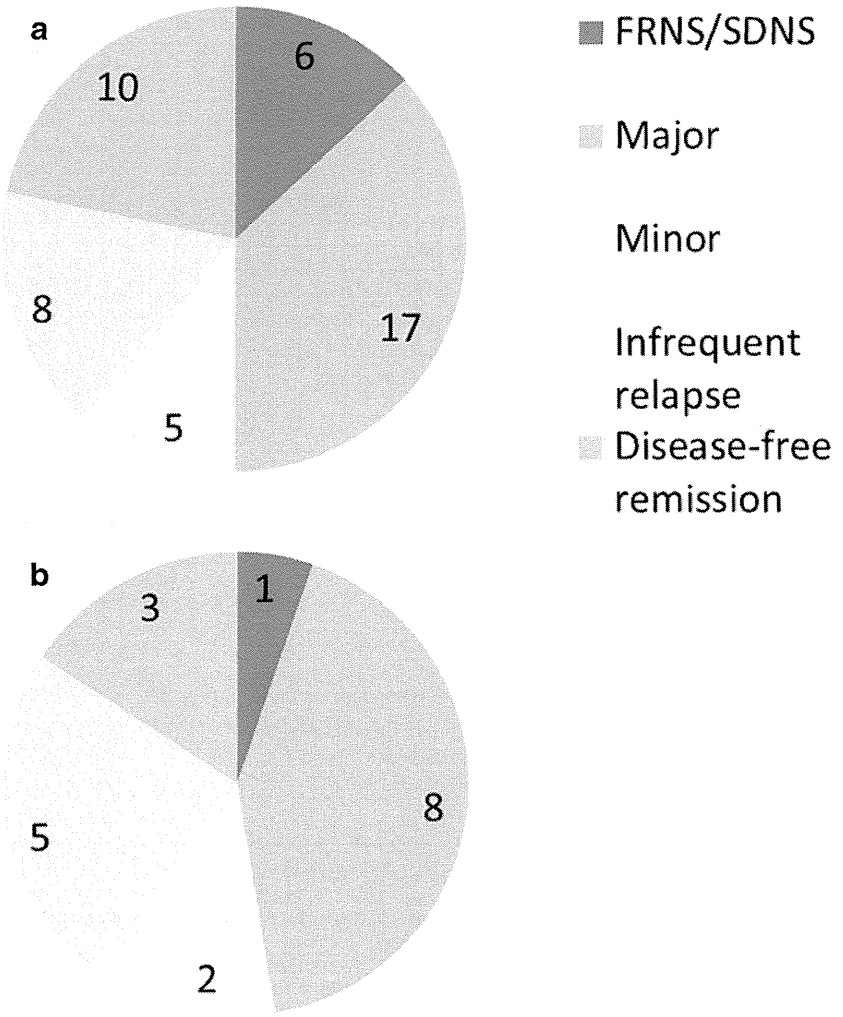

Fig. 2 Relapse of nephrotic syndrome at last observation. **a** All patients (n=46), **b** patients aged ≥18 years (n=19). *FRNS* Frequently relapsing nephrotic syndrome, *SDNS* steroid-dependent nephrotic syndrome, *Major* major immunosuppression (use of immunosuppressants, including cyclosporine or high-dose mizoribine ≥300 mg/day for the control of FRNS/SDNS at last observation), *Minor* minor immunosuppression (use of regular-dose mizoribine <300 mg/day at last observation), *Infrequent relapse* relapse during the last 2 years but not to the extent to be defined as FRNS/SDNS, *disease-free remission* no relapse for at least 2 years before the time of last observation without immunosuppressants and steroids

Table 2 Proportional odds model of contributing factors for relapse at last observation

Variable	Odds ratio	95 % CI	p value
Relapse during RCT			
Yes	2.89	0.84–9.98	0.09
No	1.00		
Age at onset of NS			
Continuous	0.96	0.82–1.12	0.57
CPM before RCT			
Yes	1.43	0.40–5.08	0.58
No	1.00		
SDNS before RCT			
Yes	1.57	0.43–5.70	0.49
No	1.00		

In this proportional odds model analysis, the outcome variable had three levels: (1) low, disease-free remission; (2) medium, infrequent relapse and minor immunosuppression; (3) severe, FRNS/SDNS and major immunosuppression.

CI, confidence interval; NS, nephrotic syndrome; RCT, randomized controlled trial; CPM, cyclophosphamide; SDNS, steroid-dependent nephrotic syndrome

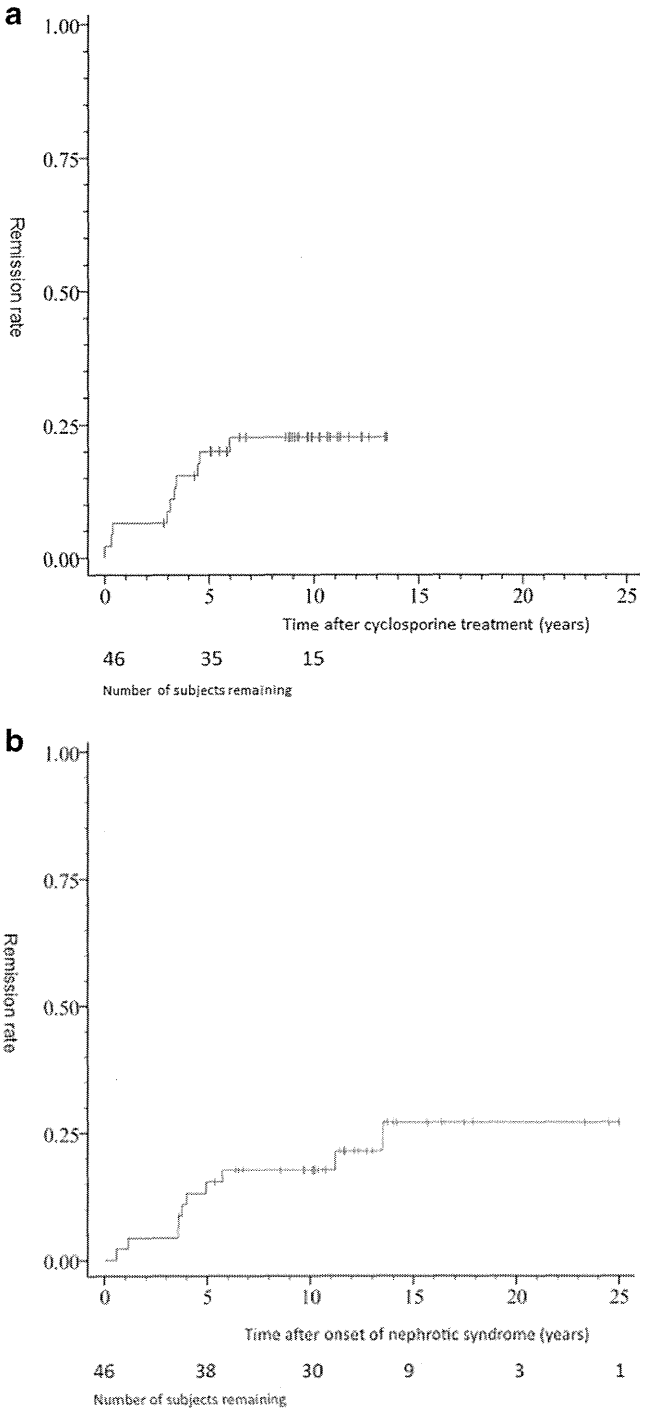

Fig. 3 Time to disease-free remission from the start of protocol treatment (**a**) and from the onset of nephrotic syndrome (**b**). The 10-year remission rate from the start of protocol treatment and from the onset of nephrotic syndrome was 22.7 and 17.7 %, respectively

child-onset FRNS under current therapy should be regarded as a long-term condition which extends beyond adolescence and into adulthood.

