Healthcost and Clinical Benefits of Rituximab in Steroid Sensitive Nephrotic Syndrome: Perspective from a Middle-Income Country (Myritux)

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ABSTRACT

Background: The use of Rituximab for frequently relapsing (FRNS) and steroid-dependent nephrotic syndrome (SDNS) is increasingly established. However, the use of Rituximab in resource-limited settings is constrained by its prohibitive cost.

Methods: This retrospective study included all children aged 1 to 18 years with FRNS and SDNS. The costs incurred when using either Rituximab or cyclosporine were calculated and compared. Clinical data were retrieved from medical records.

Results: Twelve patients received rituximab while 11 patients were treated with cyclosporine. Annualised relapse rate reduced from 5.07 to 1.52 in the Rituximab group and 1.01 in the cyclosporine group. Total health cost was MYR 75,339.81 in the rituximab group and MYR83,098.25 in the cyclosporine group. Cost to reduce one relapse with Rituximab was MYR 1,104.95 /episode compared to Cyclosporine, MYR 1,500.42 /episode. We observed a greater reduction in the amount of prednisolone use in the rituximab group (114.33mg/kg versus 99.91mg/kg in the cyclosporine group). Both demonstrated a significant reduction in their body mass index z-score. There were no infusion-related Reactions in the rituximab group and cyclosporin group were also well tolerated.

Conclusion: This is the first study to compare the healthcare costs of using rituximab to be carried out in a middle-income country. Findings suggest that in such a setting, a single infusion of Rituximab as a steroid-sparing agent among children with steroid-sensitive nephrotic syndrome remains efficacious and feasible.

INTRODUCTION

Idiopathic childhood nephrotic syndrome (NS) is the most encountered glomerular disease in children. The majority of affected children are steroid sensitive and respond well to glucocorticoid therapy. About 50% of these children would develop frequent relapses and become steroid dependent.[1] However, the prolonged use of high-dose glucocorticoids is associated with an array of adverse effects and toxicities.[2] These include increased appetite and weight gain, posterior subcapsular cataract, rise in intraocular pressure, hypertension, hyperglycaemia, infection and insulin resistance, Cushing-like syndrome, aggression/neuropsychiatric problems, peptic ulcers and even osteoporosis. The need for steroid-sparing agents is crucial in the management of these children. Nevertheless, a clinical dilemma exists between maintaining remission and minimising complications from treatment.

Calcineurin inhibitor (CNI) such as cyclosporine has been established as a first-line steroid-sparing agent, even

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though there are known adverse events, and up to 5% of patients develop nephrotoxicity.[3] Thus far, B lymphocyte-depleting therapy has been increasingly used in the developed world, both as a second-line steroid-sparing agent in children who tried CNI and potentially, even in children who develop dependency for CNI or CNI toxicity. Rituximab has been shown to have excellent efficacy and a good safety profile[4-8]

Despite its excellent safety profile and efficacy, many centres tend to reserve Rituximab only for selected cases due to its prohibitive cost. A study done in the Japanese adult population showed that Rituximab has superior cost-effectiveness compared to CNI while another involving the paediatric population in the US showed similar expenditure in both the Rituximab and CNI groups [9-10]. These cost-analyses studies are mainly conducted in high-income countries. Due to the varied medicine and healthcare costs in different regions, there is a need for studies that look into locally applicable data in order to guide resource decisions. The main objective of this study is to compare healthcare costs of Rituximab against Cyclosporine when used as steroid-sparing agents in steroid-sensitive nephrotic syndrome in the setting of a public-funded health system in a middle-income country.

METHODOLOGY

Study design

This is a retrospective study that included all children aged 1 to 18 years who had steroid-dependent nephrotic / frequently relapsing syndrome and were treated with either cyclosporine and/or rituximab from January 2015 to June 2021 at Hospital Tunku Azizah, Kuala Lumpur and Hospital Tuanku Ja'afar, Seremban. Data was retrieved from the hospital electronic database. All patients were followed up for a minimum of 12 months. This study was approved by the Medical Research Ethics Committee and registered with the National Medical Research Registry (NMRR ID: NMRR ID-22-00320-57C).

Inclusion and exclusion criteria

The inclusion criteria for the study were children aged ≥ 2 to <18 years with the diagnosis of steroid-sensitive idiopathic NS. Children with impaired renal function (estimated glomerular filtration rate, eGFR < 60mls/min1.73m^2), steroid resistant nephrotic syndrome, secondary causes of nephrotic syndrome and concomitant use of other immunosuppressive medication such as mycophenolate mofetil (MMF) were excluded.

Definitions

Nephrotic-range proteinuria Urinary protein creatinine ratio (UPCR) ≥ 200 mg/mmol (2 mg/mg) in a spot urine, or proteinuria ≥ 1000 mg/m2 per day in a 24-h urine sample corresponding to 3 + (3001000 mg/dL) or 4 + (≥ 1000 mg/dL) by urine dipstick.

