



The efficacy of rituximab in treatment of childhood steroid resistant and steroid dependent nephrotic syndrome: A systematic review and Meta-analysis

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ABSTRACT

Corticosteroid resistant and dependent nephrotic syndrome in children is a challenge and there are some difficulties in treating such patients. We reviewed the current studies that evaluated therapeutic role of a relatively new immunosuppressive drug "rituximab" in reducing proteinuria and reduction of relapse rate in less than 16 year old patients with non-responsive or steroid dependent nephrotic syndrome.

We searched Medline, Embase, web of science and Cochrane library with appropriate keywords and conducted the complete remission, relapse rate and the mean number of relapses 12 month after therapy on Meta-analysis. We put the data on two different subgroups; steroid resistant nephrotic syndrome and steroid dependent or frequent relapser nephrotic syndrome. In Steroid Resistant Nephrotic syndrome children, the complete remission was 0.27 (0.2- 0.34). In Steroid Dependent Nephrotic syndrome patients, the overall standard mean differences of mean number of relapses 12 mo after treatment in pooled four studies (56 cases) was 2.63 (2.03, 3.24). In these dependent patients, the data on relapse rate after treatment pooled on 6 studies (162 cases) and yield to the rate of 0.42 (0.15, 0.69) with the range of 0.09 to 0.83.

In conclusion, Rituximab is a reasonable therapy for Steroid Dependent and Steroid Resistant Nephrotic syndrome children. In view of paucity of randomized data, we suggest to perform newer controlled multicenter studies.

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Introduction

Nephrotic syndrome (NS) is a unique and relatively common entity in pediatric fields of medicine. Most children with this syndrome present with a complex of symptoms, signs and laboratory findings. Edema, hyperlipidemia, hypoalbuminemia and severe proteinuria more than $40\text{mg}/\text{m}^2/\text{hr}$ is classic tetrad of disease.¹ In contrast to adults, nearly 90 percent of nephrotic syndrome in children is due to idiopathic form and others secondary to glomerulonephritis, infections, malignancies and drugs. Histologically, 85% of idiopathic NS has minimal change in light microscopic examination and was named the same.¹ Focal segmental glomerulosclerosis and mesangial types are mostly the other forms. More than 90 percent of minimal change nephrotic syndrome (MCNS) and less than half the cases of other forms of NS respond well to standard therapy but some patients do not respond properly.^{1, 2}

Classic treatments consist of high dose of oral corticosteroids for 4-6wk and then the lower dose alternate daily prednisolone for another 4wk.³⁻⁶

The goal of therapy is to clinically improve edema and biochemical remission defined as less than $4\text{mg}/\text{m}^2/\text{hr}$ protein excretion for three consecutive days.³

Approximately 10 percent of children do not respond to corticosteroid therapy despite having 4-6 wk daily prednisolone therapy thus, named as steroid resistant Nephrotic syndrome (SRNS).³

One important and conflicting features of nephrotic syndrome is a strong potential for relapse. Only one fifth to one third of the patients experience no relapse or one of its episodes. On the other hand, 10-50 percent of children have numerous disabling episodes of relapse known as frequent relapser.⁷ The occurrence of equal or more than four episodes of relapse in any of the 12-month period, or

experience of two or more episodes in the first six months of therapy is essential for defining patient as frequent relapser nephrotic syndrome (FRNS).³

Some patients respond well to high dose steroid therapy but experience relapse during tapering or in the first months after discontinuation of the drug, they are referred as steroid dependent nephrotic syndrome (SDNS).³

Steroid resistant and steroid dependent or frequent relapser patients may need to alternative drugs such as cyclophosphamide, cyclosporine and mycophenolate.^{4, 8-11} Recently the increasing incidence of nephrotic children resistant to corticosteroid and all other alternative drugs have been reported.¹

The strategies employed for treating these refractory cases are different.¹² Rituximab is a new medication recommended for these patients.¹³⁻¹⁵ Rituximab is a monoclonal antibody against CD-20 marker that prevents proliferation and differentiation of B lymphocytes.^{16, 17} Some diverse reports of treating SRNS and SDNS cases with this drug were found.¹⁸⁻²⁵ We studied the literature for published data about the role of this drug for treatment of refractory cases of nephrotic syndrome in children. We reviewed the published data for the efficacy of rituximab in reducing absolute proteinuria or relapse episodes in less than 16 years old patients with SRNS, SDNS or FRNS in contrast with placebo or other drugs.