We also analyzed a number of risk factors for long-term morbidity, including relapse during the treatment protocol with cyclosporine, age at onset of nephrotic syndrome, administration of cyclophosphamide before protocol treatment and steroid dependency before protocol treatment. None of the factors included in the model was statistically significant, while recognizing that the sample size was relatively small. We previously showed that patients who experience relapse during treatment with cyclosporine are at high risk of relapse during the first 2 years after its discontinuation [16]. Although the effect of relapse during the treatment protocol on long-term relapse was not significant in our present follow-up study, there was a possible suggestion of an association (odds ratio 2.89, $p = 0.09$). Given the paucity of other long-term findings, risk stratification based on this issue can be suggested. Age at onset has been shown to predict outcome in several studies [6, 8, 17, 18], with most showing that younger age was a risk for poor outcome. While age at onset was not significant in our study (odds ratio 0.96, $p = 0.57$), it was at least in the same direction. Since younger patients are also more vulnerable to problems in growth and development, they require particular attention when it comes to long-term management. In contrast, in terms of the effect of cyclophosphamide administration and steroid dependency before protocol treatment on relapse, our results were inconclusive and possibly non-significant. On this basis, initial treatment of FRNS with cyclosporine or cyclophosphamide appeared to have no significant effect on long-term outcome. The finding that steroid dependency was not associated with long-term relapse is consistent the results of our previous study in which steroid dependency was not a risk factor for relapse during the treatment protocol with cyclosporine [19] or in the first 2 years after its discontinuation [16].

Despite the high relapse rate among our patients, we observed no lethal events, no decrease in renal function and/or no development of SRNS, which is consistent with the results of earlier long-term studies [6–9, 18]. Although confirmatory biopsy at last observation was not performed, no renal dysfunction due to cyclosporine was seen in any patient. In fact, recent clinical trials, including the earlier RCT of the present follow-up study, show that 2-year administration of cyclosporine with blood concentration monitoring for children with FRNS is safe with regard to nephrotoxicity, with only 6.5–20.0 % of children experiencing mild nephrotoxicity [10, 19, 20]. The current prognosis of SSNS is good, regardless of the occurrence of relapse over the long term. Nevertheless, a number of participants in our cohort experienced adverse effects from the treatment, particularly due to corticosteroids. The mean height SD score was above −2 SD, but six patients had severe growth failure, with a minimum of −4.7 SD. Similar results were observed for body weight, with four patients having a BMI of>97th percentile of the Japanese reference value. Osteoporosis or decreased bone mineral density was also frequent in these patients. Importantly, stratification of adverse effects by main outcome showed that, with the exception of one patient with obesity, all cases of adverse

Table 3 Adverse effects stratified by main outcome

Adverse effects	FRNS, Major	Others	Total	*p*
Excessive body weight (obesity)[a]	6 (3)	1 (1)	7 (4)	0.10 (0.61)
Short stature	6	0	6	0.02
Osteoporosis (decrease in BMD)	6	0	6	0.02
Cataract	3	0	3	0.23
Hypertension	2	0	2	0.49
Glaucoma (increase in IOP)	1	0	1	1.00
Epilepsy	1	0	1	1.00
Psychosis (transient)	1	0	1	1.00
Femur head necrosis	1	0	1	1.00

Major, Major immunosuppression (use of immunosuppressants, including cyclosporine or high-dose mizoribine ≥300 mg/day for the control of FRNS/SDNS at the last observation); BMD, bone mineral density; IOP, intraocular pressure; FRNS, frequently relapsing nephrotic syndrome; SDNS, steroid-dependent nephrotic syndrome

[a] Value in parenthesis refers to obesity

effects occurred in the 23 of our 46 patients with the more severe outcomes of FRNS/SDNS or the need for major immunosuppression, with these effects having the potential to severely impact the quality of life of these patients. These results confirm the critical importance of controlling relapse over the long term, with particular attention to maintaining a minimal adverse effects profile well beyond any initial period of treatment.

Importantly, no currently available immunosuppressant is able to provide a long-term cure of nephrotic syndrome. Fakhouri et al. found that cyclosporine itself was a risk factor [6], albeit only on univariate analysis, with the association lost on subsequent multivariate analysis. This finding should also be considered in view of the methodological issues mentioned above. In their multivariate analysis using a linear regression model, Ruth et al. identified the administration of cyclosporine as the only predictive covariate for relapse of nephrotic syndrome in adulthood, although their study design prevented the assigning of a causal relationship [7]. Regarding other agents, cyclophosphamide and rituximab also cannot maintain remission. Relapse after cyclophosphamide therapy has been reported [8, 21], and a recent study reported disappointing results, with a 5-year relapse-free survival rate of only 13 % [22]. Similar limitations have been reported with the emerging drug rituximab [23, 24], and no long-term data are available for other new drugs, such as mycophenolate mofetil or tacrolimus. Several studies of rituximab in severe FRNS are now ongoing (UMIN000001405, UMIN000001406 [http://www.umin.ac.jp/ctr/index.htm], Clinicaltrials.gov NCT 01268033 [http://www.clinicaltrials.gov/ct2/show/NCT01268033]), but these will not provide long-term results for many years.

Several limitations warrant mention. First, although adverse effects in the present follow-up study were mostly attributed to prednisolone, the association of adverse effects with treatment was not absolutely clear. Data on the cumulative dosage of prednisolone and other immunosuppressants were not available. Moreover, some of these problems may have been attributable to disease activity and related conditions, such as frequent admission. Second, cyclosporine was not the initial treatment in all patients; this means that the population was not fully homogenous. Third, the nine children who dropped out were older and may have therefore had a different severity of disease, which would have introduced some bias. Fourth, interpretation of the results was hampered by the use of mizoribine, which has not yet been established as a treatment of FRNS in children [1]; high-dose mizoribine may nevertheless have sufficient efficacy [25, 26], and we accordingly classified it as "major immunosuppression." Fifth, the age standard for bone mineral density on DEXA was based on Japanese data [12], which may not be applicable in other countries. Finally, our analysis was limited to information from the 2-year period before the last observation, except for the last relapse and some information regarding immunosuppressant use, which were followed throughout the entire period. In addition, the administration of immunosuppressants and their control during the follow-up period was ultimately decided at the discretion of the physician in charge, and data on dose and trough level throughout the entire follow-up period were not comprehensive. Nevertheless, the design of our follow-up study provides valuable insights into long-term outcome in children with FRNS.

In conclusion, after 2-year treatment with cyclosporine, the majority of children with FRNS continued to experience relapses of nephrotic syndrome at 10 years after the treatment protocol, namely, beyond adolescence and into adulthood. Outcome in terms of survival and renal function was favorable. Our findings suggest that these patients require an adaptive, well-planned treatment strategy for long-term management into adulthood which avoids both the complications of disease and the adverse effects of treatment. Considering the

relatively low prevalence of renal toxicity of cyclosporine, a longer treatment protocol with cyclosporine may be an option, particularly for those who experience relapse during cyclosporine treatment. Like cyclosporine, current new treatments, such as rituximab, are not curative. The discovery of new treatments with a curative mechanism is eagerly anticipated.

