A. 研究目的

小児期発症ネフローゼ症候群は，寛解に至っても頻回に再発することが多く，それにつれてステロイド使用頻度が多くなるため，成長発達に大きな影響を及ぼすとともに再発時に血栓症や感染症の危険性が高まる，重大な疾患のひとつである．

ネフローゼ症候群では血液粘稠度の増加や抗凝固因子の漏出，ステロイドによる凝固能の亢進などの複合的な要因により血栓症の発症リスクが高まる．つまり再発を繰り返す度に血栓症のリスクが高まっているといえる．免疫抑制薬を用いても再発の頻度が高く頻回のステロイド治療を要する難治性頻回再発型ネフローゼ症候群や，ステロイド治療を行っても寛解に至らないステロイド抵抗性ネフローゼ症候群などの難治性ネフローゼ症候群では，血栓症のリスクはさらに高いものとなる．

したがって血栓症合併ネフローゼ症候群患者と血栓症非合併ネフローゼ症候群患者について凝固能検査を比較検討することで，有用な評価項目を作成する必要があると考えた．従来 D-dimer やトロンビン-アンチトロンビン複合体(TAT)は血栓症診断に有用とされているが，胸水や腹水で D-dimer を産生し尿中にアンチトロンビンを喪失するネフローゼ症候群においては，その正確性について示されてはいない．またフィブリノゲン(Fib)高値例は血栓形成のハイリスクとされるが，血栓形成により消費されると低下傾向となるため，Fib 値単独でも評価は困難である．以上より，複数の測定値を複合的に評価することが望ましいと考え，Fib の相対的低値(アルブミン(Alb)低下幅やコレステロール(TC)増加幅に比して Fib 増加幅が低い場合を血栓形成による消費と考える)を評価するために指標(UCS index＝$Fib^2/\{(4\text{-}Alb)\times TC\}$)を作成し，血栓症診断における感度特異度を D-dimer や TAT とともに検討した．

本研究の目的は，血栓症合併の危険因子を検討し，抗凝固療法の開始基準を明らかにすることである．

B. 研究方法

対象は 2012 年 1 月から 2013 年 12 月に東京都立小児総合医療センター腎臓内科を受診した小児ネフローゼ症候群患者のうち，Fib，Alb，TC，D-dimer，TAT の全てを測定し，かつ Alb≦3.0g/dL を呈したネフローゼ症候群初発もしくは再発の患者 31 例と，同項目すべてを測定した血栓症合併ネフローゼ症候群患者 3 例である．

血栓症合併例と血栓症非合併例について，D-dimer，TAT，UCS index をそれぞれ比較検討し，血栓症の危険因子を同定した．

(倫理面への配慮)

この研究は疫学研究に関する倫理指針を遵守し，すでに研究計画書は研究代表者施設の倫理審査委員会の審査を受け承認を得ている(平成 26 年 7 月)．また同指針に基づいて，あらかじめ研究の実施についての情報をインターネットで公開している(http://www.byouin.metro.tokyo.jp/shouni/tiken/rinnshou_shounin.html)．またデータセンターで扱う患者情報はすべて匿名化情報とした．

さらに本研究はヘルシンキ宣言に基づく倫理的原則を遵守し，個人情報管理に万全を期して実施した．また研究代表者の所属医療機関での利益相反委員会で，研究者の利益相反管理の申出を行った．

C. 研究結果

この結果，元来有用とされている D-dimer や TAT は，血栓症症例では有意に高いことが示されたが，血栓症の有無を明確に評価可能な閾値を規定することは不可能だった．UCS index でも同様の検討を行い血栓症合併例では低値を取る傾向を認めたが，こちらでも閾値を規定できなかった(図)．

重篤な合併症である血栓症を見逃さないためにいずれのパラメータにおいても感度 100%を保つと，

TAT≧10ng/mL で特異度 83.9%，D-dimer≧2.5μg/mL で特異度 77.4%，UCS index≦160 で特異度 83.9%と，十分な特異度は得られなかった．このため，これらを複合的に用いることで，検査精度の向