Materials and methods:

Search strategies

We found all studies published in English up to March 2013 about this topic. We selected every study with nephrotic syndrome as the field of study in children and focused on the studies that evaluated nonresponsive cases on FRNS, SDNS

or SRNS. We paid special attention to rituximab as the essential drug to study.

Medline, Embase, web of science and Cochrane library were searched with appropriate keywords. The basic words selected were [nephrotic syndrome or SRNS or SDNS or FRNS] and [rituximab and rituxan] and [pediatric or children but not the adults]. In addition, we searched the references list of articles for other studies. No limitation for geographic region was applied but we searched only the studies until March 2013 in English language. All the studies were selected for screening. The search was performed by two independent authors and matched than.

Review strategy

We considered some important data from studies including study design, population characteristics, definition of disease, inclusion and exclusion criteria, dose and duration and route of drug administration and response to treatment. Response to drug was assessed in two groups of studies.

Because of paucity of RCT and small sample of studies, we selected other studies apart from RCT such as prospective, retrospective, cohort and case series for review.

According to the diversity of population, we put the data on two different subgroups; steroid resistant nephrotic syndrome in one subgroup and steroid dependent or frequent relapser nephrotic syndrome in another subgroup of patients. The statistical heterogeneity of the studies was assessed through the calculation of I^2 .

The response to therapy in SRNS group of patients was defined as remission “full, partial and no remission”. In contrast to SDNS group, response was defined as relapse rate in 6 or 12 months after therapy. Some researchers reported other factors such as the mean number of relapses, time of the first relapse and steroid-free days.

Because the number of relapse was continuously measured, we used standard mean differences (SMD) as the effect measurement. A large number of studies on relapse rate and complete remission have been published; we looked at the summary relapse rate and complete remission prevalence. A random effect model was applied, unless the I^2 was under 25% in which case a fixed effect model would be used. The generation of a funnel plot and the Egger and Begg p-value allowed the determination of the potential publication bias of included studies. All analyses were done with SATA software (Version 10)

Results

Included studies

Our search led to finding 655 articles, 43 of them were duplicated. We evaluated them and excluded 487 studies according to the title and 57 articles were based on reading the abstract. Finally, we read full text of 58 selected papers and found 15 of them appropriate for analysis (Figure 1). We did not find any more articles with hand searching. From the 15 selected articles, 2 were RCT, 8 prospective, 3 retrospective and 2 case studies. According to patients included, 6 studies evaluated SRNS and 11 studied SDNS. In two studies, both groups were included. The trial characteristics of the included studies were summarized in tables 1 and 2.

The dose of drug administered to patients is similar in both groups and nearly in all studies. Rituximab was prescribed as 375mg/m² intravenously in weekly period for one to four times.

Complications

The complications of the drug were reported in different studies as mild up to 50% of the patients. Most researchers found that the most complications are indeed minor reactions such as itching, skin rash, fever, headache,

Table1. characteristics of studies that evaluated SRNS patients

Trial reference	Year	Study design	No of Population	Complete Remission	Partial Remission	Proteinuria In baseline	Proteinuria After RIT	Percentage reduction
Magnasco ²⁶	2012	Randomized Clinical Trial	31	18.7%	Not reported	2.4g/day/m ² (1.7-3.5)	1.4g/day/m ² (0.9-2.8)	-12 (-73 to110)
Bagga ²⁷	2007	Case series	5	60%	40%	8.3±5.7 pr/cr	0.84±0.97 pr/cr	-
Kari ²⁸	2011	Case series	4	25%	Not reported	7.5±6.8 g/dl	4.6±5.1 g/dl	-
Ito ²⁹	2013	retrospective	74	31.6%	31.6%	Not reported	Not reported	Not reported
Prytula ³⁰	2010	retrospective	70	22%	44%	Not reported	Not reported	Not reported
Gulati ³¹	2010	Cohort	33	27.2%	21.2%	Not reported	Not reported	Not reported