Nephrotic syndrome

Nephrotic-range proteinuria and either hypoalbuminemia (serum albumin < 30 g/L) or oedema when serum albumin is not available.

Complete remission

UPCR (based on first morning void or 24 h urine sample) ≤ 20 mg/mmol (0.2 mg/mg) or < 100 mg/m2 per day, respectively, or negative or trace dipstick on three or more consecutive days.

Steroid-sensitive nephrotic syndrome (SSNS)

Complete remission within 4 weeks of prednisolone at standard dose (60 mg/m2/day or 2 mg/kg/day, maximum 60 mg/day).

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Steroid-resistant nephrotic syndrome (SRNS)

Lack of complete remission within 4 weeks of treatment with prednisolone at standard dose [11]

Treatment protocol

Steroid

At initial diagnosis, all patients were treated with a standard regimen of oral prednisolone at a dose of 60 mg/m^2 daily for an initial 4 weeks followed by alternate day prednisolone of 40mg/m^2 for 4 weeks and then tapered over 4 weeks for total treatment of 12 weeks duration. Relapse was treated with oral prednisolone at a daily dose of 60 mg/m^2 (maximum 60 mg/ day) until remission then the dose of steroid was then reduced to 40 mg/m^2 on alternate days (maximum 40 mg/day) and tapered off.

Cyclosporine

Patients were given cyclosporine at the time of entering remission as a steroid sparing agent. The cyclosporine dose was 3–5 mg/kg (150 mg/m^2) divided in two doses per day. A trough level of 80-100 ng/ml was desirable and the lowest possible dose to maintain remission was preferred. Steroids were tapered as above while patients commenced on cyclosporine. [12-13]

Rituximab

In both centres, Rituximab was reserved for patients with steroid-dependent or frequent relapses who had responded poorly to at least 2 other immunosuppressive therapies.

Rituximab was administered after the patient achieved remission. All patients were admitted for the infusion. A single dose of 375 mg/m^2 rituximab was given. Rituximab was diluted in normal saline at a concentration of 1mg/ml and infused over 8-10 hours. Thirty minutes before infusion, patients were premedicated with intravenous hydrocortisone/ methylprednisolone, paracetamol and chlorpheniramine. Pre-infusion screening included serology testing for Hepatitis B, Hepatitis C and chest radiograph to look for evidence of latent tuberculosis. We avoided the use of rituximab in patients who did not receive Bacille-Calmette Guerin (BCG) vaccination, given the endemic nature of tuberculosis in our country.

Primary and secondary endpoints

Costs

Data for costs referred to readily measurable healthcare related expenditure. In this manuscript, healthcare cost refers to the summation of expenditure incurred for laboratory tests, outpatient consultation (unscheduled emergency department visit inclusive) and inpatient admission. The cost of the study medication (Rituximab and Cyclosporine) were also obtained. This refers to the cost of the drug itself, cost of screening pre-infusion as well as hospital admission for infusion (Rituximab) and cost of routine clinic visits and trough monitoring (Cyclosporine). Ratio of cost of the study medication and number of relapses were calculated to reflect the cost to reduce one relapse in this study. Unit cost was derived from the charges information that would appear in the patient's hospital bill in a subsidized public health institution. In a fully funded institution, this cost would be totally absorbed by the public healthcare programme.

Efficacy

Parameters on efficacy of treatment drugs were number of relapses, number of hospital admissions, cumulative amount of corticosteroids prescribed and body mass index z-score (BMI) before and after starting the treatment drug. Adverse effects of medications and occurrence of infection throughout the study period were monitored. In view of the relapsing remitting nature of the disease, annualised relapse rate was calculated as the number of relapses experienced by that patient divided by the number of days the patient participated in the

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study, and the ratio multiplied by 365.25.

Statistical methodology

We described continuous data as median (interquartile range, IQR) and categorical variables in percentages. Wherever possible, demographic parameters were expressed as z-scores. Tests for normality were conducted with the Shapiro–Wilk test. Comparison between groups were performed using either the Mann-Whitney U or simple t- test. Level of significance was set at $P < 0.05$. All statistical analysis was performed using the SPSS software, version 23.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Demographics of the study population

A total of 23 children were included in the study (Table 1). Twelve children were given a single dose of Rituximab as a steroid sparing agent while another 11 children received cyclosporine.