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RENAL (R PAREKH, SECTION EDITOR)

Rituximab Treatment for Nephrotic Syndrome in Children

Kazumoto Iijima · Mayumi Sako · Kandai Nozu

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Abstract In the past 10 years, many reports have suggested that rituximab, a chimeric anti-CD20 monoclonal antibody, is effective for children with complicated, frequently relapsing or steroid-dependent nephrotic syndrome (FRNS/SDNS). However, those reports were case reports, case series, retrospective surveys, and single-arm or short-term trials. Therefore, well-designed controlled trials are required to establish the value of rituximab in this condition. To evaluate the efficacy and safety of rituximab in childhood-onset, complicated FRNS/SDNS, a multicenter, double-blind, randomized, placebo-controlled trial was carried out by the Research Group of Childhood-onset Refractory Nephrotic Syndrome (RCRNS) in Japan (RCRNS01). RCRNS01 showed that rituximab is safe and effective for the treatment of childhood-onset, complicated FRNS/SDNS. In 2014, the use of rituximab for patients with complicated FRNS/SDNS was approved, first in the world, by the Ministry of Health, Labour and Welfare, Japan.

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Keywords Rituximab · Nephrotic syndrome · Frequently relapsing · Steroid-dependent · Multicenter, double-blind, randomized, placebo-controlled trial

Introduction

Children afflicted with nephrotic syndrome lose proteins to urine, resulting in hypoproteinemia and generalized edema. Idiopathic nephrotic syndrome occurs in two or more children out of 100,000 [1] and is the most common chronic glomerular disease in children. Many patients have minimal change nephrotic syndrome, and most respond well to steroid therapy, but up to half of them develop frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome (FRNS/SDNS) [2]. A total of 10–20 % of idiopathic nephrotic syndrome patients show steroid resistance (steroid-resistant nephrotic syndrome: SRNS), defined as persisting proteinuria after a 4-week course of oral steroids [2]. Standard treatments for FRNS/SDNS are immunosuppressive agents, such as cyclophosphamide, chlorambucil, cyclosporine (CyA), and levamisole, and CyA is often used for treatment of SRNS [3–5]. Most affected children are helped by these drugs; however, some still show complicated clinical courses. A total of 10–20 % of children with FRNS/SDNS on CyA have frequent relapses [6, 7], and approximately 30 % of childhood SRNS patients have steroid-sensitive frequent relapses after achievement of complete remission [8]. In addition, CyA can cause side effects, especially chronic nephrotoxicity [9, 10], suggesting that CyA treatment should be discontinued after its long-term use. However, discontinuing CyA almost always results in frequent relapses or steroid dependence, requiring long-term steroid therapies, which also pose a long-term risk to children. Collectively,

at least 10–20 % of children with idiopathic nephrotic syndrome still show frequent relapses or steroid dependence under or after immunosuppressive therapies. We have defined these conditions as "complicated FRNS/SDNS". Additionally, approximately 2–3 % of children with idiopathic nephrotic syndrome show resistance for steroids and any immunosuppressive agents, which is defined as "refractory SRNS", posing a high risk of end-stage renal failure (Table 1). Therefore, development of new treatments for complicated FRNS/SDNS and for refractory SRNS is urgently needed.

Rituximab Treatment for Nephrotic Syndrome

Rituximab is a chimeric anti-CD20 monoclonal antibody, which inhibits CD20-mediated B-cell proliferation and differentiation, resulting in depletion of peripheral blood B lymphocytes. This drug was developed for the treatment of B-cell non-Hodgkin's lymphoma and is now indicated for the treatment of patients with autoimmune diseases, including rheumatoid arthritis, Wegener's granulomatosis, and microscopic polyangiitis [11, 12].

Table 1 Definitions of terms in nephrotic syndrome

Frequent relapsing nephrotic syndrome (FRNS)	Two or more relapses within 6 months after initial remission or 4 or more relapses within any 12-month period
Steroid-dependent nephrotic syndrome (SDNS)	Two consecutive relapses during the reduction of steroid therapy or within 2 weeks of discontinuation of steroid therapy
Steroid-resistant nephrotic syndrome (SRNS)	When the daily administration of prednisolone at 60 mg/m^2/day does not lead to remission within 4 weeks
Complicated FRNS/SDNS	(1) Diagnosed with frequent relapse (FRNS) or steroid dependence (SDNS) after completion of immunosuppressive drug therapy (such as cyclosporine, cyclophosphamide, mizoribine, or mycophenolate mofetil) (2) Diagnosed with frequent relapse (FRNS) or steroid dependence (SDNS) during immunosuppressive drug therapy (such as cyclosporine, cyclophosphamide, mizoribine, or mycophenolate mofetil) (3) With a history of steroid resistance and diagnosed with frequent relapse or steroid dependence during or after the completion of immunosuppressive drug therapy (such as cyclosporine or combination of cyclosporine and methylprednisolone)
Refractory SRNS	When the combination of steroids and immunosuppressive agents including calcineurin inhibitors does not lead to remission

In the past 10 years, there have been anecdotal reports of rituximab being effective for nephrotic syndrome. In 2004, a patient suffering from SDNS complicated with idiopathic thrombocytopenic purpura underwent rituximab treatment, resulting in long-term remission of nephrotic syndrome and idiopathic thrombocytopenic purpura [13]. In 2005, Nozu et al. reported that rituximab treatment induced long-term remission in recurrent nephrotic syndrome and posttransplant lymphoproliferative disorder after renal transplantation [14]. The findings from their report were confirmed by Pescovits et al. in 2006 [15]. However, other reports have shown that none of the patients treated with rituximab achieved remission in recurrent nephrotic syndrome after renal transplantation [16]. Bagga et al. reported three complete and two partial remissions in five patients with refractory SRNS receiving rituximab [17]. Kamei et al. treated 10 children with refractory SRNS with additional rituximab and methylprednisolone pulse therapy. Seven patients achieved complete remission and preserved normal renal function without proteinuria [18]. Although other case reports and case series, as well as the above-mentioned reports, have suggested that rituximab treatment is effective in some patients with refractory SRNS [19–24], there is no evidence that rituximab is effective in patients with refractory SRNS. Indeed, Magnasco et al. reported the results of an open-label, randomized trial including 31 children with refractory SRNS who received calcineurin inhibitors and prednisolone, and 16 of them received an additional two rituximab infusions. However, proteinuria remained unchanged in rituximab-treated patients and none of them had partial or complete remission [25].

Several case reports and case series, as well as survey studies, have suggested that rituximab is effective for patients with complicated (difficult to treat) FRNS/SDNS, allowing discontinuation or reduction steroids and/or immunosuppressants [22, 24, 26–30]. Recent relatively large case series have also shown promising results. Ravani et al. treated 46 children with idiopathic nephrotic syndrome maintained in remission with steroids and calcineurin inhibitors (i.e., complicated FRNS/SDNS) with one to five rituximab courses. They found that the 6-month probability of remission was 48 % after the first remission [31•]. Ruggenenti et al. reported the effects of rituximab therapy followed by immunosuppression withdrawal on disease recurrence in 30 patients (including 10 children) with complicated FRNS/SDNS. In their report, participants received one or two doses of rituximab, and all of them were in remission at 1 year [32•]. Ravani et al. conducted an open-label, randomized, controlled trial to examine the short-term effects of rituximab in children with steroid- and

calcineurin-dependent nephrotic syndrome (i.e., complicated FRNS/SDNS). They concluded that rituximab and lower doses of prednisone and calcineurin inhibitors are non-inferior to standard therapy in maintaining short-term remission [33•]. Taken together, these findings suggest that rituximab is effective for children with complicated FRNS/SDNS. However, these studies were case reports, case series, retrospective surveys, and single-arm or short-term trials. Therefore, well-designed controlled trials are required to establish the value of rituximab in this condition.

A Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of Rituximab Therapy for Childhood-Onset Complicated FRNS/SDNS

To evaluate the efficacy and safety of rituximab in childhood-onset complicated FRNS/SDNS, a multicenter, double-blind, randomized, placebo-controlled trial was carried out by the Research Group of Childhood-onset Refractory Nephrotic Syndrome (RCRNS) in Japan (RCRNS01) (Clinical Trials Registry ID: UMIN000001405). At the same time, an open-label, multicenter, pharmacokinetic trial (RCRNS-02) (Clinical Trials Registry ID: UMIN000001406) was also carried out. These two trials were investigator-initiated clinical trials, which sought to gain approval from the Ministry of Health, Labour and Welfare, Japan to make rituximab available for patients with childhood-onset complicated FRNS/SDNS. These trials were supported by a Health and Labor Sciences Research Grant for the Large Scale Clinical Trial Network Project (CCT-B-2001). The study design of RCRNS01 is shown in Fig. 1. The protocol for RCRNS01 is available at http://www.med.kobe-u.ac.jp/pediat/pdf/rcrn01.pdf. When patients developed relapse of nephrotic syndrome, they underwent a screening examination and were registered once their eligibility, including steroid sensitivity, was verified. The rituximab group received intravenous rituximab of 375 mg/m^2 body surface area (maximum 500 mg) once weekly for 4 weeks, and the placebo group received placebo at the same frequency. Prednisolone treatment was gradually discontinued after obtaining remission, and patients were treated with prednisolone when they developed relapses during the study period. Tapering of the CyA dose was started on day 85, and the drug was discontinued by day 169. Other immunosuppressive agents were discontinued by day 85. All of the patients were observed for 1 year, unless the patients dropped out of the study. Patients were considered to have treatment failure if (1) relapse occurred by Day 85, (2) FRNS or SDNS was diagnosed between Day 86 and Day 365, or (3) steroid resistance was diagnosed during the observation period. The primary endpoint was the relapse-free period. The secondary endpoints were time-to-treatment failure, relapse rate, time to FRNS/SDNS, and steroid dose after randomization. Safety endpoints, including frequency and severity of adverse events, were also evaluated. A gold standard, double-blind, placebo-controlled trial was adopted because the use of rituximab in treatment of nephrotic syndrome was not yet approved in any country. In the trial, treatment failures were defined, and in the event that patients had treatment failure, the allocation code was urgently disclosed. If patients were allocated to the placebo group, they were able to enter a separately conducted rituximab pharmacokinetic trial (RCRNS02) after discontinuation or completion of RCRNS01.

Sixty-three patients were screened, and 52 were randomized. Twenty-seven patients were allocated to the rituximab group and 25 to the placebo group. Twenty-four patients in each group (total 48) received the intervention

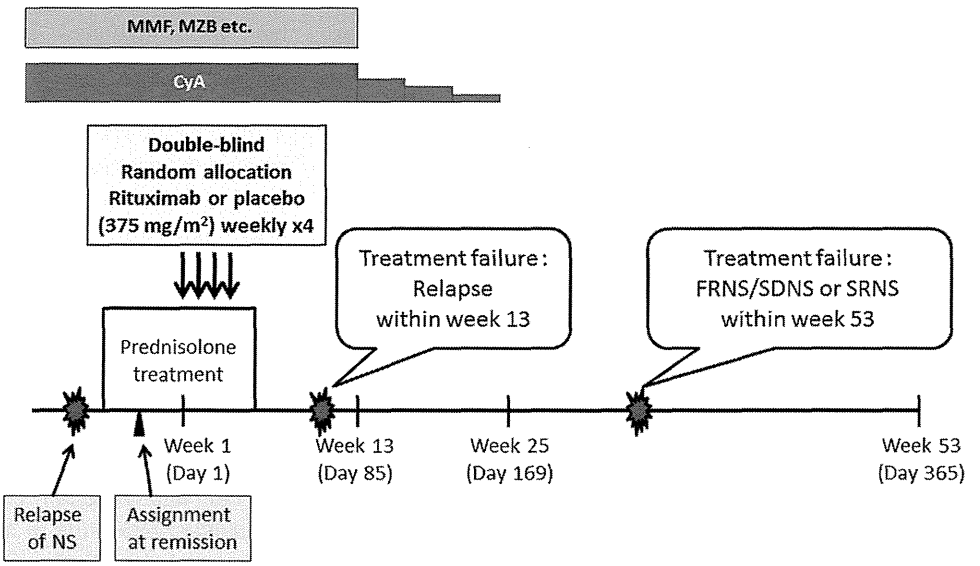

Fig. 1 Study design. *NS* nephrotic syndrome, *MMF* mycophenolate mofetil, *MZB* mizoribine, *CyA* cyclosporine

and were included in the analysis on an intention-to-treat basis. Four patients from the rituximab group and 20 from the placebo group had discontinued the intervention, mostly because of treatment failure. However, no patients dropped out of the study before the first relapse (the primary endpoint). All of the patients with treatment failure in the placebo group were enrolled into RCRNS02 after discontinuation ($N = 18$) or completion ($N = 2$) of RCRNS01. Baseline characteristics were similar between the two groups. All of the patients were treated with steroids and/or immunosuppressants at relapse immediately before assignment. Over 70 % of patients reported side effects from steroid treatment.

By the end of the observation period, relapses were reported in 17 patients in the rituximab group and 23 in the placebo group. The 50 % relapse-free period was 267 days [95 % confidence interval (CI) 223–374 days] in the rituximab group and 101 days (95 % CI 70–155 days) in the placebo group. This relapse-free period was significantly longer in the rituximab group than in the placebo group (hazard ratio [HR] = 0.267, 95 % CI 0.135–0.528, $p < 0.0001$). Treatment failure was reported in 10 patients in the rituximab group and 20 in the placebo group. The time-to-treatment failure was significantly longer in the rituximab group than in the placebo group (HR = 0.268, 95 % CI 0.122–0.589, $p = 0.0005$), and the relapse rate was significantly lower in the rituximab group than in the placebo group (1.542 [29/18.81] vs. 4.171 [46/11.03] per person-years, HR = 0.370, 95 % CI 0.231–0.591, $p < 0.0001$). Significantly, fewer patients in the rituximab group experienced frequent relapses or steroid dependence compared with those in the placebo group (HR = 0.169, 95 % CI 0.061–0.464, p = 0.0001). The daily steroid dose after randomization in the rituximab group was significantly lower than that in the placebo group (9.12 ± 5.88 vs. 20.85 ± 9.28 mg/m^2/day, $p < 0.0001$). The majority of adverse events that were reported were mild and no deaths were reported. Although the rate of serious adverse events was higher in the rituximab group than in the placebo group (42 % [10/24] vs. 25 % [6/24]), but this difference was not significant (Fisher's exact test, $p = 0.3587$). Mild infusion reactions were reported more frequently in the rituximab group (79 % [19/24]) than in the placebo group (54 % [13/24]), but this difference was not significant (Fisher's exact test, $p = 0.1246$). No Grade 3 or 4 infusion reactions were reported in either group. In conclusion, rituximab is safe and effective, at least for 1 year, for the treatment of childhood-onset, complicated FRNS/SDNS [34••].

Based on the results from RCRNS01 and RCRNS02, the use of rituximab for patients with complicated FRNS/SDNS was approved, for the first time, by the Ministry of Health, Labour and Welfare, Japan on August 29, 2014.