Pr/cr: Protein/Creatinin,

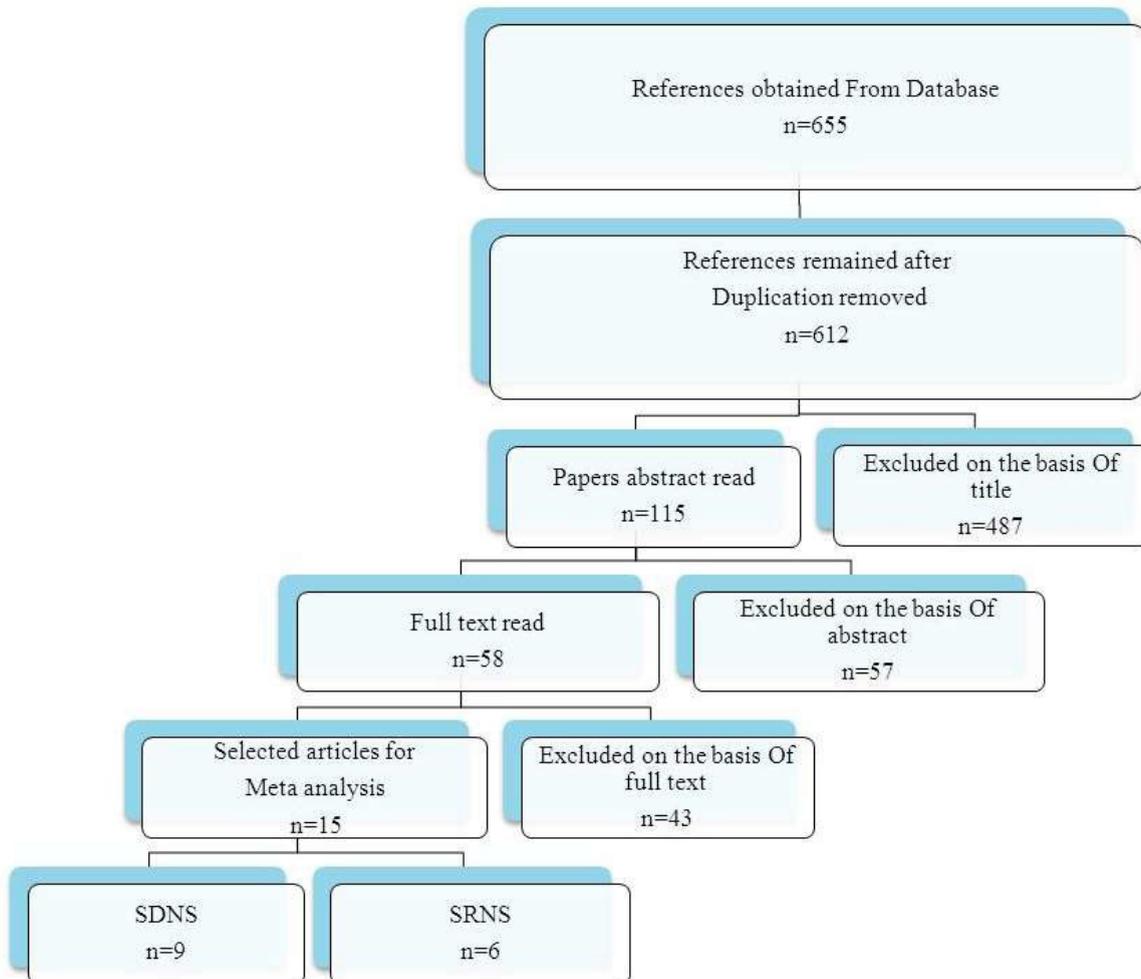


Figure 1 .The trial flow diagram

Table2. Characteristics of studies that evaluated SDNS patients

Trial reference	Date	Study design	No of Population	Relapse rate At 12mo	Mean number Of relapse before Rituximab	Mean number Of relapse after Rituximab	Mean difference (95% CI)
Prytula ³⁰	2010	Retrospective	70	Not reported	Not reported	Not reported	Not reported
Gulati ³¹	2010	Cohort	33	83.3%	4±0.4	0.2±0.3	3.9(3.6-4.1)
Kamei ³³	2009	Prospective	12	Not reported	2.83±1.19	1.08±1.08	Not reported
Kemper ³⁶	2012	Retrospective	37	64.8%	Not reported	Not reported	Not reported
Sinha ³⁵	2012	Retrospective	10	Not reported	3.1±1.1	0.8±1	2.3±1.4 (1.7-3.7)
Ito ⁴⁰	2011	Prospective	9	Not reported	5.7	2.3	Not reported
Ravani ³²	2011	Randomized Clinical Trial	54	18.5% vs48.1% (control)	-	-	OR= 4.08 (1.19-13.9)
Fujinaga ³⁴	2010	Prospective	10	Not reported	4.1±1.7	0.6±0.6	Red rate 86%
Guignonis ³⁷	2008	Prospective	22	9%	Not reported	Not reported	Not reported
Sellier-leclerc ³⁸	2010	Prospective	22	40.9%	Not reported	Not reported	Not reported
Sellier-leclerc ³⁹	2012	Prospective	30	37%	Not reported	Not reported	Not reported