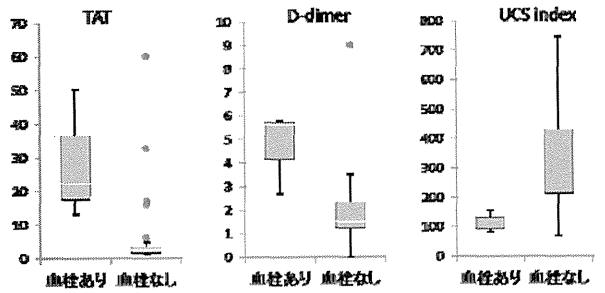

図　血栓症の有無における各パラメータの分布

上を図った. D-dimer≧2.5μg/mL かつ UCS index ≦160 とすることで, 感度 100%, 特異度 96.8%という結果が得られた.

D. 考察

本研究は, 小児ネフローゼ症候群における血栓形成リスク評価法の作成を行った.

小児ネフローゼ症候群において, D-dimer≧2.5μg/mL かつ UCS index≦160 は血栓形成のハイリスクであることが示唆された. TAT の他にフィブリンモノマー(FM)などが血栓形成の指標として有用とされるが, いずれも専門機関への外注検査であることがほとんどで, 抗凝固療法の有無が必要なタイミングでの評価が難しい. 今回示した検査項目はいずれも即時評価しやすいものであり, 実臨床において有用な危険予測法であるといえる.

今後はこの結果を踏襲し, これらを指標として治療介入を行った結果の成績について, 再度検討する必要がある. またさらに検査データを蓄積し, 今回示したデータの再現性や, より良い指標の作成を目指す.

E. 結論

これまで明らかとされていない, 小児ネフローゼ症候群の血栓症発症リスク評価法を作成した. さらなるデータの蓄積を行い, 本評価法の妥当性評価やさらに有用な評価法の開発が期待される.

F. 健康危険情報

なし

G. 研究成果の公表

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H. 知的財産権の出願・登録状況

1. 特許取得

該当なし

2. 実用新案登録

該当なし

3.その他

該当なし

厚生労働科学研究費補助金（医療技術実用化総合研究事業）
分担研究報告書

小児難治性ネフローゼ症候群に対する新規治療法の開発を目指した全国多施設共同臨床試験

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薬剤の用量と安全性の検討、臨床試験体制整備のアドバイス

研究分担者　中村秀文　国立成育医療研究センター臨床研究開発センター　開発企画主幹

研究要旨
本年度は，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を対象としたリツキシマブ治療併用下でのミコフェノール酸モフェチルの多施設共同二重盲検プラセボ対照ランダム化比較試験（JSKDC07）と小児期発症難治性ステロイド抵抗性ネフローゼ症候群を対象としたリツキシマブ＋ステロイドパルス療法の多施設共同単群臨床試験（JSKDC08）について，先進医療事前相談をうけ，プロトコル改訂を行い，先進医療Bに申請する際の、プロトコル、申請書、照会事項対応についてのアドバイスを行うとともに、必要に応じて文書作成を支援し、また体制に対するアドバイスを行った。JSKDC07 試験（申請医療機関：神戸大学）は，先進医療として承認された（厚生労働省告示第十八号）。JSKDC08 試験（申請医療機関：国立成育医療研究センター）は，第 25 回先進医療技術審査部会（平成 27 年 1 月 22 日）にて「条件付き適」と評価された、現在試験開始準備が進められている。

A．研究目的

本研究で行われる，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を対象としたリツキシマブ治療併用下でのミコフェノール酸モフェチルの多施設共同二重盲検プラセボ対照ランダム化比較試験（JSKDC07）と小児期発症難治性ステロイド抵抗性ネフローゼ症候群を対象としたリツキシマブ＋ステロイドパルス療法の多施設共同臨床試験（ＪＳＫＤＣ08）について，班会議での検討，先進医療事前相談，先進医療技術審査部会審査をふまえて，プロトコル、申請書、照会事項対応についてのアドバイスを行うとともに、必要に応じて文書作成を支援した。また体制についてのアドバイスを行った。