Safety of Rituximab

More than 500,000 patients worldwide have received rituximab. Serious adverse events have occurred in only a limited number of these patients, while in the majority of patients, rituximab is safe and well tolerated [35]. However, notably, there have been several reports on serious adverse events related to rituximab. Progressive multifocal leukoencephalopathy is a serious adverse event of rituximab (http://www.fda.gov/safety/medwatch/safetyinformation/safetyrelateddruglabelingchanges/ucm123013.htm). Fetal hepatitis by reactivation of hepatitis B virus is also a serious adverse event induced by rituximab [36]. In recent studies of patients with complicated nephrotic syndrome who had been taking rituximab, a pediatric patient died because of pulmonary fibrosis [37]. Kamei et al. also reported that respiratory events, such as cough, bronchospasm, and dyspnea, are relatively common as adverse effects of rituximab [38]. Sellier-Leclerc et al. reported a patient with fulminant myocarditis due to enterovirus who underwent heart transplant surgery [39]. Additional severe adverse effects reported in childhood nephrotic syndrome include Pneumocystis carinii pneumonia [28, 40] and severe immune-mediated ulcerative colitis [41]. These complications might have been underestimated in the literature. Although long-term safety data on anti-CD20 therapy are broadly reassuring, a mortality rate of 3 % has been reported in the 3 years following its initiation in patients with a variety of autoimmune diseases [42], mainly due to infection. The long-term consequences of rituximab infusions in children are not known.

Mechanisms of Rituximab in Nephrotic Syndrome

The exact pathogenesis of nephrotic syndrome is unknown, but T-cell-mediated immunological abnormalities are thought to play a role [43]. A number of studies have shown that B cells promote T-cell activation, mediate antibody-independent autoimmune damage, and provide co-stimulatory molecules and cytokines, which can sustain T-cell activation in autoimmune diseases [44–47]. Rituximab induces inhibition of B-cell proliferation and B-cell apoptosis [48]. This action leads to B-cell depletion, and thus suppression of B-cell–T-cell interactions, which might prevent recurrence of nephrotic syndrome. Impaired regulatory T (T-reg) cell function in patients with minimal change nephrotic syndrome and induction of remission in nephrotic syndrome by T-reg cells have been previously reported [49–51]. Rituximab may induce an increase in the number and function of T-reg cells [52]. Rituximab-maintained remission in nephrotic syndrome might be due to restoration of T-reg cell function.

Fornoni et al. recently reported that rituximab directly binds to an acid sphingomyelinase-like phosphodiesterase 3b on the cell surface of podocytes, resulting in stability of podocyte structure and function [53]. This may lead to prevention of recurrent focal segmental glomerulosclerosis. Whether a similar mechanism functions in complicated FRNS/SDNS remain to be determined.

Conclusions and Future Perspectives

Rituximab is a promising option for the treatment of complicated FRNS/SDNS. However, this drug does not cure nephrotic syndrome because all of the patients in the RNRNS01 trial had relapsed by 19 months [34••]. To extend the relapse-free period, further modification of rituximab therapy, including repeated courses and adjunct immunosuppressive therapies, may be necessary. Indeed, a multicenter, double-blind, randomized, placebo-controlled trial to examine the efficacy and safety of mycophenolate mofetil after rituximab therapy for treatment of complicated FRNS/SDNS in children will be started in 2015 in Japan. Moreover, comparison of the efficacy, safety, and cost-effectiveness of various rituximab dosing regimens and B-cell-driven regimens remains to be examined [54]. Further studies are required to examine the long-term effects of rituximab use, particularly in children. A retrospective long-term follow-up study of patients enrolled in RCRNS01 and RCRNS02, focusing on clinical courses, treatments after the clinical trial, growth, and late adverse effects, will be carried out soon in Japan. At present, there is no evidence that rituximab is effective in patients with refractory SRNS. However, Kamei et al. recently reported that additional rituximab combined with conventional methylprednisolone pulse therapy and immunosuppressive agents is a promising option for overcoming refractory SRNS [55]. A multicenter, single-arm trial to examine efficacy and safety of rituximab combined with methylprednisolone pulse therapy and immunosuppressive agents will be started in 2015 in Japan.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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特集：ネフローゼ症候群

ネフローゼ症候群におけるリツキシマブ治療の現状

—微小変化型を中心に—

Rituximab for the treatment of nephrotic syndrome

飯島一誠

Kazumoto IIJIMA

はじめに

リツキシマブはB細胞表面に発現する分化抗原CD20に対するモノクローナル抗体であり，分子標的治療薬の一つである。その本質は，ヒト免疫グロブリンの定常部領域(IgG1κ)とマウス抗CD20抗体の可変部領域から成るキメラ型の抗CD20モノクローナル抗体である。

リツキシマブはCD20陽性のB細胞を特異的に傷害することから，B細胞の異常に起因する各種疾患に有効とされ[1,2]，国内ではCD20陽性のB細胞性非ホジキンリンパ腫(B細胞性リンパ腫)への適応の承認を取得しており，最近，ウェゲナー肉芽腫症および顕微鏡的多発血管炎の適応が追加承認された。B細胞性リンパ腫の治療薬としては，日米欧など世界100カ国以上で承認されている。さらに欧米では，抗TNF治療抵抗性の難治性関節リウマチの治療薬としても承認されている。

本稿では，ネフローゼ症候群に対するリツキシマブ療法の現状について，微小変化型を呈することの多い小児難治性頻回再発型/ステロイド依存性ネフローゼ症候群(FRNS/SDNS)を中心に概説し，今後の展開についても述べる。

小児ネフローゼ症候群に対する標準治療とその問題点

小児の特発性ネフローゼ症候群の初期治療薬が副腎皮質ステロイド薬(以下，ステロイド)であることは世界的にもコンセンサスが得られている。ステロイド投与により80～90％は完全寛解となり，ステロイド感受性ネフローゼ症候群と呼ばれる。一方，残りの10～20％はステロイド投与にもかかわらず蛋白尿が持続するステロイド抵抗性ネフローゼ症候群(SRNS)である。ステロイド感受性ネフローゼ症候群は，組織型としては大半が微小変化型であり，ほとんど腎不全に進行することはなく腎予後は良好であるが，その40～50％は頻回に再発する頻回再発型ネフローゼ症候群(FRNS)となり，そのうちの約70％はステロイドの減量に伴い再発を繰り返すステロイド依存性ネフローゼ症候群(SDNS)である。FRNSやSDNSでは，長期のステロイド投与に伴う種々の副作用が出現しやすく，ステロイドの減量中止を目的に免疫抑制薬が用いられることが多い。一方，SRNSは，そのまま高度蛋白尿が持続すると末期腎不全に進行する可能性が非常に高いため，寛解導入を目的に，やはり何らかの免疫抑制薬が用いられる。

日本小児腎臓病学会学術委員会は，「小児特発性ネフローゼ症候群薬物治療ガイドライン1.0版」を改訂した「小児特発性ネフローゼ症候群診療ガイドライン2013」[3]を2013年9月に作成したが，そのなかで，FRNS/SDNSの免疫抑制薬治療として，シクロスポリン，シクロホスファミド，ミゾリビンの3剤のいずれかの使用を推奨している。またSRNSに対しては，シクロスポリンあるいはシクロスポリンとステロイドパルス療法の併用を推奨している。

上記のごとく，FRNS/SDNSの治療として，シクロスポリン，シクロホスファミド，ミゾリビンのいずれかが用いられることが多いが，これらの薬剤を用いても頻回再発型あるいはステロイド依存性のままでステロイドからの離脱ができない患者が少なからず存在する。実際，3剤のなかで最もステロイドからの離脱の確率が高いと思われるシク

