Rituximab in the Treatment of Nephrotic Syndrome
A Systematic Review

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Recently, the role of B cells in the pathogenesis of nephrotic syndrome is explained by some researchers. It has also been shown that the anti-CD20 antibody, *rituximab*, may be an option in the treatment of these patients. In this systematic review, we performed extensive search and identified studies on rituximab use in children with nephrotic syndrome. There are some case reports as well as larger series in this regard. The majority of these case reports and series have demonstrated the success of rituximab in the treatment of nephrotic syndrome, especially in pediatric patients with steroid-dependent and frequent-relapsing nephrotic syndrome. Nevertheless, the treatment strategies before and after rituximab infusion are not clear to date. On the other hand, it is believed that positive results on rituximab use in nephrotic syndrome are much more reported by researchers than the negative results and this is an important bias. Although most reports on rituximab use in pediatric patients have not recognized significant side effects, the long-term adverse events of rituximab are not known. Thus, controlled long-term studies are required to be done to assess the risk-benefit profile of rituximab in childhood nephrotic syndrome.

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Review

INTRODUCTION

Rituximab is a monoclonal antibody against CD20 antigens of premature and mature B cells. This antigen is only expressed on B cells in high levels. Once bound to CD20, rituximab can inhibit proliferation and differentiation of B cells and ultimately death of these cells. Rituximab destroys B cells through 3 mechanisms: complement-dependent cytotoxicity, antibody dependent cytotoxicity, and apoptotic pathway.[1] There is evidence for contribution of B cells to the pathogenesis of nephrotic syndrome. The permeability factor in focal segmental glomerulosclerosis p`atients may be an immunoglobulin fragment.[2-4] One-third of minimal change nephrotic syndrome patients have immunoglobulin deposits in the mesangium of kidney biopsy.[5] Another piece of evidence is that both B-cell and T-cell activation occur in relapse of steroid-sensitive nephrotic syndrome. Kemper and colleagues have shown activation of both soluble CD23 (a marker of B-cell activation) and soluble CD25 (a marker of T-cell activation) in children with relapse.[6] Additionally, it is apparent that B cells have some functions other than antibody production, including lymphoid tissue development, regulation of T-cell and dendritic cell functions by cytokine production, and T lymphocytes activation. Memory B-cell depletion due to rituximab can prevent the activation of autoreactive T cells. Thus, this medicine affects both B cells and T cells. Studies have also shown that some CD20+ T cells are a target for rituximab. This explains the effects of rituximab on T cell function. This function on T cells may help nephrotic syndrome patients to gain recovery by rituximab.

METHODS

Extensive search was done for this systematic review using the MeSH and non-MeSH terms on the PubMed for the relevant articles. Additional search was done in the EMBASE, the Cochrane Central Register of Controlled Trials (Cochrane Library), and reference lists of the retrieved articles. The key words were *nephrotic syndrome*, *pediatric*, *children*, and *rituximab*.

RESULTS

Rituximab in Nephrotic Syndrome

Treatment of steroid resistant-, dependent-, and frequent-relapsing nephrotic syndrome (SRNS, SDNS, and FRNS, respectively) is a challenging problem in children, despite some alternative medications such as cyclophosphamide, levamisol, cyclosporine, and mycophenolate mofetil. These therapeutic problems, in addition to the complications of these alternative medications have resulted in the use of other medications such as rituximab.