B．研究方法

先進医療事前相談をふまえてプロトコルを検討し，改訂を行う際のアドバイス・作成支援を行う。先進医療Bに申請し，先進医療技術審査部会の指摘・指示により，プロトコル改訂を行う際のアドバイス・作成支援を行う。また適宜、体制についてのアドバイスを行う。

（倫理面への配慮）

JSKDC07 試験と JSKDC08 試験のプロトコルは，「臨床研究に関する倫理指針」に従って作成し，ICH-GCP に準拠して実施する。

C．研究結果

＜JSKDC07 試験＞

平成 26 年 6 月 1 日に行った班会議での検討及び同年 6 月 17 日に行った先進医療事前相談の指摘を踏まえ，プロトコル委員と協議し，プロトコル改訂作業が進められたが、この内容について適宜アドバイスを行った。同年 8 月 29 日に薬事･食品衛生審議会医薬品第一部会にてリツキシマブの効能追加の一部変更承認申請が承認されたことを反映し，プロトコル 2.1 版（作成日：同年 9 月 4 日）に改訂された。

翌 9 月 6 日に先進医療実施届出書をはじめとする申請資料一式が提出されたが、この作成についてのアドバイスを行った。また照会事項への回答作成を指導し、状況に応じて文書作成支援を行った。同年 10 月 2 日の第 23 回先進医療会議にて先進医療 B としての申請が承認された。同年 10 月 9 日の第 22 回先進医療技術審査部会にて，条件付き適と評価された。同年 10 月 27 日に条件付き適に係る承認条件に従い，対象疾患の定義を明確にするため，1. 背景及び 5.1 選択基準（3）について記載整備したが、この内容についてもアドバイスを行い，その結果を踏まえてプロトコル 2.2 版（作成日：同年 11 月 5 日）に改訂された。平成 27 年 1 月 9 日の第 26 回先進医療会議にて承認され，承認条件を踏まえて，指摘通りにプロトコル 2.3 版（作成日：同年 1 月 21 日）に改訂された。またこの内容について平成 27 年 2 月 11 日にキックオフミーティングで説明が行われた際に、適宜留意点等についてのアドバイスを行った。

＜JSKDC08 試験＞

審査対象とすべき症例数，安全性評価項目及び評価時期を詳しく検討し，プロトコル改訂作業を進めたが、この作業を補佐した。また，設定根拠の記載が一部整備された。さらに同年 8 月 29 日に薬事･食品衛生審議会医薬品第一部会にてリツキシマブの効能追加の一部変更が承認されたことを踏まえて，プロトコル 3.0 版（作成日：同年 11 月 1 日）に改訂されたが、その際のアドバイスを行った。

同年 11 月 27 日に先進医療実施届出書をはじめとする申請資料一式が提出され、平成 27 年 1 月 15 日の第 26 回先進医療会議で先進医療 B としての申請が承認され，同年 1 月 22 日の第 25 回先進医療技術審査部会にて，「条件付き適」と評価された。指摘事項・修正指示に従い，改訂が行われたが、その作業へのアドバイスを行った。プロトコルをはじめとする修正申請資料は平成 27 年 2 月 16 日に提出され，本報告書作成時点では先進医療会議の受審を待っている状況である。

D．考察

本研究は，両試験を先進医療 B として実施し，ミコフェノール酸モフェチルの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に対する適応拡大，リツキシマブの小児難治性ステロイド抵抗性ネフローゼ症候群に対する適応拡大を目指すものである。本年度は，先進医療 B の申請・承認をうけ，速やかに両試験を開始することを目指した。そこで，両試験について，平成 26 年 6 月 1 日班会議を行った後，平成 26 年 6 月 17 日に先進医療事前相談を受けた。