Table 1 Clinical characteristics of rituximab and cyclosporine groups

	RTX(n=12)	**CSA(n=11)**
Age in years (median, IQR)	12.0(8.9-14.3)	5.7(3.9-10.4)
Gender, n(%)Male Female	9(75) 3(25)	8(72.7) 3(27.3)
Ethnicity	7Malay,3Indian,1 Chinese	9Malay,2Chinese
Disease duration in years (median, IQR)	6.9(4.9-10.1)	1.8(0.6-7.6)

Costs

Unit cost for rituximab at the time of study was MYR4321.50 (USD 907.52) per vial of 500mg. The cost for 25mg and 100mg of cyclosporine were MYR3.25 (USD 0.68) and MYR13.00 (USD 2.73) respectively. Total cost of the study medication was MYR48,617.98 (USD 10,209.78) in the rituximab group and MYR70,519.85 (USD 14,809.17) in the cyclosporine group. This amount spent reduced the number of relapses by 44 episodes and 47 episodes respectively. Incorporating this cost and its associated healthcare cost, we observe that the figure was lower in the rituximab group compared to the cyclosporine group. (See Figure 1 and Table 2).

{At the time of writing, MYR1 equals USD0.21 (11th December 2023)}

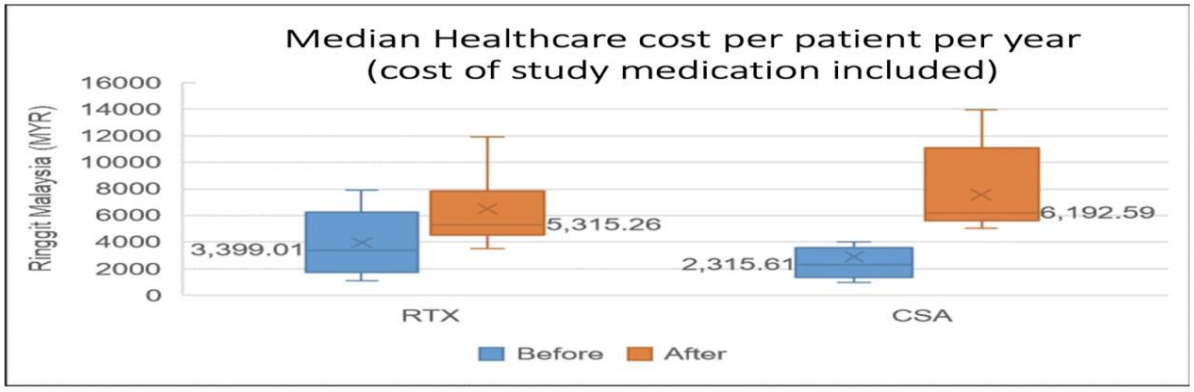

Figure 1 Median healthcare cost per patient per year (cost of study medication inclusive)

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Table 2 Costing measurements (Values in Malaysian Ringgit, MYR)

	RTX(n=12)	**CSA(n=11)**
Median healthcare cost per patient (pre)	3,399.01 (1,712.41-6278.63) USD713.78 (359.60-1318.51)	2,315.61 (1,357.76-3,556.11) USD486.28 (285.13-746.78)
Median healthcare cost per patient (post)	5,315.26 (4,494.94-7,846.71) USD1,116.20 (943.93-1,647.80)	6,192.59 (5,604.62-11,110.78) USD1,300.44 (1,176.97-2,333.26)
Median Cost of study medication per patient	4,577.27 (3,388.86-4,577.29) USD961.23 (711.66-961.23)	5,026.75 (4,926.75-8,821.81) USD1,055.62 (1,034.62-1,852.58)
Total cost of the study medication	48,617.98 USD10,209.78	70,519.85 USD14,809.17
Total cost of the study medication+ healthcare cost(post)	75,339.81 USD15,821.36	83,098.25 USD17,450.63
Cost to reduce one relapse in this study 44episodes in RTX group;47 episodes in CSA group	1,104.95 USD232.04	1,500.42 USD315.09

We inferred that the cost to reduce one relapse in our cohort was relatively cheaper with Rituximab, MYR 1,104.95 (USD 232.04) /episode compared to Cyclosporine, MYR 1,500.42 (USD 315.09) /episode.

Efficacy of treatment

The total number of relapses reduced significantly in both groups. The median annualised relapse rate was 5.07 (4.06 - 6.85) and 5.07 (5.07-6.09) before treatment for the Rituximab and Cyclosporine group respectively. Post treatment (at the end of 12 months), the median annualised relapse rate reduced to 1.52 (0.00 - 2.79) and 1.01 (0.00 - 1.01) respectively. (See Table 3).