There are several reports about the use of rituximab in children with nephrotic syndrome. It seems that the effects of rituximab are better in SDNS and FRNS rather than in steroid-resistant nephrotic syndrome.[7,8] The majority of studies have shown some benefits of rituximab in SDNS and steroid-sensitive nephrotic syndrome (SSNS). Most of these studies focused on the use of rituximab in patients with cyclosporine failure or toxicity. In these reports, rituximab was effective to prevent relapses, to discontinue steroid, and to reduce other immunosuppressive medications. In a recent open-labeled randomized trial, 54 children with steroid or calcineurin dependency were randomized into 2 treatment protocols[9]: patients who received prednisolone and calcineurin inhibitors and those who received rituximab and low-dose prednisolone and calcineurin inhibitor. They showed the degree of proteinuria and relapse rates were significantly reduced in rituximab-treated children. Sixty-three percent of the children who treated with rituximab were drug-free at 3 months, compared with 4% of children treated with steroid and calcineurin inhibitors alone. This trial shows promising results for treatment of children with steroid and calcineurin inhibitor dependency.[9] In contrast, Sinha and colleagues reported a retrospective study and compared the children who received 2 to 3 doses of rituximab with the patients who received tacrolimus for12 months.[7] They found the same efficacy regarding the relapse rates. However, the studies focusing on rituximab use in nephrotic syndrome have reporting bias. It is possible that studies with positive results are more likely to be reported, and many patients with negative response to rituximab are not reported. Thus, there is a need for further studies and registries, especially clinical trials in order to confirm recommendations of the use of rituximab in SRNS children.

When and How to Start Rituximab

The starting dose of rituximab is varying in studies focusing on nephrotic syndrome; thus, we do not know the optimal initial dose of rituximab in SDNS and FRNS patients. It is also not clear whether the patients need a single dose or multiple doses of rituximab infusion in the beginning. Some studies suggested weekly infusion of 375 mg/m^2 of rituximab for 4 weeks, which is similar to the protocol being used in patients with B-cell lymphoma. Some other reports have recommended 2 weekly doses of the same or even only a single dose of 375 mg/m^2. However, it appears that more than one dose of rituximab at the initiation is less associated with relapses in future than a single dose. Additionally, it seems that a single-dose infusion of rituximab induces short-term remission in comparison with more doses at initiation of treatment. A recent study from Japan has shown the complete response to rituximab in all 12 patients with single-dose rituximab, but relapse occurred in most patients at a median of 129 days.[5]

Another problem is the time of rituximab starting in these patients. Most of studies on the use of rituximab in SDNS and FRNS have been done on patients with cyclosporine failure or toxicity. We still do not know if it is better to start rituximab before or after immunosuppressive therapies (cyclophosphamide, cyclosporine, etc). Meanwhile, a more important point is to administer rituximab in proteinuria-free phase. It is believed that the effect of rituximab is lower in proteinuria phase, which may be due to some causes. A significant amount of anti-CD20 antibodies is lost in urine in proteinuria phase,[10] which results in lower serum rituximab levels and faster recovery of B cells.[11] In addition, the noncirculating B cells do not fall completely in these patients despite complete

circulating B cell depletion in the peripheral circulation. In proteinuria phase, it might be needed to administer further doses of rituximab to deplete noncirculating B cells even more.

Repeated Doses of Rituximab

One of the most important problems is the relapse of nephrotic syndrome several months after rituximab infusion. Even though long-term remission was reported in some patients with the first rituximab infusion, most patients experience relapse 9 to 12 months after the initial rituximab infusions. Most studies have shown that the relapses are usually associated with the increase in CD19 cells, necessitating additional rituximab use to continue the suppression of B cells.[11] A suggested protocol is to administer 2 to 4 rituximab doses at the beginning and repeat doses when peripheral CD19 cell counts increase to more than 1%.[12] In another protocol suggested by Guigonis and colleagues,[11] the repeated doses of rituximab depend on the occurrence of relapses in the first 6 months after rituximab treatment. If there is any relapse during the first 6 months of treatment, they suggest additional doses of rituximab for duration of 18 months CD19 cells suppression.