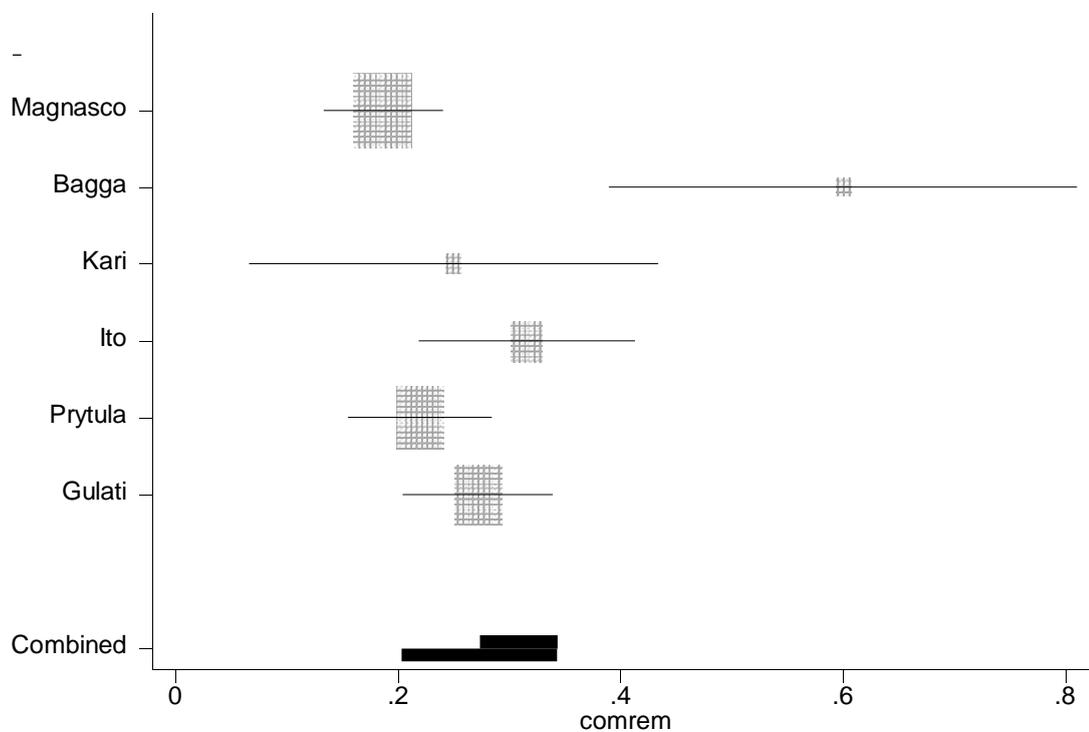


Figure 2. Pooled complete remission prevalence after rituximab therapy in steroid resistant nephrotic syndrome patients