Table 3 Efficacy parameters

	RTX(n=12)	**p***	**CSA(n=11)**	**p***
Number of relapses(pre)	64	p<0.001	60	p<0.001
Number of relapses(post)	20		13	
Number of reduction in relapses	44		47	

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XII Issue VII July 2025

Annualised relapse rate (median(IQR);pre)	5.07(4.06-6.85)		5.07(5.07-6.09)	
Annualised relapse rate (median(IQR);post)	1.52(0.00-2.79)		1.01(0.00-1.01)	
Number of admissions(pre)	25	p=0.089	16	p=0.016
Number of admissions (post)	13		1	
Cumulative prednisolone dose mg/kg(median;pre)	189.28 (160.15-248.72)	p=0.097	164.10 (133.69-249.34)	p=0.008
Cumulative prednisolone dose mg/kg(median;post)	74.95 (25.89-138.23)		64.19 (36.67-79.78)	
BMI z-score kgm- 2 (median;pre)	1.12(-0.15to2.09)	p=0.007	1.78 (0.53to2.42)	p=0.039
BMI z- score kgm- 2 (median; post)	0.63 (-0.825to1.72)		1.55 (-0.41to2.11)	

* Comparison of p is performed within the group (pre- and post-treatment)

There were no infusion-related reactions in the rituximab group, and cyclosporine was also well tolerated. One patient reported to have community-acquired pneumonia in the RTX group but recovered well soon after discharge; this may be an unrelated adverse effect.

DISCUSSION

Cyclosporine is commonly used in our country as a steroid-sparing agent among steroid-sensitive nephrotic syndrome children who continue to relapse after being given a trial of either levamisole, cyclophosphamide or both. Rituximab is reserved for children who continue to relapse despite multiple immunosuppressive medications, including cyclosporine. Analysing real-world data, the cohort of patients in the Rituximab group was older and had a longer disease vintage compared to the cyclosporine group. The rituximab group also had more relapses, hospital admissions, as well as more exposure to steroids at baseline.

The total healthcare cost (pre) for patients was higher in the Rituximab group, as expected, due to the more complicated course of disease. In both groups, the overall cost of treatment incurred (cost of the study medication and associated healthcare costs) was higher after the introduction of the studied steroid-sparing agents due to the high cost of the respective drugs. Nevertheless, the increment in this cost was lower in the Rituximab group compared to the Cyclosporine group. The recurring dosing of Cyclosporine over 1 year and the need for regular monitoring of trough levels potentially contributed to this observation.

Iorember et al[10] reported a comparable expenditure of Rituximab and calcineurin inhibitors (either Cyclosporine or Tacrolimus) in a retrospective analysis of their practice at Louisiana. In another population study in Far East Asia, Takura et al[9] demonstrated evidence of effectiveness, shown by reduced number of relapses and reduced total medical costs, which collectively supported cost-effectiveness of Rituximab in clinical practice. Our data showed that the cost to reduce one relapse was lower in Rituximab. This is potentially an important piece of information to consider when determining distribution of resources. In Malaysia, provision of healthcare at public health facilities is heavily subsidized by the government. Although a parallel private healthcare pathway is available, the burden on the public funding remains steep.[14] To our knowledge, this is the first study looking at cost parameters for Rituximab use in children with nephrotic syndrome in our country.

The secondary outcome of this study was to evaluate the practice of using a single dose of Rituximab to maintain remission in this group of children by comparing it with the existing standard therapy in our setting, which is Cyclosporine. A single dose of Rituximab has been reported to be effective literature. In this study, the performance of Rituximab is comparable to that of Cyclosporine as illustrated by the significant reduction of the number of relapses, the annual relapse rate and improvement in body mass index z-score. The disease burden that affects the psychosocial development of patients and the dynamics of their affected families is a significant entity. Incorporating health-related quality of life and patient-reported outcomes is the key to any successful health programme. It is evident from the literature that children with idiopathic nephrotic syndrome have lower health-related quality of life scores. Those with prolonged disease vintage and difficult-to-treat phenotypes have poorer quality.[15-18] In our study, reduction in hospital admission, relapses and improvement in BMI z-scores are indirect markers to suggest possible improvement in quality of life. This supports the use of Rituximab as an economically feasible alternative to Cyclosporine, with a lower cost per relapse episode, making it a valuable contribution to paediatric nephrology and public health. The real-world nature of this study makes it highly relevant to healthcare providers in similar settings.

The limitations of our study include its retrospective nature and the small sample size. In real-world practice, the utility of Rituximab is limited by its seemingly high cost. In addition, many aspects of quality-adjusted life year (QALY) in children are not fully developed yet, and this limits the analysis of the pharmacoeconomic aspects of Rituximab in our study. [19-22] In future, a prospective study with a larger cohort with a comprehensive evaluation of quality of life would strengthen the findings.

In conclusion, a single dose infusion of Rituximab as a steroid-sparing agent among children with steroid-sensitive nephrotic syndrome is efficacious and feasible, even in a middle-income country. Clinicians should consider the benefits of maintaining remission in these children from medical as well as psychosocial perspectives, and not be hindered by the seemingly high cost of treatment.

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