In contrast to abovementioned studies, some other studies have shown that not all patients relapse despite the increase in CD19 cells,[11] and it is also possible that the relapses occur despite sustained B cell suppression. Thus, these studies believe that factors other than the number of circulating B cells are also responsible for these relapses. This may be due to the lack of association between circulating B cells and the number of these cells in other compartments (noncirculating B cells). B cells in nonperipheral compartments are more resistant to rituximab-induced depletion and have important roles in response to rituximab and the relapse raters.[13] These types of B cells may not be detected completely by the measurement of circulating B cells. Thus, we cannot propose a precise therapeutic strategy for rituximab re-infusion based on the circulating CD19 cells changes. We need more studies about the role of B cells in nephrotic syndrome, especially B cells subtypes. Preliminary studies have assessed the changes of the B cell subclasses in different times after rituximab infusion in nephrotic patients. It seems that the time of regeneration of memory B cells (CD27) is more associated with the relapse time in comparison with the circulating total B cells.[14] Identification of accurate roles of different types of B cells in nephrotic syndrome relapse may help the clinicians to predict the relapse in the future; however, this needs more investigations. Now it is suggested that repeat doses of rituximab be administered based on clinical symptoms, and not the number of circulating B cells.[12] Table 1 shows the studies performed on SDNS and FRNS children treated with rituximab. This table also shows the patients who needed additional doses of rituximab. These additional doses were often tolerated. Most studies have shown the efficacy of repeated doses of rituximab in the treatment of relapses and some studies have not.[12] However, the long-term efficacy and complications of these repeated doses are unclear. It seems that the repeated doses of rituximab may induce antibodies that are responsible for rituximab resistance. New generations of humanized anti-CD20 antibodies do not have this problem. We need more studies to determine the guidelines and protocols for repeated doses of rituximab in nephrotic syndrome.

Strategies to Reduce Relapses After Rituximab Administration

There are some suggestions for reduction of relapses in nephrotic children treated with rituximab. It appears that more initial rituximab doses (1 to 2 versus 3 to 4 doses) can reduce future relapses and extend the remission period.[15] Although some studies have shown the efficacy of only 1 dose of rituximab, the duration of this remission is short and lower than 1 year in most of cases.[16]

Some authors also suggest the use of mycophenolate mofetil after initial rituximab administration for maintenance of remission in patients. Mycophenolate mofetil may eliminate the need to repeat rituximab infusions,[17,18] and consequently reduces the side effects of its repeated doses. Sharma and Filler reported a case treated with rituximab and mycophenolate mofetil. Relapse did not occurred in this patient despite the increase in CD19 cells.[17] Ito and colleagues also performed a cohort study and followed 9 patients who received mycophenolate mofetil after rituximab infusion and 7 patients as the control group without mycophenolate mofetil administration

Table 1. Studies Focusing on the Use of Rituximab in Steroid-dependent and Frequent-relapsing Nephrotic Syndrome

Study	n	Response			Starting Dose	Relapse	Median Time to Relapse	Response of Relapses	Conclusion
		Complete	Partial	No					
Guigonis et al[10]	20	19	0	0	375 mg/m^2, 2 to 4 doses per week	3	…	…	Rituximab is effective in steroid-dependent patients, especially in combination with other immunosuppressive drugs and during a proteinuria-free period.
Kamei et al[16]	12	12	0	0	375 mg/m^2, single dose	9	4 mo	Varied	Single-dose rituximab is effective in refractory steroid-dependent patients for a short time.
Smith et al[31]	1	1 (9 mo)	0	0	375 mg/m^2, single dose	0	…		Single-dose rituximab is recommended for steroid-dependent patients.
Sellier-Leclerc et al[32]	30	30	0	0	Initial 375 mg/m^2/w (1 to 4 doses), repeated doses for 15 months; B cell depletion	12	…	B cell depletion in 10 patients	Long-term B cell depletion for 15 mo leads to long-term remission after rituximab cessation in two-thirds of patients.
Kemper et al[15]	37	26 (> 1 y)	0	0	375 mg/m^2/w (1 to 4 doses)	24	9 mo	Long-term remission in 20 patients	Time to first relapse is significantly shorter in patients receiving 1 or 2 versus 3 or 4 doses at initiation.
Prytula et al[8]	28	23	0	3	375 mg/m^2/w (1 to 4 doses)	13	6 mo	…	There was a high response rate to initial rituximab infusion.
Benz et al[33]	1	1 (13 mo)	0	0	375 mg/m^2, 4 doses	0	…	…	…
Beco et al[34]	1	1 (14 mo)	0	0	375 mg/m^2, 2 doses	0	…	…	…
Gilbert et al[35]	1	1 (1 y)	0	0	375 mg/m^2, 4 doses	1	12 mo	…	Relapse was documented with rising in B cells
Fujinaga et al[19]	10	10	0	0	375 mg/m^2, single dose	5	…	…	Relapse was seen in patients with cyclosporine discontinuation after rituximab infusion.
Hofstra et al[36]	1	0	1	0	1000 mg, 2 doses	…	…	…	…
Gulati et al[7]	24	20	0	0	375 mg/m^2, 2 doses	3	…	…	…
Dallocchio et al[37]	1	1 (> 1 y)	0	0	375 mg/m^2, 3 doses	0	…	…	…

