Ma et al. Ann Nephrol 2018, 3(1):24-27
DOI: 10.36959/832/393 | Volume 3 | Issue 1

Annals of Nephrology

Research Article Open Access

Rituximab for Steroid Dependent Nephrotic Syndrome in Chinese Children

Alison LT Ma[1*], Fiona Lai[2], Euan Soo[1], Norman Chan[1], Ivan Lam[1], Pak-chiu Tong[1], Wai-ming Lai[1] and Niko Tse[1]

[1]*Paediatric Nephrology Centre, Princess Margaret Hospital, Hong Kong*

[2]*Department of Pharmacy, Princess Margaret Hospital, Hong Kong*

Abstract

Objective: This study aims to review the effect of rituximab on Chinese children who suffer from steroid dependent (SD) or frequently relapsing nephrotic syndrome (FRNS) in Hong Kong.

Method: A retrospective 5-year review was performed on 11 children (mean age of 14.6 yrs (8.1-18 yrs), 8 boys and 3 girls) who had SD or FRNS from April 2009 to April 2014. All patients were in remission for at least 4 weeks before the start of Rituximab, and they received two doses of intravenous rituximab (500 mg). Their demographics (body weight, height, renal pathology, and number of relapses a year before rituximab, previous and concomitant medical treatment) were recorded. These patients were followed up for 1 year. Clinical parameters including their post rituximab body weight and height, laboratory parameters (serum creatinine, eGFR, albumin, cholesterol and urine protein/creatinine ratio) were recorded and analyzed. The number of relapses and the feasibility of immunosuppressive withdrawal post rituximab were studied.

Results: By one year, seven patients were still in sustained remission. The median time for first relapse was 322 days (158-531 days). Comparing with the year before administration of rituximab, the mean number of relapses reduced significantly from 3.55 to 1.18 after rituximab ($p = 0.009$). After rituximab, the dose of maintenance prednisolone was significantly reduced from 0.3 to 0.1 mg/kg/day at 1 year follow up ($p = 0.036$). The threshold dose of prednisolone required to sustain remission was also significantly lower after the use of rituximab ($p = 0.013$). Rituximab was well tolerated with no reports of severe infection or adverse effects. No significant difference was noted with regard to the eGFR, growth and biochemical parameters of the patients.

Conclusion: Our study shows that rituximab is an effective and safe steroid-sparing agent in the management of difficult nephrotic syndrome in children.

Keywords

Childhood nephrotic syndrome, Rituximab, Immunosuppressants

Introduction

Nephrotic syndrome is a common renal disease in childhood [1]. Up to 80% of relapse rate had been reported [1] despite of good respond to steroids in a majority of children with nephrotic syndrome. The use of long-term combination drug treatment with other immunosuppressants, including mycophenolate mofetil (MMF), cyclosporine A (CsA) or Tacrolimus (TAC), to sustain remission are associated with inherent side effects [2]. Rituximab, a monoclonal antibody directed against CD20, was shown to inhibit B cell differentiation and proliferation [3,4] and was first reported to be successful in the treatment of nephrotic syndrome in children in 2004 [5-7]. Studies have shown that rituximab is a promising steroid sparing agent, which was safe and effective to maintain patients on remission, allowing withdrawal of oral therapy in half of the patients [4]. Here we present our case series on the use of rituximab

***Corresponding author:** Alison LT Ma, Associate Consultant, Paediatric Nephrology Centre, Princess Margaret Hospital, Hong Kong

Accepted: August 14, 2018; **Published online:** August 16, 2018

Citation: Ma ALT, Lai F, Soo E, et al. (2018) Rituximab for Steroid Dependent Nephrotic Syndrome in Chinese Children. Ann Nephrol 3(1):24-27

in 11 Chinese children with steroid dependent nephrotic syndrome (SDNS) or frequently relapsing nephrotic syndrome (FRNS). We aim to report the effect and safety of the drug and the dosing changes for steroid and other immunosuppressive agents in our cohort of children after its use.