JSKDC07 試験では，先進医療事前相談を踏まえて，申請医療機関を研究代表者の所属する神戸大学とし，申請資料準備とともにプロトコル改訂作業を進めたが、この作業に対するアドバイスと適宜、内容修正の作業を行った。また，同年 8 月 29 日に薬事・食品衛生審議会医薬品第一部会にてリツキシマブの効能追加の一部変更承認内容を確認したうえで，プロトコル 2.1 版（作成日：同年 9 月 4 日）に改訂した。本試験（申請医療機関：神戸大学）は，先進医療として承認された（厚生労働省告示第十八号）。試験薬の準備が整い次第，申請医療機関にて患者登録を開始する予定である。参加予定施設では協力医療機関としての申請準備を進めている。

来年度には両試験ともに開始される。試験開始後は，定期的中央モニタリング結果から，プトロコル逸脱防止対策を研究分担者の佐古と共に行い，必要に応じてプロトコル改訂を行う。

E．結論

本年度は，JSKDC07 試験と JSKDC08 試験を先進医療 B として実施するために，先進医療 B に申請されたが、その申請書、プロトコルの内容及び照会事項への対応についてのアドバイスと一部文書作成支援、また体制などへのアドバイスを行った。JSKDC07 試験（申請医療機関：神戸大学）は，先進医療として承認された（厚生労働省告示第十八号）。JSKDC08 試験（申請医療機関：国立成育医療研究センター）は，第 25 回先進医療技術審査部会（平成 27 年 1 月 22 日）にて「条件付き適」と評価された。

F．健康危険情報

なし

G．研究発表

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H. 知的財産権の出願・登録状況
（予定を含む。）

1. 特許取得
なし

2. 実用新案登録
なし

3. その他
なし

III.　研究成果の刊行に関する一覧表

IV.　研究成果の刊行物

研究成果の刊行に関する一覧表

発表者氏名	論文タイトル	発表誌	出版年等
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DOI 10.1007/s00467-014-2792-9

ORIGINAL ARTICLE

Impact of rituximab on height and weight in children with refractory steroid-dependent nephrotic syndrome

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Abstract
Background Children with steroid-dependent nephrotic syndrome (SDNS) often suffer from serious adverse events, including growth retardation and obesity. Rituximab (RTX) is a promising therapeutic option to overcome steroid dependency. We have examined the impact of RTX on growth and obesity in children with SDNS.
Methods Thirteen pediatric patients with SDNS who were refractory despite treatment with multiple immunosuppressive agents received RTX infusions. Mean follow-up was 2.3 years from the first administration of RTX. Improvement in the height and obesity indexes from prior to the initial RTX infusion through to the last visit was assessed.
Results After RTX, the number of relapses [2.8 (before RTX) vs. 0.8/year (after RTX); p=0.0008] and the prednisolone dose (287.9 vs. 70.7 mg/kg/year, respectively; p=0.0002) were significantly decreased. Marked improvement in the height standard deviation score (SDS) was achieved by ten of the 13 patients (77 %) [n=13; −1.6 (before RTX) vs. −0.8 SDS (after RTX); p=0.03]. Notably, the height SDS of seven of the eight patients whose height was less than average at the first RTX improved from −2.6 to −1.4 SDS with RTX therapy. At the same time, the obesity index of 12 of the 13 patients (92 %) significantly improved (n=13; 16.9 vs. 3.1 %; p= 0.004).
Conclusion Therapy with RTX may contribute to an improvement in the growth and obesity indexes in some patients suffering from severe side effects of steroids.

Keywords Nephrotic syndrome · Rituximab · Steroid · Growth · Obesity

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Introduction

While most patients (90 %) with idiopathic nephrotic syndrome respond to steroid therapy, up to 60 % of patients experience frequently relapsing nephrotic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS) [1–3]. Patients with FRNS/SDNS may require prolonged steroid therapy which can lead to serious adverse events, including growth retardation, obesity, osteoporosis, osteonecrosis, glaucoma, cataracts and hypertension. Alternative therapeutic options, including cyclophosphamide (CPA), chlorambucil, cyclosporine A (CsA), tacrolimus, mizoribine (MZR) and mycophenolate mofetil (MMF), have been developed to avoid or minimize such adverse events. However, despite the various immunosuppressive agents currently available, some patients remain refractory.