after rituximab. They found that the number of relapses were significantly lower in patients who treated with the combination of rituximab and mycophenolate mofetil within 1 year of treatment (0.4 versus 2.3, $P < .005$). Additionally, the amount of daily prednisolone dose was significantly less in patients treated with mycophenolate mofetil and rituximab than patients who treated with rituximab alone (0.11 mg/kg/d versus 0.46 mg/kg/d, $P < .05$).

In another study, the continuation of cyclosporine after single dose rituximab has been shown to maintain remission despite reduction of prednisolone dose.[19] We need clinical trial to show the efficacy of mycophenolate mofetil and cyclosporine in continuation of remission in patients receiving rituximab. In these clinical trials we should measure the serum mycophenolate mofetil or cyclosporine levels to determine the best dose of these medicines for maintaining remission. Another important point in these patients is the rate of steroid tapering. There is time lag between rituximab infusions and the onset of its effects. This time is usually between 2 to 4 weeks and is longer if rituximab is infused in proteinuria phase and may reach to 10 weeks.[20] Thus it is suggested that the steroid full dose is administered following rituximab administration and for 4 weeks and then tapering is started slowly.[19]

Rituximab in Steroid-resistant Nephrotic Syndrome

Rituximab is also suggested for SRNS patients by some studies. The number of studies on the use of rituximab in SRNS children is low with variable results. Some studies have not reported convincing response to rituximab in patients with SRNS,[21-23] while other studies have shown complete or partial response in SRNS children treated with rituximab.[24] The optimal dose in SRNS patients is not clear. The recommended dose has been 375 mg/m^2 as a single dose in some case series, but this dose was not effective or was associated with delayed response.[24] Another important drawback in studies on the use of rituximab in SRNS is to lack of genetic study before rituximab administration. It seems the conflict between these studies is due to no exclusion of patients with podocytopathy who are resistant to all immunosuppressive medicines. The degree of sclerosis in kidney biopsy at the time of rituximab administration is another important point to determine the response to rituximab in SRNS patients. Patients with more than 80% sclerosed glomeruli have shown no response to rituximab.[12] Table 2 shows the studies on the use of rituximab in SRNS children.

Side Effects of Rituximab

It seems that rituximab infusion is safe and well tolerated in most pediatric patients. More than 500 000 patients have received rituximab for different diseases worldwide to date.[25] A few side effects have been reported in these patients. These side effects are mostly mild and transient and often happened during intravenous infusion. The infusion-related complications are due to nonehumanized anti-CD20 antibodies and usually occur in the first infusion and do not recur after that. These complications include fever, chills, rashes, bronchospasm, hypotension, and anaphylaxis. These infusion-related symptoms can be relieved by premedication with steroid and antihistamin. Infections are also other complications of rituximab. It is suggested to administer cotrimaxazole as prophylaxis for *Pneumocystis carni* for 6 months.[22] Some serious complications such as progressive multifocal leukoencephalopathy have been reported in systemic lupus erythematosus patients who received this medicine, but it is still not clear whether this complication is due to systemic lupus erythematosus or due to rituximab.[26]