神戸大学大学院医学研究科内科系講座小児科学分野

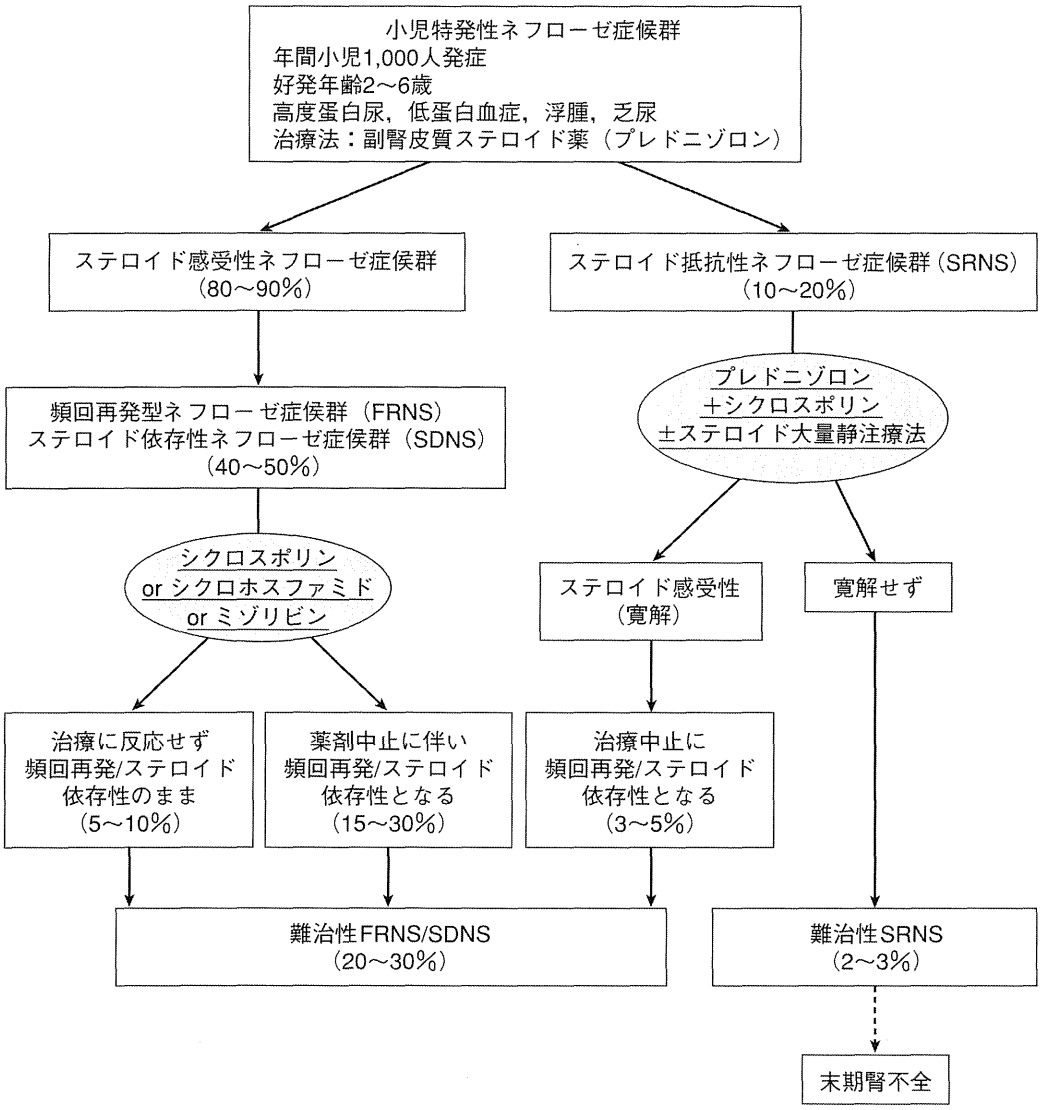

図 1 小児ネフローゼ症候群の臨床経過

ロスポリンを内服しても，約 10～20 %の患者は頻回再発型あるいはステロイド依存性のままであると考えられる[4]。一方，SRNS に対するシクロスポリンあるいはシクロスポリンとステロイドパルス療法のいずれかの併用により，80 %を超える高い頻度での寛解導入が可能となったが，シクロスポリン内服下で FRNS/SDNS となる症例も 15～30 %存在することが明らかとなった[5]。

シクロスポリンの副作用の最も重大なものの一つとしてシクロスポリン慢性腎毒性があげられるが，慢性腎毒性発症のリスクファクターとして長期間にわたる投与があげられる[6,7]。シクロホスファミドには性腺障害(特に男性不妊)という重篤な副作用があり，2～3 mg/kg で 8～12 週間を超える投与は避けるべきである[8]。したがって，シクロスポリンやシクロホスファミドなどで長期寛解を維持できるが，シクロスポリン慢性腎毒性やシクロホスファミドの性腺障害などの重篤な副作用回避のために，これらの薬剤を中止したり，再投与を断念せざるをえないことが多く，それに伴って再び FRNS/SDNS となる症例も少なからず存在する。

われわれは，これらの症例を難治性 FRNS/SDNS と呼んでいるが，結局，これらの患者の大半は，長期間ステロイド投与を継続せざるをえず，ステロイドの有害事象(成長障害，骨粗鬆症，高血圧，白内障，緑内障，糖尿病，中心性肥満，感染症，消化管潰瘍，精神障害，副腎機能不全など)が著明となることが多い。特に小児では，低身長と骨粗鬆症が問題となる。思春期前から思春期にかけてプレドニゾロンを服用すると低身長から脱することは難しい。骨粗鬆症による圧迫骨折や大腿骨頭壊死を呈すると入院期間が長

期に及び，患者の quality of life は低下し，日常生活に著しい影響を及ぼす。

また稀ではあるが，シクロスポリンあるいはシクロスポリンとステロイドパルス療法などにも抵抗性の難治性 SRNS 症例も依然として存在する。したがって，このような症例に対する有効で安全な治療法を開発することが急務であった(図 1)。

小児難治性ネフローゼ症候群に対するリツキシマブ治療

リツキシマブの小児ネフローゼ症候群への応用は，特発性血小板減少性紫斑病(ITP) を合併した 16 歳の難治性ネフローゼ症候群患者(発症年齢 2 歳)において，ITP の治療目的で投与したリツキシマブによりネフローゼ症候群が寛解したという報告が最初である[9]。ほぼ時を同じくして Nozu らは，巣状分節性糸球体硬化症が原疾患で腎移植を受けた小児患者(12 歳)が，移植直後よりネフローゼ症候群を再発し，その後，EB ウイルス関連移植後リンパ増殖性疾患(PTLD)の発症と同時にネフローゼ症候群も増悪したが，PTLD の治療目的でリツキシマブを投与したところ，PTLD が治癒しただけでなくネフローゼ症候群も速やかに寛解したと報告した[10]。本症例の経験がその後のリツキシマブ治療開発研究の大きなヒントになった。

2007 年，Bagga らは，小児難治性 SRNS 患者 5 例(2.8〜15 歳，発症年齢 1〜3.3 歳)に，375 mg/m^2/回(最大投与量 500 mg/回)4 回投与を行ったところ，5 例中 3 例が寛解，2 例が不完全寛解し，ステロイドと免疫抑制薬の減量が可能となり，infusion reaction と重症感染症は認められなかったと報告した[11]。Nakayama らは，難治性ステロイド抵抗性巣状分節性糸球体硬化症の小児患者に，375 mg/m^2/回(最大投与量 500 mg/回)1 回投与を行ったところ，蛋白尿が消失し，ステロイドと免疫抑制薬の減量中止が可能となった 2 症例を報告したが，本報告は，SRNS に対するリツキシマブの有用性を示唆する本邦で初めての報告である[12]。

2004 年以降，難治性 FRNS/SDNS 患者にリツキシマブを投与し，ネフローゼ症候群が寛解し，ステロイドの減量または離脱と免疫抑制薬の減量または離脱が可能となったという症例報告やケースシリーズが海外の学術雑誌や国際学会で散見されるようになった[9,13〜17]。これらの報告では，リツキシマブ療法として，375 mg/m^2/回(最大投与量 500 mg/回)4 回投与が主に行われ，リツキシマブ特有の有害事象である infusion reaction を含む軽度の有害事象を認めるが，重篤な有害事象は認められていない。