Growth retardation and obesity are likely to be related to the duration and intensity of the steroid treatment. Alteration of the secretory pattern of growth hormone, inhibition of insulin-like growth factor-1 bioactivity and a direct effect on the skeletal tissue matrix are actions that have been attributed to steroids [4]. Catch-up growth after cessation of steroid treatment can be expected in patients who outgrow SDNS or are treated with alternate-day prednisolone (PSL). However, the effectiveness of PSL may be insufficient in patients with refractory SDNS [5–8].

Growth retardation and obesity negatively influence a patient's self-esteem and quality of life. Additionally, cosmetic issues, such as hypertrichosis, acne and cutaneous striae, especially in adolescence, often disrupt a patient's adherence to steroids, resulting in poor control of the disease. Furthermore, steroids can cause psychological problems in patients, creating mental stress for parents and caregivers [9]. Therefore, the therapeutic goal in SDNS/FRNS has always been to accomplish a sustained longer remission with a minimal dose of steroids. However, the appropriate treatment

strategy for patients with refractory SDNS remains challenging as severe growth retardation and obesity are likely to develop despite the use of alternative immunosuppressive agents. For such patients, rituximab (RTX), an anti-CD20 monoclonal antibody, is an emerging option [10–14]. We have previously reported that RTX significantly reduces the number of relapses and required doses of steroids in patients with refractory SDNS [12]. However, to our knowledge, there are no reports focusing on the efficacy of RTX to improve height and weight in pediatric patients with SDNS/FRNS. Consequently, in this study, we attempted to determine the clinical benefits of RTX on these two aspects.

Patients and methods

Treatment strategy

We retrospectively analyzed 13 patients with SDNS who were refractory—that is, unresponsive to conventional immunosuppressants such as CsA, CPA, MZR and MMF. These patients were treated with RTX from January 2007 until December 2010 in the National Center for Child Health and Development, Tokyo, Japan. Patients aged >18 years and those who had reached adult bone age were excluded from the study. RTX was introduced as a therapeutic option for patients who required high doses of steroids to maintain remission or who were suffering from severe steroid-related side effects, such as growth retardation or obesity.

Steroid dependency was defined as the occurrence of two consecutive relapses during the tapering-off period, or within 2 weeks from the discontinuation of steroid therapy. Steroid treatment was based on the International Study of Kidney Disease in Children protocol. At primary onset, patients were initially treated with PSL at a dose of 60 mg/m^2/day for 4 weeks. Thereafter, the PSL dose was reduced to 40 mg/m^2 on alternate days for 4 weeks. Relapse was treated with PSL at a dose of 60 mg/m^2/day until remission (0 or trace proteinuria for 3 consecutive days) was achieved, following which PSL was reduced to the same dose given on alternate days for 2 weeks. The dosage was subsequently further reduced to 40 mg/m^2/2 days for 2 weeks, followed by 20 mg/m^2/2 days for 2 weeks. Prior to the initiation of RTX treatment eight patients had suffered from steroid-resistant nephrotic syndrome (SRNS) and were treated with methylprednisolone pulse therapy to induce remission.

Upon receiving approval from the ethics committee in our institution for off-label use of RTX together with parental consent, we administered RTX (375 mg/m^2) to the patients. The median follow-up after the first RTX infusion was 2.3 (range 1.0–3.8) years. A total of 26 courses of RTX were administered, with six, three, two and two patients receiving one, two, three and four courses, respectively. All patients continued to receive immunosuppressive agents, including CsA (n=5), MZR (n=1) and MMF (n=10), after RTX therapy to prevent further relapse.

Using the same set of clinical records, we retrospectively assessed improvement of the patients' height and obesity indexes prior to and after RTX therapy. Height is expressed as a height standard deviation score (SDS). Standard height and weight were based on Japanese children's growth curves. The obesity index was calculated by the following method: obesity index (%)=100×(body weight − standard body weight)/standard weight. The normal range for the obesity index is −20 to 20 %). Standard weight was based on the standard height of Japanese children.