Rituximab has also been associated with respiratory complications such as interstitial pneumonitis, acute respiratory distress syndrome, and fatal pulmonary fibrosis, although the frequency of these complications is unknown. Kamei and colleagues have been found 32 reports with a total of 62 cases with respiratory side effects of rituximab. It seems these respiratory side effects are more common in elderly people and in the patients with a previous pulmonary disease.[27] There have been 2 reports in children with SRNS that show rituximab induces respiratory involvement.[27-29] Other reported side effects of rituximab include ulcerative colitis[30] and hypogammaglobinemia requiring intravenous immunoglobulin administration.[28] Some articles suggest monitoring of hypogammaglobinemia in patients treated with rituximab and substitution, if necessary. Even though serious complications due to rituximab are not expected, all nephrologists must

Table 2. Studies Focusing on the Use of Rituximab in Steroid-resistant Nephrotic Syndrome

Study	N	Response			Starting dose	Relapse	Time to Relapse	Conclusion
		Complete	Partial	No				
Makiko et al[23]	2	2	0	0	375mg/m^2, single dose	2	5 and 8 mo	Rituximab is effective in steroid-resistant cases. No relationship was found between re-increase in B cells and relapse.
Jameela et al[21]	4	1	0	3	375mg/m^2, single dose	1	1 mo	Single-dose rituximab is not effective in steroid-resistant cases despite complete B cell depletion.
Prytula et al[8]	17	11	0	3	Single dose, 2 or 4 weekly doses	9	5 mo (median)	A high response rate was reported by this multicenter study
Bagga et al[22]	5	4	1	0	375 mg/m^2, 2 doses	1	6 mo	Rituximab may be a promising treatment in steroid-resistant nephrotic syndrome.
Suri et al[38]	1	1	0	0	375 mg/m^2, 4 doses	0	...	...
Gulati et al[7]	33	9	7	17	375 mg/m^2, 4 doses	3	...	...
Guigonis et al[10]	2	0	...	...	375 mg/m^2, 2 to 4 weekly doses	...	...	Rituximab is not effective in steroid-resistant nephrotic syndrome patients.

be familiar with these side effects and consider the possibility of these complications in their patients. Additionally, there is a need for clinical trials to determine the safety of this drug, especially in long term. In the future, the use of humanized forms of these antibodies will reduce the infusion-related allergic reactions.

CONCLUSIONS

Rituximab is used since 2006 as a promising treatment of nephrotic syndrome. Rituximab has reduced proteinuria or induced complete remission in most studies. It has improved the response to steroid and cyclosporine in these patients. On the other hand, this medicine is an important steroid-sparing agent. Nonetheless, the studies focusing on the use of rituximab in nephrotic syndrome have some problems. There is a publication bias, because positive response to rituximab has usually been reported by most authors. It is strongly possible that some physicians have administered rituximab for their patients without response, but they have not reported their results. Additionally, we still do not know when we should start rituximab in patients with SDNS and SRNS and have no guidelines on dose and duration of treatment. We need more studies to determine the dose of re-treatment of rituximab in relapses. We also cannot predict the side effects, especially long-term complications.

To overcome these problems, we need to collect all data worldwide by setting up a registry. Clinical trials and long-term studies are also needed to examine the safety and efficacy of rituximab in children with nephrotic syndrome, especially in long-term period. In this case, we will be able to recommend rituximab as a routine treatment of nephrotic syndrome in the future if the results of these trials are promising. We might also consider rituximab as a substitute for cyclophosphamide and cyclosporine, both of which have significant short-term and long-term side effects.

CONFLICT OF INTEREST

None declared.

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