) as appropriate

[§]Estimated glomerular filtration rate was calculated using creatinine-based “Bedside Schwartz” equation (2009)

*The calculation follows that used by the National Health and Nutrition Examination Survey (NHANES)

[§]N. relapses in six months preceding RTX and six months following RTX infusion

MCD, minimal change disease; FSGS: focal and segmental glomerulosclerosis; eGFR: estimated glomerular filtration rate

Two potentially pathogenic genetic mutations were identified: one patient with SRNS non-responder to RTX treatment was an heterozygote carrier of the mutation c.1927G>A (p.Ala643Thr) in the gene PLCE1, of undetermined clinical meaning; another patient was found to carry an heterozygotic mutation c.3497G>Cp.(Gly1166Ala) in the gene PTPRO, also not described to this date as having clinical significance.

Adverse reactions

From a total of 43 infusions of RTX performed in 11 patients, none were accompanied by acute infusion reactions. We did not observe life threatening anaphylactic reactions either. Till the end of this study none of the patients developed any sort of oncologic disorder. One patient with refractory nephrotic syndrome, non-responder to RTX, and in need of recurrent albumin infusions developed an episode of respiratory infection requiring inpatient care.

DISCUSSION

The treatment of idiopathic nephrotic syndrome is often complicated by a refractory and relapsing course, with risk of drug toxicity and progressive renal failure. To our knowledge this is the first Portuguese cohort assessing RTX efficacy in decreasing relapses of difficult-to-treat nephrotic syndrome.

The mechanisms mediating the effects of RTX in nephrotic syndrome have not been clarified, but it was proposed that induction of regulatory T cells may lead to a late effect on decreasing proteinuria long after completion of therapy.^{11,12} Most participants in the present study and other trials remained in remission for several months after reconstitution of CD20 B cells, also suggesting that the clinical effect of RTX may remain beyond its biologic activity on CD20.^{21,23,25}

The limited toxicity of RTX and the potential benefits of maintaining disease remission, while avoiding steroids and CNI, support the use of RTX as a steroid-sparing agent in juvenile SDNS. However, patients with SRNS did not achieve similarly enthusiastic results. Magnasco *et al* report the results of the first RCT including 31 children with nephrotic syndrome resistant to steroids and CNIs for ≥ 6 months. Intervention arm (n=16) was treated with two doses of RTX (375 mg/m²) at a weekly interval, minimum follow-up of three months.¹⁸ Unfortunately, RTX therapy did not reduce proteinuria in the overall treatment group. CD20 counts remained low (< 1%) during this time, and serum levels of RTX indicated adequate therapeutic levels. The disappointing results of this study are in contrast with the cohort study that reported RTX in SRNS (and SDNS) by Gulati *et al*, in which 9 of 33 (27%) children achieved complete remission at six months, which was sustained beyond 12 months in seven children.²⁶ There was a lack of response in 51.5% of patients, and the remaining achieved partial remission. None of these studies reported association of histology findings with response to RTX. Most recently Ahn YH reported partial or complete response in 9 (39.1%) of 23 patients with SRNS in the

single-arm study treated with RTX in a Korean multicenter open-label trial.¹⁹ This study also included patients with steroid or CNI-dependent nephrotic syndrome, reporting significant reduction in remission rates (74.3% vs 31.3, p=0.003) and relapse-free time (9.0 vs 2.9 months, p=0.004) in the RTX group vs control group. RTX group received one or two RTX (375 mg/m²) infusions, if the first dose failed to achieve depletion of CD19 (+) cells.¹⁹ In our cohort, we report three patients with SRNS: two were non-responders; the other one, who was also CNI sensitive, followed remission for 12 months with a single RTX infusion. One of the non-responders presented with advanced chronic kidney disease at the time of RTX treatment and quickly progressed to end-stage renal disease. However, this patient relapsed after kidney transplantation (nine months after RTX infusion and during the first month post-kidney transplantation) and was successfully treated with FSGS relapse protocol plus RTX infusion, remaining relapse-free for additional 35 months.

In 2011, Ravani and colleagues reported an open-label short RCT with 54 children SDNS or CNI dependent, to randomly receive one to two doses of RTX or to receive standard of care with steroids and CNI.²⁰ RTX group was found to have reduced proteinuria in three months (70% lower in the RTX arm) as compared with standard therapy and lower relapse rates (18.5% vs 48.1%, p=0.029), allowing prednisone withdrawn in all except one patient in RTX arm. Fifty percent of patients in RTX group were in stable remission without drugs after nine months.