Simultaneously, we assessed the decrement in steroid dose and the number of relapses before and after RTX therapy.

Statistical analysis

Data are expressed as medians. Statistical analysis was performed with GraphPad Prism software (GraphPad Software, Inc., San Diego, CA). All p values are two-sided, and p values of <0.05 were considered to be statistically significant. Comparisons were performed using the Wilcoxon nonparametric test.

Results

Characteristics of patients

Thirteen pediatric patients (12 males, 1 female) were included in this study. Table 1 shows characteristics of the patients prior to the initiation of the RTX infusions. Before the commencement of the RTX infusions, one patient had experienced vertebral fracture and femoral head necrosis, three patients had cataracts and one patient had glaucoma. Eight patients were using alendronate, of whom six were also using alfacalcidol, and one was using a luteinizing hormone-releasing (LHRH) analog in addition to alendronate and alfacalcidol to delay puberty and prolong his growing period. The median age at the last visit in 2010 was 13.6 (range 5.8–19.9) years. The median follow-up period after the discontinuation of RTX therapy was 2.3 (range 1.0–3.8) years. Renal biopsy revealed focal and segmental glomerulosclerosis in two patients, and minimal change nephrotic syndrome in 11 patients. Although all patients had been treated with various immunosuppressive agents, including CsA (n=13), CPA (n=10), MZR (n=13) and MMF (n=1) in combination with PSL, they suffered from SDNS. Eight patients had a previous history of SRNS (2 with primary SRNS and 6 with late SRNS). All patients had a glomerular filtration rate, estimated from serum creatinine, that fell within the normal range throughout the follow-up period.

Table 1 Characteristics of patients at initiation of rituximab treatment

Patient	Sex	Age at diagnosis (years)	First response to steroid	History of SRNS (times)	Treatment before RTX	Age at RTX infusion (years)	No. of relapses before RTX (times/year)	Dose of PSL for 1 year before RTX therapy (mg/kg/year)	Height (SDS) at first administration of RTX	Weight at first administration of RTX (obesity index, %)	Bone age at first administration of RTX (years old)	Length of follow-up period (years)
1	Male	2.7	Sensitive	0	CsA, MZR, CPA	5.3	4.9	239	1.78	13.3	n.d	3.3
2	Male	4.3	Sensitive	0	CsA, MZR, CPA	7.6	4.9	308.4	0.96	16.9	n.d	2.2
3	Male	10.7	Sensitive	0	CsA, MZR, CPA	13.9	2.8	84.4	0.28	−14.5	n.d	2.3
4	Male	5.7	Sensitive	1	CsA, MZR, CPA, MPT	16.8	1.3	287.9	−1.6	20.4	13.4	1.8
5	Male	2.1	Sensitive	1	CsA, MZR, CPA, MPT	6.4	2.9	815.5	−1.6	10.6	n.d	1.4
6	Male	2.3	Resistant	2	2 CsA, MZR, MPT	4.8	2	398.1	0.68	16.8	n.d	1.0
7	Male	5.0	Sensitive	0	CsA, MZR, CPA	14.3	1.5	309.9	−5.6	43.1	6.9	3.8
8	Male	8.6	Sensitive	1	CsA, MZR, MPT	16.3	1.9	89.3	−0.8	4.3	13.8	3.6
9	Male	4.4	Sensitive	2	CsA, MZR, CPA, MPT	12.8	3.8	79.3	−2	15.6	12.3	3.5
10	Male	8.3	Sensitive	1	CsA, MZR, CPA, MPT	10.1	4.2	305.1	−2.5	48.4	n.d	3.5
11	Female	4.8	Sensitive	0	CsA, MZR, CPA	9.5	4.7	258.3	−2.2	21.6	n.d	2.6
12	Male	3.0	Resistant	1	CsA, MZR, CPA, MMF, MPT	16.5	2.4	80.2	−4.3	76.2	12.2	1.9
13	Male	2.3	Sensitive	1	CsA, MZR, MPT	5.3	2.2	780.7	0.33	53.7	n.d	1.4
Total or median	12 males, 1 female	4.4	11 sensitive, 2 resistant	1.0	CsA, 13; MZR, 13; CPA, 10; MMF, 1; MPT 8	10.1	2.8	287.9	−1.6	16.9	−3.5	2.3

