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Efficacy and Safety of rituximab in children with difficult-to-treat nephrotic syndrome; a systematic review

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ABSTRACT

To date, several studies have been done on efficacy and safety of drugs in children with refractory nephrotic syndrome (NS). Rituximab (RTX) might be a hopeful treatment for this syndrome. However, the long-term effects and cost-effectiveness of RTX treatment were not fully assessed. This study aims to do a systematic review about the efficacy and safety of RTX in children with difficult-to-treat NS. For this research, an electronic literature search was conducted to identify appropriate investigations. The search term was ("nephrotic syndrome" or "minimal change disease" or "focal segmental glomerulosclerosis" or membranous) and ("rituximab" or "CD20"). We included all randomized trials and observational studies about using RTX in children with difficult-to-treat NS. Two independent reviewers extracted data from the papers according to the selection criteria. Eligible studies were included in this systematic review. The literature search and reference mining yielded 919 potential relevant papers. We removed 340 articles because of duplication. We also excluded 513 papers after reviewing the titles and abstracts. Finally, 17 studies were included in the systematic review. Efficacy of RTX in children with NS in most of the studies was assessed with relapse-free survival or complete remission rates. Acknowledging the limitations of the study due to the size and nature of the studies included, our systematic review shows that RTX was effective in the treatment of refractory NS in children, and it could reduce the use of steroid and immunosuppressants. However, further large randomized trials are suggested.

Implication for health policy/practice/research/medical education:
RTX was effective in the treatment of refractory NS in children, and it could reduce the use of steroid and immunosuppressants. However, further large randomized trials are suggested.

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Review

Introduction

Nephrotic syndrome (NS) is a complication diagnosed by heavy proteinuria, hypoalbuminemia (serum albumin <2.5 g/dL), often associated with hypercoagulability and dyslipidemia. According to the NS clinical guidelines, for the management of children who develop frequently-relapsing NS (FRNS) or steroid-dependent NS (SDNS), a low-dose alternate day steroid regimen, as the first-line treatment, is prescribed (1). Long-term glucocorticoid use in FRNS/SDNS patients leads to reduced bone mineral density, hypertension, increased infection risks, co-morbidities such as cushingoid habitus, growth retardation, striae and acne, cataracts, pseudotumor cerebri, impaired glucose tolerance and hypercholesterolemia (2). Approximately 20% of children do not respond completely and have steroid-resistant NS (SRNS), and 80%–90% of children with steroid-sensitive NS (SSNS) experience relapses. Among these relapsing children, 50% develop

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SDNS (3). Refractory nephrotic refers to patients with FRNS, SDNS, and SRNS which are difficult to be controlled by variable immunosuppressants (4). Rituximab (RTX) might be a hopeful treatment for refractory NS in children, but the long-term effects and cost-effectiveness of RTX treatment have not been fully assessed (3). Several studies have suggested RTX as a proper drug for the treatment of children with FRNS/SDNS (5-8). This study aims to have a systematic review to identify the efficacy and safety of RTX in children with difficult-to-treat NS.

Methods

We searched Embase, DOAJ (Directory of open access journals), PubMed, the Cochrane Library, Science Direct, Scopus, and Web of Science (updated up to July 2017). Search term was ("nephrotic syndrome" or "minimal change disease" or "focal segmental glomerulosclerosis" or membranous) and ("rituximab" or "CD20"). We scanned bibliographies in relevant papers and conference proceedings. Studies by the same author were checked for possible overlapping participant groups. If the study was reported as duplicate, only the most recent or complete study was comprised. The following selection criteria were applied; we included all randomized trials and observational studies about using RTX in children with difficult-to-treat NS.

Data extraction and quality assessment

Two independent reviewers extracted data from the papers according to the selection criteria. Disagreements were resolved by discussion between two reviewers considering the opinion of a third reviewer. The following information was abstracted from each contained investigation; first author and year of publication, design of investigation, sample size, mean age of individuals, intervention regime, follow-up duration, and outcome measures for each group. All the analysis were based on previously published investigations. Hence, no ethical approval or patient consent was required.