Patients and Methods

A retrospective medical record review was performed on all children with SDNS or FRNS between April 2009 and April 2014 at the Pediatric Nephrology Centre, Princess Margaret Hospital, Hong Kong. All patients were treated with rituximab. SDNS was defined as two consecutive relapses during steroid therapy, or within 14 days of steroid discontinuation. FRNS was defined as 4 or more relapses within 1 year. All patients underwent renal biopsy with their histological diagnoses reported. Patients had to be in remission for at least 4 weeks before the start of Rituximab. Rituximab infusions were given at dose of 375 mg/m^2 (max 500 mg) every 1 week for 2 to 4 doses. The infusions were diluted in normal saline to a final concentration between 1 and 4 mg/mL and were initiated at rate of 25 mg/hour. The infusion rates were doubled every 30 minutes until a maximum of 200 mg/hour if well tolerated. To prevent infusion-related reactions, all patients received intravenous methylprednisolone, intravenous chlorpheniramine and oral paracetamol as pre-medications prior to the rituximab infusion. The infusions were stopped in case of infusion-related reactions and were restarted at 50% of the previous rate when the reactions abated. Lymphocyte subsets were measured 7-10 days after the last dose of rituximab to ensure the depletion of B cells, defined as less than 0.5% of CD19 positive B cells (Normal 9-24%). Patients' demographics (age, sex, body weight, height), laboratory parameters (estimated glomerular filtration rate (eGFR) by Schwartz equation, albumin levels, urine protein/creatinine ratio, CD19 count 7-10 days post Rituximab), number of disease relapses and doses of prednisolone, immunosuppressants and anti-hypertensive medications before and after Rituximab were recorded. All adverse effects related to Rituximab were also documented. All patients were closely followed up for one year post-Rituximab administration.

This study was approved by the Research ethics committee of Kowloon West Cluster of the Hospital Authority, Hong Kong.

Statistical Analysis

The data was analyzed using SPSS version 16 using Wilcoxon Signed-ranked test and ANOVA tests as appropriate.

Results

A total of 11 Chinese patients (8 males and 3 females), with a mean age 14.7 ± 3.45 years at time of rituximab administration, were included. All of the patients were diagnosed to have nephrotic syndrome before the age of 10 years and none was lost to follow up at the end of one year. Results from renal biopsies showed that six patients had minimal change disease (MCD), three had focal segmental glomerulosclerosis (FSGS) and two had C1q nephropathy. Prior to the use of rituximab, four patients were maintained on the combination of prednisolone, CsA and MMF while seven were on prednisolone, TAC and MMF. The clinical data and outcomes after rituximab therapy are shown in Tables 1, Table 2 and Table 3.

B cell depletions were achieved in all patients in 7-10

Table 1: Patient characteristics before Rituximab.

Patient number	Histological diagnosis from renal biopsy	Type of nephrotic syndrome	Sex	Age at disease diagnosis	Years of disease before treatment	Previous treatments	Use of ACEI or ARB before Rituximab
1	MCD	SDNS	M	2	11	Pred/TAC/MMF	No
2	MCD	SDNS	F	3	15	Pred/CsA/MMF/Oral CTX	Yes
3	FSGS	SDNS	M	2	18	Pred/TAC/MMF/Oral CTX	No
4	FSGS	SDNS	F	9	8	Pred/TAC/MMF/Oral + IV CTX	No
5	MCD	SDNS	M	4	13	Pred/TAC/MMF	No
6	MCD	SDNS	M	10	3	Pred/TAC/MMF/Oral CTX	Yes
7	C1Q nephropathy with FSGS	SDNS	M	2	2	Pred/TAC/MMF/IV CTX	Yes
8	FSGS	SRNS	M	2	11	Pred/CsA/MMF	Yes
9	MCD	SDNS	M	2	11	Pred/CsA/MMF/Oral CTX	No
10	C1Q nephropathy	SRNS	F	2	6	Pred/TAC/MMF/Oral CTX	No
11	MCD	SDNS	M	6	7	Pred/CsA/MMF	No

ACEI: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker; CsA: Cyclosporin A; CTX: Cyclophosphamide; FGS: Focal Glomerulosclerosis; FSGS: Focal Segmental Glomerulosclerosis; MCD: Minimal Change Disease; MMF: Mycophenolate Mofetil; Pred: Prednisolone; SDNS: Steroid Dependent Nephrotic Syndrome; SRNS: Steroid Resistant Nephrotic Syndrome; TAC: Tacrolimus.

Table 2: Follow up after rituximab therapy.