SRNS, Steroid-resistant nephrotic syndrome; RTX, rituximab; CsA, cyclosporine A; MZR, mizoribine; CPA, cyclophosphamide; MMF, mycophenolate mofetil; MPT, methylprednisolone pulse therapy; PSL, prednisolone; SDS, standard deviation score; n.d., not done

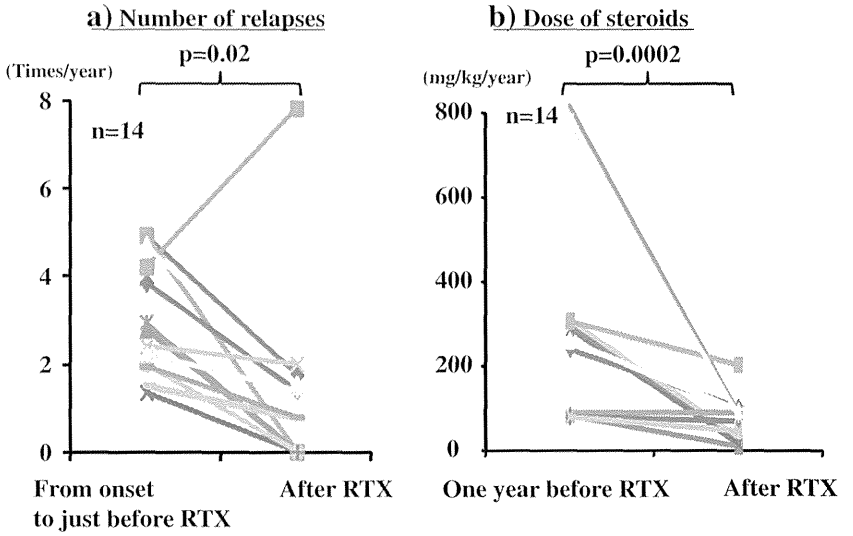

Fig. 1 Changes in the number of relapses and in steroid dose after initiation of rituximab (*RTX*) therapy. After RTX infusions, the number of relapses [2.9 (before RTX) vs. 0.8/year (after RTX); p=0.0008, Wilcoxon non-parametric test] and the prednisone dose [287.9 (before RTX) vs. 70.7 mg/kg/year (after RTX); p=0.0002, Wilcoxon non-parametric test] were significantly decreased compared with those before RTX infusions

Number of relapses and steroid dose before and after RTX

Following RTX therapy, the number of relapses [2.8 (before RTX) vs. 0.8/year (after RTX); p=0.02, Wilcoxon non-parametric test; Fig. 1a] and the PSL dose [287.9 (before RTX) vs. 70.7 mg/kg/year (after RTX); p=0.0002, Wilcoxon non-parametric test; Fig. 1b] were significantly decreased.

RTX impact on height

Changes in height before and after RTX use are shown in Fig. 2. At the initial administration of RTX, eight patients had a height SDS of less than zero (growth-retarded patients), and their median duration from disease onset to administration of the first RTX dose was 7.7 (range 1.8–11.1) years. In comparison, the median duration from disease onset to the first RTX dose in the five patients whose SDS were more than the average 0 SDS (non-growth retarded patients) at the initiation of RTX therapy was 3.0 years (range 2.5–3.3 years; p=0.02). In total, the height SDS of ten of the 13 patients (77 %) improved significantly after RTX therapy. The mean value of −1.6 SDS before RTX improved to −0.8 SDS after RTX therapy (Fig. 2; p=0.03). Among the eight growth-retarded patients, seven achieved an improvement of height SDS from −2.6 SDS to −1.4 SDS with RTX therapy (not significant). The remaining patient who experienced increased relapses despite RTX therapy (Fig. 1a) had severe progressive growth retardation (−2.5 to −3.8 SDS; Fig. 2). Annual changes in the height SDS after RTX therapy are shown in Fig. 3, while bone age at the first administration of RTX is shown in Table 1.