Results

Search results and characteristics

The literature search and reference mining yielded 919 potential relevant papers. We removed 340 papers because of duplicate publication. We also excluded 513 papers after reviewing the titles and abstracts while they were books, book sections, and review papers. Thus, they were not relevant. Then, we reviewed full-text of selected articles and removed 49 studies because the topics were not relevant to the subject. Finally, 17 investigations were included in the systematic review (4-20). The flow diagram of study selection is shown in Figure 1. Characteristics and the details of the studies are illustrated in Table 1.

Outcome

The summary of outcomes of our study is provided in Table 2. Efficacy of RTX in children with NS in most of the studies was assessed with relapse-free survival or complete remission rates. In a study (5), reduction of median yearly number of relapses with use of RTX was reported (5). Some of the studies reported biochemical indicators such as proteinuria (14).

Discussion

Almost all studies showed that RTX was effective in the treatment of refractory NS in children, and it could

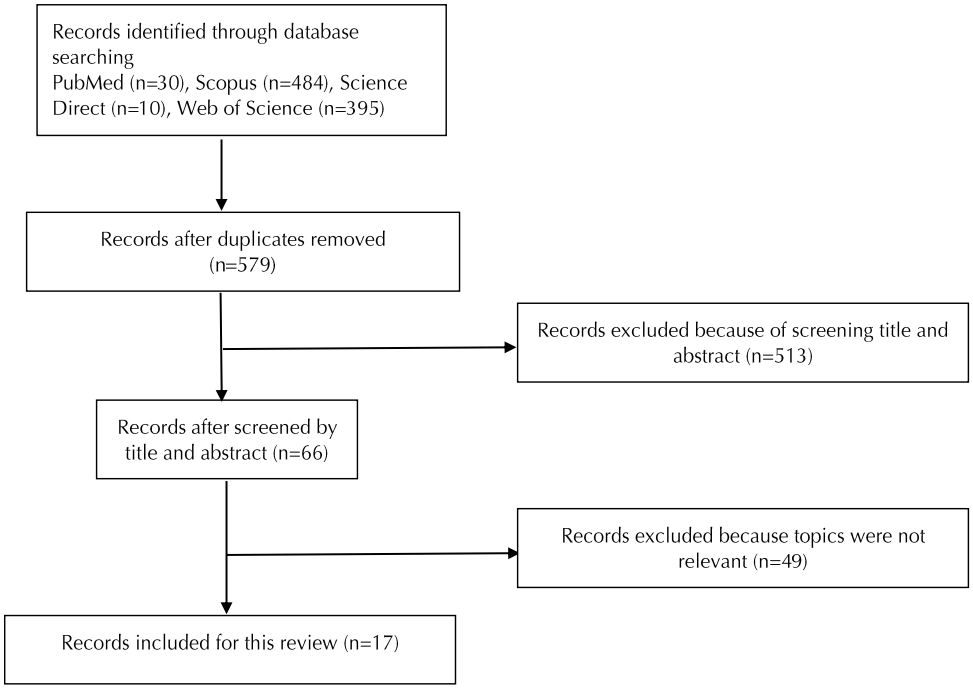

Figure 1. Flow-chart of study selection process.