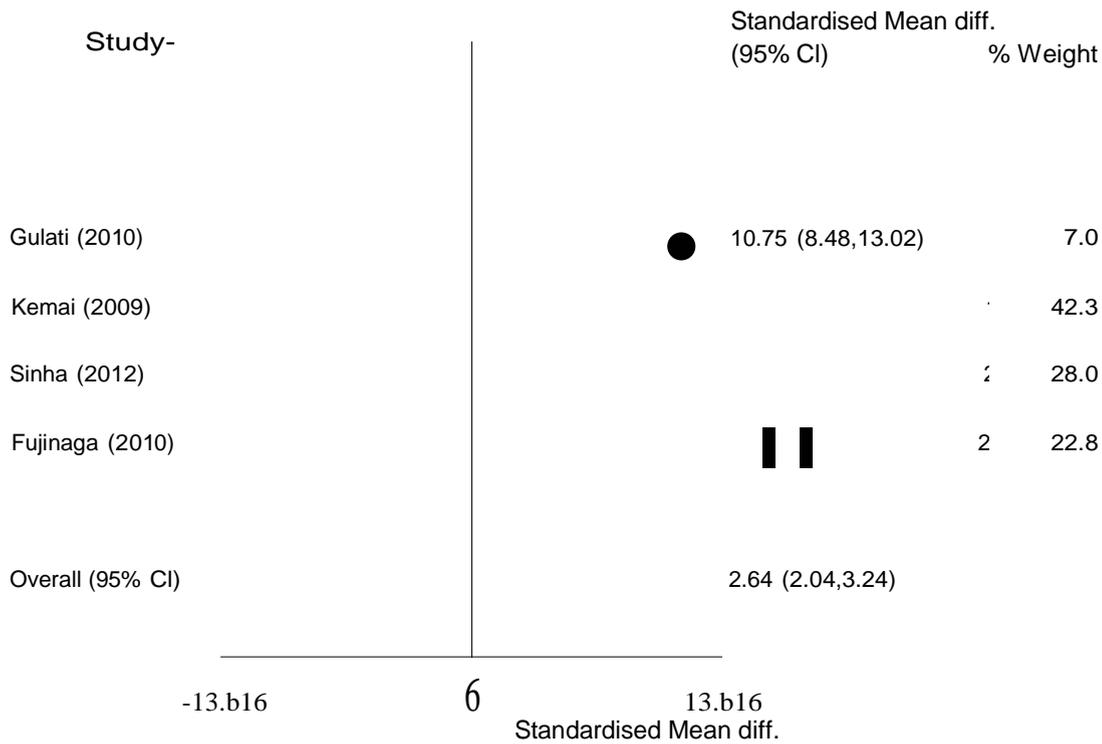


Figure 3. Forest plot of comparison in Steroid dependent nephrotic syndrome patients: after (Rituximab therapy) vs. before (no therapy), outcome: Number of relapse

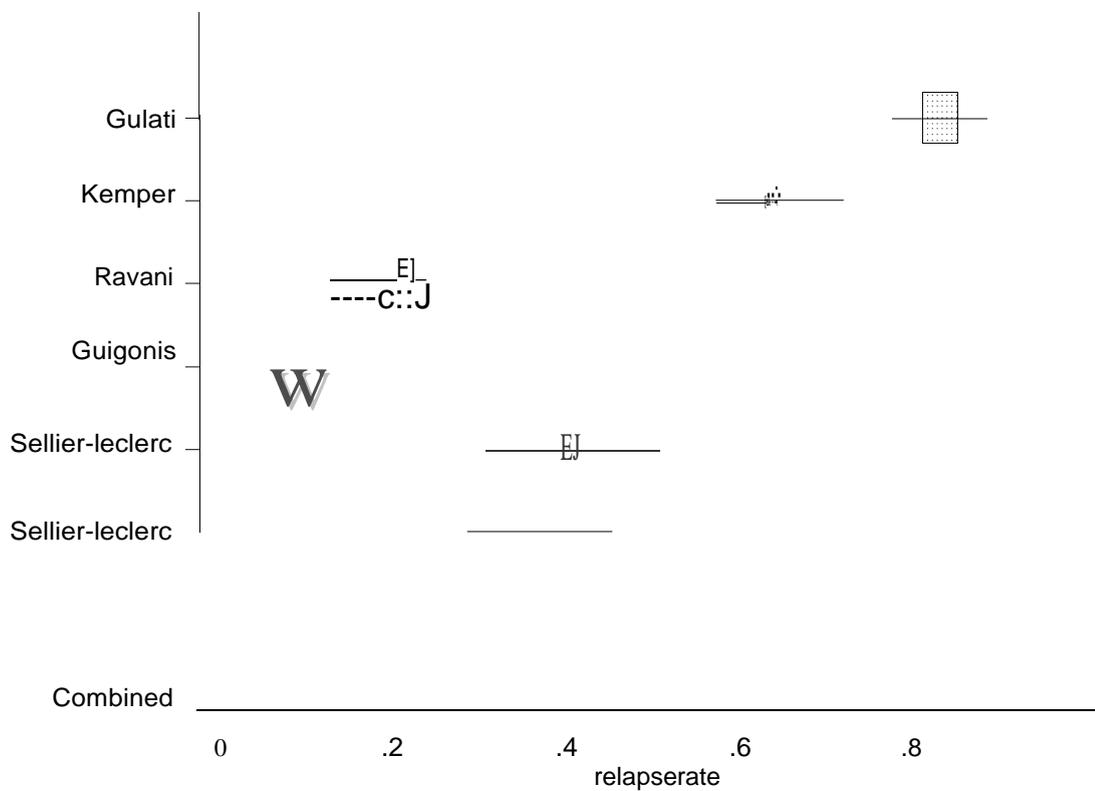


Figure 4. Pooled rate of relapse after rituximab therapy in steroid dependent nephrotic syndrome patients