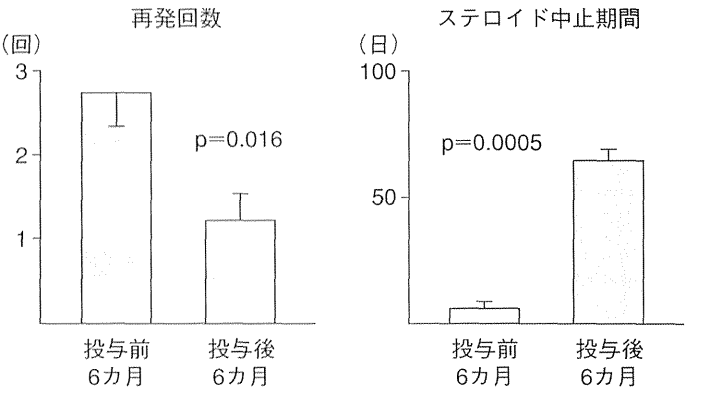

図 2　難治性頻回再発型/ステロイド依存性ネフローゼ症候群に対するリツキシマブ単回投与の効果

小児期に発症した 22 歳の難治性ネフローゼ症候群患者に，1,000 mg/回 2 週間間隔で 2 回投与し，ネフローゼ症候群が寛解(5 カ月間寛解維持)し，ステロイドと免疫抑制薬の減量が可能となったとの報告もある[18]。

Kamei らは，小児難治性 FRNS/SDNS 患者 12 例(5〜19 歳)にリツキシマブ療法として，375 mg/m^2/回(最大投与量 500 mg/回)1 回投与を行うパイロット研究を行った。その結果，全例がステロイドを中止することができ，リツキシマブ投与前 6 カ月間と比較して，投与後 6 カ月間では再発頻度は有意に減少し，ステロイド中止期間も有意に長かった(図 2)[19]。

Ruggenenti らは，小児難治性 FRNS/SDNS 患者 10 例に対してリツキシマブ 375 mg/m^2/回を 1 回ないし 2 回投与し，リツキシマブ投与後 3 年間の経過観察を行っているが，再発回数の減少のみならず，ステロイド減量・中止の効果と思われる成長障害からの回復も認めたと報告している[20]。

上記以外にも，小児難治性 FRNS/SDNS に対してリツキシマブが有効であることを示唆する報告がある[21〜24]。

成人微小変化型ネフローゼ症候群に対するリツキシマブ治療

上記のごとく，ネフローゼ症候群に対するリツキシマブの応用は小児例が中心であったが，最近になり，成人の頻回再発やステロイド依存性を呈する微小変化型ネフローゼ症候群に対してリツキシマブが有効であることを示唆する報告が散見されるようになった。

Munyentwali らは，17 例の成人の FRNS や SDNS を呈する微小変化型ネフローゼ症候群に対してリツキシマブ 375 mg/m^2/回を 1〜4 回投与し，平均 26.7 カ月観察したところ，11 例はその後再発せず，ステロイドおよび免疫抑制薬治療から離脱したと報告した[25]。Takei らは，成人の SDNS 患者 25 例を対象に，リツキシマブ 375 mg/m^2/回を 6 カ月間隔で 2 回投与し 12 カ月観察したところ，再発回数およびステロイド投与量を有意に減少させることができたと報告した[26]。さらに，前述の Ruggenenti らの報告では，20 例の成人 FRNS/SDNS も対象としており，リツキシマブ 375 mg/m^2/回を 1 回ないし 2 回投与し 1 年間観察したところ，再発回数およびステロイド投与量を有意に減少させることができたと報告した[20]。

このようにリツキシマブは，小児だけでなく成人の FRNS/SDNS に対しても有効である可能性が示唆された。

リツキシマブの作用機序仮説

1974 年に Shalhoub が特発性ネフローゼ症候群の原因は T 細胞機能障害であるという仮説を提唱し[27]，それ以降，T 細胞由来の液性因子がネフローゼ症候群の原因と考えられてきたが，依然としてその実態は明らかではない。一方，B 細胞による T 細胞の活性化促進や，抗体非依存性の自己免疫による組織損傷の介在，自己免疫疾患における持続的な T 細胞の活性化を促す共刺激分子やサイトカインの発現など，自己免疫疾患における B 細胞の重要性はよく知られたところである[28〜31]。リツキシマブは B 細胞の増殖を阻害しアポトーシスを誘導することで，末梢血 B 細胞を枯渇させ，結果として B 細胞-T 細胞の相互作用を抑制することによりネフローゼ症候群の再発を防止する可能性が考えられる[32]。微小変化型ネフローゼ症候群では，制御性 T 細胞の機能異常があることや制御性 T 細胞の誘導によりネフローゼ症候群が寛解することが報告されていることから[33〜35]，リツキシマブは制御性 T 細胞の数の増加や機能強化を促進することでネフローゼ症候群の寛解を維持する可能性がある[36]。あるいは，もっと単純に，リツキシマブによる末梢血 B 細胞の枯渇により，B 細胞由来の因子が減少することでネフローゼ症候群の寛解が維持されるのかもしれない。

Fornoni らは，巣状分節性糸球体硬化症(FSGS)の移植後再発に関して，リツキシマブがポドサイト細胞膜の acid sphingomyelinase-like phosphodiestarse 3b に結合し，その結果，ポドサイト細胞骨格が安定することで移植後再発を抑制する可能性を報告したが[37]，FRNS/SDNS においても同様の作用機序で再発を防止するのか否かは明らかではない。

小児難治性 FRNS/SDNS に対するリツキシマブ開発研究

上記のごとく，リツキシマブは小児期発症および成人の難治性 FRNS/SDNS 患者に対する有効で安全な薬剤として期待されている。しかし，小児難治性 FRNS/SDNS に対するリツキシマブ療法は症例報告，比較的小規模なコホート研究，単群試験が主で，これまでに行われたただ一つの比較試験も研究デザインは非劣性試験であり[23]，有効性と安全性を明らかにするための質の高い臨床試験は実施されていなかった。

臨床試験には，大きく分けて「治験」と，「研究者(医師)主導臨床試験」とがある。「治験」とは，厚生労働省による新薬としての承認や適応拡大の承認を得ることを目的とし，主に製薬企業が主体となって行う臨床試験であり，医師自らが「治験」を実施する場合は「医師主導治験」と呼ばれる。一方，研究者(医師)主導臨床試験は，研究者(医師)が主体となって非営利で行うもので，これまで厚生労働省で承認された薬，治療法や診断法を用いて，そのなかから最良の治療法や診断法を確立すること，薬のより良い組み合わせを確立することなどを目的とする。

われわれの目標は，単に，リツキシマブの有効性・安全性を明らかにするだけではなく，小児期発症難治性ネフローゼ症候群に対するリツキシマブの適応拡大を目指すものであり，「研究者主導臨床試験」では不十分で「治験」を行う必要があった。しかし，小児期発症難治性ネフローゼ症候群は稀少疾患であり，そのマーケットの小ささや，わが国の制度上の問題などで，製薬企業が主体となって「治験」を行う状況ではなかった。

そこで，医師主導治験を行うことを計画し，社団法人日本医師会治験促進センターの支援する治験推進研究事業(治験計画)の研究課題として「小児難治性ネフローゼ症候群に対するリツキシマブ療法」(主任研究者：飯島一誠)を申請した。幸いなことに，平成 19 年 7 月 1 日付けで採択され，医薬品医療機器総合機構での事前面談や対面助言に基づいて臨床試験プロトコールを作成した。その後，医師主導治験実施のための，治験推進研究事業(治験調整管理)の研究課題として「小児期発症難治性ネフローゼ症候群におけるリツキシマブの有効性・安全性及び薬物動態に関す