Table 1. General characteristics of trials included in this systematic review

Reference	Name	Year	Country	Study design	Group		Frequency		Age (Year)		Sex (Male)	
					Case	Control	Case	Control			Case	Control
4	Van Horebeek, I.	2017	Belgium	Retrospective	RTX		9		16.08		NR	
5	Webb, H.	2016	UK	Retrospective	RTX	Cyclophosphamide	8	59	Case= 7.5	Cont=6	87%	66%
6	Niu, X. L.	2016	China	Before-after	RTX		19		8.21		10	
7	Suyama, K.	2016	Japan	Before-after	RTX, low-dose cyclosporine		5		13.9		3	
8	Kamei, K.	2016	Japan	Retrospective	RTX		114		9.45		76	
9	Grenda, R.	2016	Poland	Retrospective	RTX		5		8.5			
10	Colucci, M	2016	Italy	Retrospective	RTX		28		13.68		18 (64.%)	
11	Chan, C. Y.	2016	Singapore	Retrospective	RTX		22		14.4			
12	Sinha	2015	India	Retrospective	RTX		193		10.9		123	
13	Ravani	2015	Italy	RCT	RTX prednisone	Prednisone	15	15	Case=6.96	Control=6.96	11 (73%)	10 (67%)
14	Basu, B.	2015	India	Retrospective	RTX	MMF	24		7.8		15	
15	Sun, L.	2014	China	Case series	RTX		12					
16	Sato, M.	2014	Japan	Retrospective	RTX		30		13.6		12	
17	Kimata, T.	2014	Japan	Case series	RTX		5		6.3		3	
18	Kamei	2014	Japan	Case series	RTX		10		8		NR	
19	Iijima	2014	Japan	RCT	RTX	Placebo	20	23	Case=11.5	Control=13.6	18 (75%)	16 (67%)
20	Tellier, S.	2013	France	Retrospective	RTX		18		NR		NR	

NR, Not reported.

Table 2. Outcome of studies

Ref.	First author	Type	Follow-up Period (month)	Relapse-free survival	Complete remission events	Side effect	Result
5	Van Horebeek I	MCD=8 FSGS=1	33				RTX is effective for treatment of difficult-to-treat SDNS. It reduces the median yearly number of relapses
6	Webb H	Case: MCD=5 FSGS=1 Control: MCD=9 FSGS=2	12		Long-term remission (2 year) Case=32% Control=24%	Case: Allergic Reaction=2 Control: Neutropenia=3 Hemorrhagic cystitis=1	RTX was tried on children with difficult-to-treat FRSDNS. Longer remission time and less side effects than cyclophosphamide were reported
7	Niu XL	MCD	28.1	The number of relapses also decreased significantly	10	None	RTX was found to be an effective and safe treatment choice for children with SDNS
8	Suyama K	FSGS	3		2	None	Low-dose cyclosporine RTX is effective in FSGS patients with SRNS. It may improve the side-effects of Prednisolone and immunosuppressive drugs
9	Kamei K	MGA=92 FSGS=18 DMP=3				Agranulocytosis = 11 Acute infections = 9	RTX can be a cause of agranulocytosis in patients with refractory idiopathic NS
10	Grenda R	FSGS=2 MesPGN=2 MCNS=1	29		2	Severe recurrent bacterial infections = 1 Acute lung injury = 1	The anti-CD20 monoclonal antibody may not be effective in all pediatric patients with rapid post-transplant recurrence of NS. The ratio of benefit to risk should precisely be balanced
11	Colucci M		11.2		14		Assessment of switched memory B cell recovery after RTX may help to anticipate relapse in patients with nephritic syndrome
12	Chan CY	FSGS	26.7		12		They diagnosed prognostic markers that describe a subset of patients with FSGS having an immunologic signature, which represents hypo-responsiveness to T cell stimulation. RTX is thus more effective.
13	Sinha A		12		Sustained remission: 59		RTX is safe and effective in decreasing relapse rates and need for immunosuppressive drugs in cases with steroid-dependent and calcineurin inhibitor dependent SRNS
14	Ravani P		12	Case=14 Control=1		Nausea and skin rash were reported during infusion in the RTX group; transient acute arthritis was observed in one case	Three-month proteinuria was 42% less in the RTX group, with no statistical significance. For the treatment of juvenile SDNS, RTX was non-inferior to steroids