abdominal pain, mild dyspnea, wheezing, cough, nausea and vomiting, diarrhea, sore throat, bradycardia, tachycardia, hypotension, hypertension, nasal stiffness, leg pain and minor liver dysfunction. Major life-threatening reactions such as sepsis, leukopenia, arrhythmia, anaphylactic reactions, bronchospasm and thrombosis were reported in a minor percentage of the population.

Studies with steroid resistant population (Table 1):

Magnasco in 2012 published an RCT on 31 children under 16 years old with nephrotic syndrome resistant to the combination of prednisone and calcineurin inhibitors. He found that rituximab did not have significant effect on the course of disease as assessed by reducing proteinuria after 3 months of treatment.²⁶

Bagga used four intravenous standard dose of rituximab for five steroid resistant nephrotic children who were refractory to all routine drugs. Six months after therapy, a complete remission was maintained in three patients despite the tapering of doses of corticosteroids and calcineurin inhibitors.²⁷

Kari evaluated the efficacy of single dose of rituximab in a small group of four steroid resistant nephrotic children. Only one patient achieved remission after such therapy. He concluded low efficacy of drug but was unable to add any new insight to previous ideas because of the small size of study.²⁸

Ito reported the efficacy of rituximab weekly injections for the treatment of SDNS/FRNS and SRNS children. He found a complete or partial remission in 6 out of the 17 treated patients.²⁹

Prytula studied efficacy and safety of rituximab in three groups of children including 27 SRNS children and observed a complete and partial remission in 22% and 44% of them, respectively.³⁰

Gulati studied on 33 children with SRNS who did not respond or had toxicity with calcineurin inhibitors and were injected with two to four doses of rituximab. 27.2 percent of patients respond completely and 21.2% partially to this regimen after six months.³¹

The data on the prevalence of complete remission after rituximab therapy were available for these 6 studies (119 patients). Figure 2 shows the pooled prevalence of complete remission after rituximab therapy. As shown in figure 2, the overall pooled is 0.27 (0.2, 0.34) with the range of 0.19 to 0.6. No evidence of publication bias was provided by a funnel plot. The Egger test (P= 0.06) and Begg test (P= 0.07) for publication bias were not statistically significant.

Studies with steroid dependent population (Table 2):

We found 11 studies about steroid dependent nephrotic children, all but one reported the better effect of rituximab. Ravani in an open-label randomized controlled trial divided 54 immunosuppressive dependent nephrotic children into two groups. In control group, they administered prednisolone and calcineurin inhibitor. Rituximab was added to regimen for the intervention group of patients. In the end of the study, the mean proteinuria was 0.36g/d in the control group compared with 0.11g/d in rituximab group, with a reduction rate of nearly 70%.The risk of disease relapse in 3 months was 48.1% in the control group versus 18.5% in the intervention group (odds ratio 4.08).³²

Kamei infused single intravenous dose of rituximab to 12 SDNS children and found that the number of relapses in 6 months period reduced from 2.83 to 1.08 but their follow up revealed that this efficacy was transient.³³

Other articles had relatively similar results. The number of relapses before and after rituximab therapy was reported in four studies including

that of Kamei.³³ The number of relapses decreased from 4 to 0.2 in the study of Gulati³¹, from 4.1 to 0.6 in the study of Fujinaga³⁴ and from 3.1 to 0.8 in that of Sinha³⁵

The data on the number of relapses were available for these 4 studies (56 patients). Three of these reported significant decrease in the number of relapse after rituximab therapy and 1 study reported no significant decrease. The result of a random-effects model for the 4 before- after studies included in the meta-analysis is shown in fig.3. The overall SMD with a 95% confidence interval (CI) is 2.63 (2.03, 3.24), showing that the decrease is modest but significant ($P < 0.0001$) [$I^2 = 82$; $P < 0.001$]. The evidence of publication bias was provided by a funnel plot. The Egger test was significant ($P = 0.02$) for publication bias but not the Begg test ($P = 0.09$).