る研究」(主任研究者：飯島一誠)が平成 20 年 4 月 1 日付けで採択され，後述の医師主導治験を実施した。本治験は，小児期発症難治性 FRNS/SDNS に対する世界で初めてのリツキシマブ開発研究であり，わが国の小児腎臓病領域での初めての医師主導治験である。

本治験では小児期発症の難治性 FRNS/SDNS を対象とし，関東，関西の計 9 施設(国立成育医療センター，東京都立清瀬小児病院，東京大学，駿河台日本大学病院，順天堂大学練馬病院，神戸大学，和歌山県立医科大学，兵庫県立こども病院，岡山大学)で以下の 2 つの臨床試験を行った。

①二重盲検プラセボ対照ランダム化比較試験(RNRNS-01)(臨床試験登録 ID：UMIN000001405)：プレドニゾロンによる寛解導入後，375 mg/m^2/回(最大 500 mg)のリツキシマブあるいはプラセボを 1 週間毎に計 4 回点滴静注し，有効性および安全性を評価する。有効性の主要評価項目は無再発期間とし，投与後 1 年間経過を観察する。目標症例数は 60 例である。

②薬物動態試験(RCRNS-02)(臨床試験登録 ID：UMIN000001406)：主として，ランダム化比較試験でのプラセボ投与患者で早期に再発した患者を対象としたリツキシマブ薬物動態試験(目標症例数 20 例)。

本医師主導治験は 2008 年 9 月に開始され 2011 年末に完了した。その概略は UMIN CTR 臨床試験登録情報として閲覧可能であり，下記 URL を参照されたい。

(https:/ /upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000001680&language=J　および https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=R000001710&language＝J)

RCRNS01 は試験期間を 1 年間とする多施設共同プラセボ対照二重盲検ランダム化比較試験であり，主要評価項目を無再発期間とし，副次的評価項目を Treatment failure(早期再発，FRNS/SDNS，SRNS)となるまでの期間，FRNS/SDNS となるまでの期間，再発率，ステロイド投与量などとしたが，リツキシマブ群ではプラセボ群に比して，有意に無再発期間，treatment failure となるまでの期間および FRNS/SDNS となるまでの期間が延長し，再発率およびステロイド投与量は有意に減少した。また，安全性に関してもプラセボ群と有意な差を認めなかったことから，われわれは，リツキシマブは小児期発症難治性 FRNS/SDNS に対して有効で安全であると結論した(投稿中)。

今後の展開

上記のごとく，小児期発症難治性 FRNS/SDNS に対するリツキシマブの有効性および安全性が確認できたことを受けて，開発権を持つ製薬企業は平成 25 年末に医薬品・医療機器総合機構に対して適応拡大のための承認申請を行った。

リツキシマブは，小児期発症難治性 FRNS/SDNS の治療薬として重要なオプションであるが，本治験のフォローアップ調査により，リツキシマブ投与後 19 カ月目までには全例が再発することが明らかになり，リツキシマブは難治性 FRNS/SDNS を治癒に導くものではないことも確認された。今後は，リツキシマブにより得られた寛解期間をいかに延長させるかという点が重要であろう。

近年，Ito らにより，リツキシマブ投与後にミコフェノール酸モフェチル(MMF)を併用することで，寛解期間を延長させることが可能であることを示唆する報告がなされたが[38]，その有効性・安全性を検証するための全国多施設によるプラセボ対照二重盲検ランダム化比較試験(厚生労働科学研究)が Japanese Study Group of Kidney Disease in Children(JSKDC)の一研究(JSKDC07)として行われる予定である。

難治性 SRNS に対するリツキシマブの有効性に関しては controversial である。最近，その有効性に否定的なランダム化比較試験が報告されたが[39]，一方で，Ito らはステロイドパルス療法との併用により高い寛解率が得られること示唆するデータを得ている。小児難治性 SRNS に対するリツキシマブとステロイドパルス療法の有効性および安全性を検証するための単群試験(厚生労働科学研究)も JSKDC の一研究(JSKDC08)として行われる予定である。

おわりに

われわれが実施した医師主導治験などにより，小児難治性 FRNS/SDNS に対するリツキシマブが有効で安全であることが証明されたが，リツキシマブに関連する重篤な有害事象として，進行性多発性白質脳症，B 型肝炎のキャリアの再活性化に伴う劇症肝炎，びまん性肺線維症，潰瘍性大腸炎，ウイルス性心筋症などが報告されており[40〜42]，安易なリツキシマブの使用は厳に慎むべきである。

利益相反自己申告：申告すべきものなし

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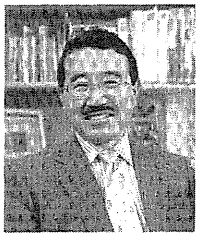

我が国における小児の未承認薬・適応外薬・剤形変更問題解決に向けての取り組み

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1. はじめに

我が国では，諸外国と比べて薬事承認が遅れるアプルーバルラグ（ドラッグラグ）が大きな社会問題となってきたが，小児ではさらにその状況は深刻である．販売後の利益が見込めない等の理由で企業が開発を敬遠する傾向にあり，添付文書上に必要十分と考えられる，適応(効能・効果)，用法・用量等の記載がある医薬品は，小児頻用薬の約1/3程度しかないと言われている[1]．

我が国では，「55年通知」に則って，適応外医薬品でも一定のルールに基づき保険上の使用を認められるようになってはいるが，米国等と異なり，基本的に保険償還と薬事承認が一対一対応しているために，未承認の医薬品はもとより，適応外薬でも，特に新規性が高いものについては，原則として保険診療の枠組みでは使えない．また承認適応であれば，副作用が出た際には副作用被害救済制度が適用されるが，未承認薬はもとより，適応外薬ですら「禁忌」もしくは「安全性が確立していない」等とされている場合，救済対象とならないことがある．さらに，重篤な副反応が出た等で訴えられた場合に医療側が敗訴する可能性もある．

未承認薬の多くは，症例数が5万未満の希少疾病用医薬品で，その多くは，海外のベンチャー企業が開発しており，国内に開発・販売企業がないものも多くある．これも，多くの未承認薬について，医療上の必要性は認識されながら，なかなか国内での開発に着手されずにいた原因となっている．一方，欧米では小児医薬品開発推進のための法令が制定され，新生児を含む小児に対して必要な医薬品開発が進められる法的枠組みができている．最近，小児医薬品の承認を推進するために，我が国でも様々な取り組みが行われているが，まだ多くの課題も残されている．本稿では，我が国における医薬品・医療機器開発の現状と取り組み，今後の課題について概説する．

2. セラピューティックオーファン，適応外薬，未承認薬とオーファンドラッグの定義

セラピューティックオーファン（Therapeutic Orphan：治療上の見捨てられた孤児）とは，小児等において，医薬品の十分な評価が行われていない状況を指す．具体的には，以下に示したより広義の「適応外使用」の状況のように小児などで十分な医薬品評価が行われていない状態を示すと考えられる．

Off-label Use（適応外使用）は，添付文書に記載がない使用という意味で，厳密には，添付文書上に小児についての効能・効果，用法・用量の記載がない，もしくは小児の特定の年齢に禁忌とされている・安全性が確立していないとされているにもかかわらず臨床現場で使用されること，を指している．しかしながら実際の臨床現場では，これら以外に，添付文書上の記載が不十分（小児についての記載が何も

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