Table 2. Continued

15	Basu B	MCD=13 FSGS=11	12		25% (6/24)	Dizziness and mild dyspnea = 1 Respiratory tract infections = 2	MMF may be a safe and effective maintenance therapy after RTX induction, as an additive immunosuppressant, to maintain remission in children with refractory SRNS
16	Sato M	MCD=11 FSGS=2	27.6			Mild acute infusion reaction=15 Agranulocytopenia=1	The number of relapses considerably decreased following RTX therapy. It may also improve the growth and obesity indexes in some patients with steroids severe side effects
17	Kimata T	MCD=4 FSGS=1	21			Mild respiratory distress=1	Following RTX therapy, the frequency of relapses considerably decreased, and the steroid-free period was notably extended. Repeated RTX in children with SDNS may be an effective therapy option
18	Kamei K				7	Agranulocytosis =1; Severe pneumonia=1; Cough =4; respiratory disturbance =3; hypoxemia = 3; abdominal pain =2; rash =2; wheezing =1; sore throat =1; nausea=1; hypertension, n=1	Additional RTX along with immunosuppressive agents and conventional methylprednisolone is a encouraging treatment
19	Iijima K	FSGS=2 FSGS=1 MCD=21 MCD=23	12	Case=6 Control=1		Case=Number of adverse events= 357 Infection=23 Infusion reaction=19 Control= Number of adverse events=251 Infection=18 Infusion reaction=13	The median of relapse free period was substantially higher in the group treated by RTX than the placebo group. RTX is a safe and effective treatment for childhood-onset, SDNS and complicated FRNS
20	Tellier S		38.4	4		Infections=4 Neutropenia=1 Flare ups of psoriasis=1 Behavioral disorders=1	This study confirms the safety and efficacy of RTX in the treatment of SDNS

MCD: Minimal Chang Disease, FSGS: Focal segmental glomerulosclerosis, SDNS: Steroid-dependent nephrotic syndrome, FRSDNS: Frequent relapses or steroid dependence nephritic syndrome, FRNS: Frequently relapsing nephrotic syndrome (More than one relapses of nephrotic syndrome within size months following the initial remission, or more than three relapses within any 12-month period), SRNS: Steroid-resistant nephrotic syndrome

decrease the use of immunosuppressants and steroid. Only one study concluded that RTX might not be effective in all pediatric cases of rapid post-transplant recurrence of NS, and they suggested that before deciding to use this protocol, the ratio of benefit to risk should carefully be balanced on an individual basis (10).

In this systematic review, 17 studied were included, but only two of them were randomized clinical trials (most of them were retrospective studies without control groups), hence we could not do a quantitative synthesis (meta-analysis). In recent year, some review articles have been published on use of RTX in treating childhood NS. The results of a review article regarding efficacy and safety of RTX in treating childhood NS were similar to our results. That study concluded significant gradual benefits for the treatment of NS by adding RTX to corticosteroid and/or calcineurin inhibitors. In safety data they collected, RTX has a limited number of adverse effects; they showed that the most common of them occurred during the infusions, but that study included only randomized control trials and is thus different from our study (1). In our investigation, some studies such as (19) clearly explained the side effects of RTX (19). Another meta-analysis study showed that for childhood refractory NS, RTX might be a promising treatment (3). They showed that RTX also made a higher rate of complete remission, and reduced the proteinuria in patients, but they expressed that the long-time effects and cost-effectiveness of RTX treatment were not fully determined. They suggested additional studies to address these issues (3). They included only four studies in their meta-analysis. One of their studied sources was done only in adults (contrary to our studies) in which the authors systematically summarized and analyzed data from preexisting studies reporting the outcome of RTX (RTX) treatment in relapsing minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS). They concluded that in frequently relapsing and SDNS due to MCD and FSGS, RTX is effective in reducing the proportion of relapses and sparing immunosuppression. They showed that during treatment with RTX, proteinuria decreased from 2.43 (0–15) g/d to 0 (0–4.89) g/d ($P < 0.001$), while serum albumin increased from 2.9 (1.2–4.6) at baseline to 4.0 (1.8–5.09) g/L ($P = 0.001$), but in most of children studies we reviewed, similar data had not been reported. In the review article of (21), the authors suggested confirmation of their finding by further controlled and prospective studies (21).

Conclusion

Acknowledging the limitations of this study due to the size and nature of the references included, our systematic review shows that RTX has been effective in the treatment of refractory NS in children, and it could reduce the use of steroid and immunosuppressants. However, further large randomized trials are suggested.

Authors' contribution

AA, YR, HMM, SBA, SN, ME and MRK were involved in drafting the manuscript and revising it critically for important intellectual content. MF revised the manuscript critically for important intellectual content. All authors read and signed the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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