In six studies including that of Gulati³¹ and Ravani³², the relapse rate after rituximab therapy was reported for comparing the efficacy of treatment. The relapse rate after treatment was reported as 83.3%, 64.8% and 9% by Gulati³¹, Kemper³⁶ and Guignonis³⁷, respectively. Anne-Laure Sellier-Leclerc in two different studies in 2010 and 2012 reported relapse rate as 40.9% and 37%, respectively.^{38, 39}

The data on the rate of relapse after rituximab therapy were available for these 6 studies (162 patients). Figure 4 shows the pooled rate of relapse after rituximab therapy. As shown in fig. 4, the overall pooled is 0.42 (0.15, 0.69) with the range of 0.09 to 0.83. No evidence of publication bias was provided by a funnel plot. The Egger test ($P = 0.57$) and Begg test ($P = 0.27$) for publication bias were not statistically significant.

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Ito et al. in 2011 conducted small prospective cohort studies with a historical control to evaluate the effect of RTX infusion followed by mycophenolate mofetil (MMF) as a maintenance therapy. They reported that the number of patients who relapsed after 1 year of RTX treatment reduced from 5.7 to 2.3 in patients who discontinued MMF and reduced from 4.1 to 0.4 in those who continued to take immunosuppressive drugs including MMF after course of rituximab.⁴⁰

Discussion

Steroid nonresponsive nephrotic syndrome is a long lasting dilemma in pediatric nephrology. Emerging newer patients who are refractory to previous classic drug or intolerant to them pulled us to administer other immunosuppressive agents such as rituximab.¹ In this review, we analyze the results of 15 studies for the efficacy of rituximab in two wide and different subgroups of children, the steroid resistant and the steroid dependent nephrotic patients.

Six studies had found that evaluated SRNS and 11 studies evaluated SDNS, in two studies both groups were evaluated separately. In SRNS children, a complete remission was 0.27 (0.2-

0.34) and in SDNS patients, the overall SMD of the mean number of relapses 12 months after treatment was 2.63 (2.03, 3.24) and the relapse rate after treatment was 0.42 (0.15, 0.69).

We found a reasonable efficacy of the drug in reducing proteinuria and relapse rate.

The common marker for response to therapy in all six studies for SRNS was complete remission. Complete remission was reported from 18.7% to 60% in the different articles. Our pooled data from 119 cases of 6 studies revealed a complete remission prevalence rate of 27%. This percentage of remission is a positive and encouraging result although except for the work of Magnasco²⁶, other studies were case series or cohort and lack any evidence for comparison. However, it was important that the report of Magnasco emphasizes on the low efficacy of drug. We found no other studies to compare RTX with other drugs in children who are resistant to multiple therapeutic agents. But if we balance these results with the response of nephrotic patients who are only steroid resistant, we conclude that this rate of remission is reasonable. In recent studies, the potential of drugs such as cyclophosphamide, cyclosporine and MMF for inducing complete and partial remission in SRNS have reported less than 60% compared with only complete remission rate of 20 – 34% in our pooled data.^{12, 41, 42}

Based on our study, we conclude that rituximab is a reasonable therapy for refractory case of nephrotic syndrome in children until the performance of newer randomized controlled studies.

In the 11 studies extracted for SDNS children, two similar markers were reported.

In four studies, the number of relapses in 12 months after therapy was compared with pre-treatment period. The standard mean difference of 2.64 in total pooled 56 cases means a relatively good effect of drug in the reduction of relapse.

In the six studies, the relapse rate after therapy was assessed. In this setting, the rate of 0.42 relapse per year in all pooled 162 cases was found. It is the number of relapse that changed to less than one episode per year, the satisfying result. Fujinaga reported that after MMF treatment, the mean 12-month relapse rates decreased from 2.5 ± 1.4 to 0.8 ± 1.2 episodes,⁴³ similar results were reported by the others.^{9, 11, 44}

Limitation of study

Our search leads to few studies with low sample size of each work. Five to 37 patients were evaluated in different studies. Only two articles were RCT type and the others were case series or cohort study. These limitations are inevitable in pediatric field of nephrology because of low prevalence of diseases.

We suggest performing multicenter and international randomized controlled study for analyzing the efficacy of RTX in treatment of SRNS and SDNS children.

Conclusion

We found rituximab as an effective therapy for steroid dependent and steroid resistant nephrotic children based on the current published data. But because of the paucity of the randomized study, we are hesitated for newer strong multicenter studies.

Conflict of Interest

None declared.

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None declared.

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