In 2014 Iijima and colleagues run a multicentre, double-blind, randomized, placebo-controlled trial including 48 children with complicated FRNS or SDNS to receive RTX (375 mg/m²) or placebo once weekly for four weeks.²² This study found RTX to be associated with significantly lower relapse rate (median 1.54 vs 4.17 relapses/person-year, p<0.0001) and longer median relapse-free time than the placebo group (267 vs 101 days, p<0.0001). No relapses were reported in the RTX group during the period of B-cell depletion. Serious adverse events were increased in RTX arm (42% vs 25%, p=0.36) compared to the placebo group, although not statistically significant.

Another trial including both adults and children, assessed RTX efficacy in idiopathic nephrotic syndrome. Ruggenti and colleagues run a multicentre off-on trial including ten children with SDNS.²⁷ Rituximab effectively and safely prevented recurrences (5-fold decrease in relapses, p=0.0045) and reduced the need for immunosuppression in SDNS or FRNS, and halted disease-associated growth deficit in children. However, 70% of the children relapsed. Most patients received a single infusion of RTX 375/m².

In the 2015 multicenter RCT, Ravani *et al* found that a single infusion of RTX allowed steroid withdrawal in 15 children with early-stage uncomplicated SDNS, with a median relapse-free time of 18 months.²¹ This study supports that most children can be maintained in remission using RTX treatment alone with repeated infusions every 9 – 30 months. Basu *et al* conducted the larger parallel-arm, open-label, RCT with 176 children with SDNS to evaluate RTX efficacy

as an alternative to tacrolimus.²³ Intervention arm received two infusions of RTX (375 mg/m²). RTX treatment was associated with higher 12-month relapse-free survival rate than tacrolimus (90 vs 63%, $p < 0.001$). In the RTX arm, no relapse episodes occurred within the first six months. Among the patients who experienced relapse, median time to first relapse was 40 weeks in the RTX group. In this study, the patients who relapsed 6 to 12 months after rituximab administration displayed significantly earlier B-cell recovery, with cell count differences emerging as early as four weeks post dosing.

Like previously mentioned studies, we did not report any relapse within six months after RTX infusion, with first relapse happening at nine months after last infusion. Likewise, we did not find any relapse during B-cell depleting period. The exceptionally low rate of adverse events to RTX treatment in our cohort can be related to under report.

A retrospective study from Kim *et al* reviewed long-term, repeated RTX therapy in children with SDNS or CNI-dependent nephrotic syndrome.²⁵ Eighteen children were managed with first cycle of RTX treatment of one to four weekly infusions of RTX (375 mg/m²) until depletion of B lymphocytes, subsequent cycles of RTX treatment, were administered upon either recovery of B-cells or relapse of nephrotic syndrome. The relapse rate of nephrotic syndrome significantly decreased from mean 3.4 ± 2.0 per year before RTX treatment to 0.4 ± 0.8 at the third year after RTX therapy ($p=0.01$). All relapses occurred after recovery of CD19-positive B-cells, with children receiving 5.2 ± 2.3 cycles of RTX with a mean interval between the cycles of 5.9 ± 0.5 months. Two severe adverse events, but reversible, were reported during the follow-up period.

The exact interval between RTX infusions, dosing and duration of treatment remains to be determined. While more doses may prolong drug-free remission, it may be at the cost of increased risk of adverse events. As other studies, we propose that B-cell count monitoring may help in the decision of additional RTX infusions when patients experience relapse. Relying on B-cell count to administer RTX infusion may not bring further benefit, instead we suggest an on-demand approach, administering RTX treatment whenever there is a combined finding of nephrotic syndrome relapse and B-cell count recovery.

To summarize, most evidence supports the use of RTX for the treatment of complicated SDNS, and a recent large RCT reports its efficacy advantage compared to CNI in the management of SDNS. Our study reports similar results, with diminished relapses in SDNS treated with RTX. Current data do not support the use of RTX in resistant forms of the disease.

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CORRESPONDENCE TO

Carla Leal Moreira
Pediatric Nephrology Unit
Centro Materno-Infantil do Norte
Centro Hospitalar Universitário do Porto
Largo Pof. Abel Salazar
4099-001 Porto
Email: moreira.l.s.carla@gmail.com

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