Patient number	RTX total dose per course (mg)	CD19 count after RTX (%)	Growth velocity (cm/year)		eGFR (ml/min/1.73 m²)		Albumin (g/dL)		Number of relapses		Time to first relapse (days)
			0	12m	0	12m	0	12m	-12m	12m	
1	1000	0	2.5	3.0	100	106	45	/	4	0	426
2	2000	0.3	0.0	0.0	124	132	38	42	4	1	213
3	1000	0.1	0.0	0.0	84	89	27	34	1	1	234
4	1000	0	0.0	0.0	46	59	33	20	4	2	266
5	1000	0	2.9	1.3	94	105	39	43	3	0	531
6	1000	0	3.0	3.7	155	133	25	28	5	1	322
7	1000	0.2	3.0	4.3	108	112	24	44	7	3	158
8	1000	0.2	5.6	12.4	97	124	42	33	2	1	349
9	1000	0.2	2.0	2.7	118	95	30	45	2	0	377
10	1000	0.2	4.1	4.9	97	112	39	38	2	0	409
11	1000	0.3	2.2	4.8	92	87	26	44	5	0	574

RTX = Rituximab; -12m = 1 year before rituximab therapy; 0 = At time of rituximab therapy; 12m = 1 year after rituximab therapy.

Table 3: Steroid doses and thresholds.

Patient number	Threshold prednisolone dose (mg/kg/day)		Maintenance prednisolone dose (mg/day)		
	0	12m	0	6m	12m
1	0.14	0.07	2.5	2.5	2.5
2	0.57	0.05	5	2.5	2.5
3	0.24	0.24	5	1	10
4	0.38	0.14	5	7.5	7.5
5	0.17	0.05	2.5	5	3
6	0.19	0.17	9	5	10
7	0.18	0.35	10	5	20
8	0.16	0.06	7	3	3
9	0.05	0.02	2.5	1	1
10	0.18	0.02	17.5	1	0.5
11	0.88	0.07	10	2.5	0

0: At time of rituximab therapy; 6m: 6 months after rituximab therapy; 12m: 1 year after rituximab therapy.

days after rituximab. At 6 months post rituximab, all except one patient (90%) with C1q nephropathy were in remission. By one year, seven patients (63.6%) were still in sustained remission. The median time for first relapse was 322 days (158-531 days). Comparing with the year before administration of rituximab, the mean number of relapses reduced significantly from 3.55 to 1.18 after rituximab ($Z = 2.607$, $p = 0.009$ (two-tailed), Wilcoxon Signed-rank test). One-way, repeated-measures ANOVA revealed a significant effect of rituximab on reducing the dose of maintenance prednisolone across different time points of measurement (i.e. just before rituximab, six months after rituximab, and one year after rituximab administration, $F(1, 18, 11.79) = 5.935$, $p = 0.028$). Pairwise (Sidak) comparison further revealed that after rituximab, the mean dose of maintenance prednisolone was significantly reduced from 0.3 ± 0.242 mg/kg/day to 0.1 ± 0.04 mg/kg/day at 6 months after the initial use of rituximab ($p = 0.036$). The threshold dose of prednisolone required to sustain remission was also significantly lower after the use of rituximab ($Z = 2.49$, $p = 0.013$ (two-tailed), Wilcoxon Signed-rank test) at one year after rituximab. The dosage of adjunctive immunosuppressants (including MMF, CsA or TAC) and ACEIs were also reduced after rituximab although the effect was not statistically significant. Three of the four patients who received angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) prior to rituximab were able to discontinue the drug after rituximab therapy. One patient with FSGS was put on ACEI after the course of rituximab. In addition, one patient required anti-hypertensive drug other than ACEI/ARB before the use of rituximab which was later stopped after rituximab. Rituximab was well tolerated with no reports of severe infection or adverse effects. No significant difference was noted with regard to the eGFR and the height velocity before and after rituximab in this group of children.

Discussion

This study shows that rituximab significantly reduced the frequency of relapses in the 11 children with relapsing nephrotic syndrome. Over the year of follow up, number of relapses was reduced substantially by three fold compared to the year prior to rituximab treatment. Three patients were remained in remission at the end of the one-year follow up period with reduction of the dosages of prednisolone and other adjunctive immunosuppressants. As previously reported by many authors, rituximab therapy is safe and well tolerated [8]. No treatment-related serious adverse events were observed during rituximab infusion. However, serious adverse events such as progressive multi-focal leukoencephalopathy have been reported in individuals who were heavily immunosuppressed [4]. Post treatment surveillance and awareness was recommended for this fatal complication.

Regarding the optimal rituximab dosing in childhood nephrotic syndrome, there is no consensus yet. The original implementation was 375 mg/m²/dose given weekly

for four weeks as in the management of relapsing lymphoma patients [4,8]. However, treatment effect has been reported in a few case series even with a single dose of rituximab [4]. It was reasoned that patients with nephrotic syndrome should have remarkably lower abnormal B cell clone, so as a result, lower dosage if required to achieve the depletion [9]. We have not measured the B cell count regularly post rituximab, but it was shown in adult study that significant B cells increase were seen in about 40% of patient within 6 months post rituximab [10]. However, not all of these patients with B cells restitution developed relapse so it was not a straight forward co-relation. Further studies are required to define the best timing and dosing of rituximab treatment.

There major limitations of the study include its retrospective nature, small sample size and single centre based with a short follow up period. Furthermore, there had been no unified protocol in the titration (or tailing) of the adjunctive immunosuppressants in this cohort of patients, which might affect the duration of sustained remission. Comparative analysis between different subgroups of patients (by age or histology) were not possible due to the small sample size.

In spite of these, the striking effect of three-fold reduction in relapses observed shortly after the use of rituximab is unlikely to happen by chance and is consistent with previous large scale studies [10]. Our study sets the scene for future large-scale prospective studies to further investigate the mechanisms of rituximab, the ideal dosing regimen, the optimal tailing regimen of adjunctive immunosuppressants in the context of the management of difficult Paediatric nephrotic patients.

Conclusion

Rituximab is safe and effective in children with relapsing nephrotic syndrome and could be considered in children who are dependent on steroid or frequently relapsing.

Acknowledgements

We would like to thank the Hong Kong Children's kidney fund (HKCKF) for their financial support on the use of rituximab in children. We would like to thank Dr. Lawrence Ma for his invaluable advice on medical statistics.

Conflicts of Interests

We have nothing to declare.

References

1. Trompeter RS, Lloyd BW, Hicks J, et al. (1985) Long term outcome for children with minimal-change nephrotic syndrome. Lancet 1: 368-370.
2. Ravani P, Ponticelli A, Sicillano C, et al. (2013) Rituximab is a safe and effective long-term treatment for children with steroid and calcineurin inhibitor-dependent idiopathic nephrotic syndrome. Kidnet Int 84: 1025-1033.
3. Bargman JM (1999) Management of minimal lesion glomerulonephritis: Evidence based recommendations. Kidney Int Suppl 70: S3-S16.
4. Ruggenenti P, Ruggiero B, Cravedi P, et al. (2014) Rituximab in steroid-depenedent or frequently relapsing idiopathic nephrotic syndrome. J Am Soc Nephrol 25: 850-863.
5. Kemper MJ, Lehnhardt A, Zawischa A, et al. (2014) Is rituximab effective in childhood nephrotic syndrome? Yes and no. Pediatr Nephrol 29: 1305-1311.
6. Benz K, Dotsch J, Rascher W, et al. (2004) Change of the course of steroid dependent nephrotic syndrome after rituximab therapy. Pediatr Nephrol 19: 794-797.
7. Tullus K, Mark SD (2013) Indications for use and safety of rituximab in childhood renal diseases. Pediatr Nephrol 28: 1001-1009.
8. Fujinnaga S, Hirona D, Nishizaki N, et al. (2010) Single infusion of rituximab for persistent steroid-dependent minimal change nephrotic syndrome after long term cyclosporine. Pediatr Nephrol 25: 539-544.
9. Cravedi P, Ruggenenti P, Sghirlanzoni MC, et al. (2007) Titrating rituximab to circulating B cells to optimize lymphocytolytic therapy in idiopathic membranous nephropathy. Clin K Am Soc Nephrol 2: 932-937.
10. Munyentwali H, Bouachi K, Audard V, et al. (2013) Rituximab is an efficient and safe treatment in adults with steroid dependent minimal change disease. Kidney Int 83: 511-516.