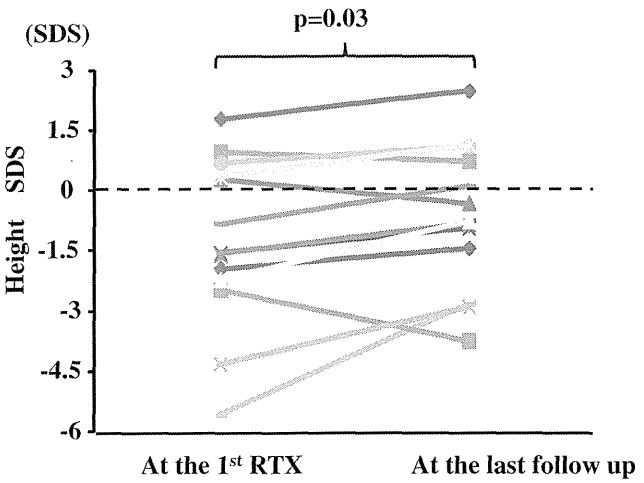

Fig. 2 Changes in height before and after rituximab (RTX) therapy. The height standard deviation score (*SDS*) of 11 of the 13 patients (84.6 %) improved significantly after RTX therapy [n=13; −1.6 (before RTX) vs. −0.8 SDS (after RTX); paired t test, p=0.03]

RTX impact on weight

The obesity index of 12 of the 13 patients (92 %) improved significantly with RTX therapy—from 16.9 % before the administration of RTX to 3.1 % after discontinuation of RTX (Fig. 4; p=0.004).

Adverse effects

Almost half of the patients suffered a mild acute infusion reaction to RTX. Agranulocytopenia was observed in one patient but was successfully treated with granulocyte-colony stimulating factor. No other adverse events were observed.

Discussion

The results of our study add to the increasing body of evidence for the efficacy of RTX against refractory SDNS. While several studies have reported that RTX can achieve a sustained

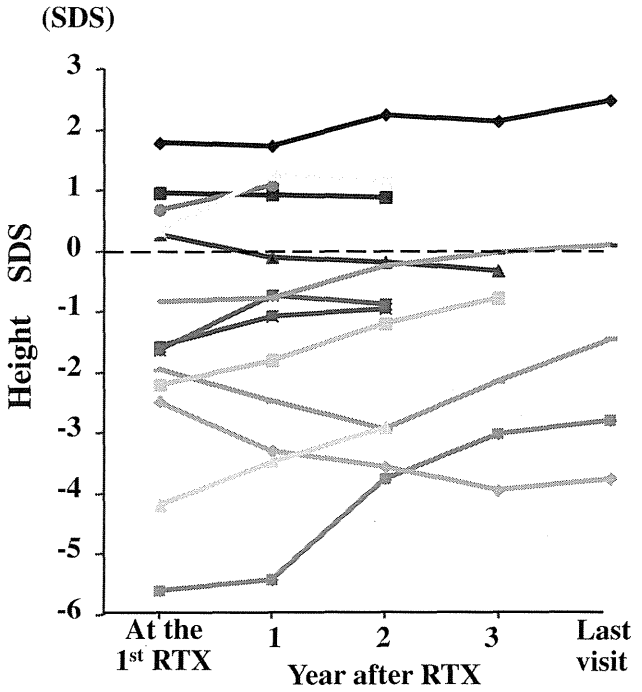

Fig. 3 Annual changes in the height standard deviation score (SDS) after rituximab (RTX) therapy

longer remission and maintain a minimal dose of steroids [10–14], they did not focus on the effect of RTX on height and weight. We found that RTX therapy significantly reduced the number of relapses and the doses of steroids (Fig. 1) and that it contributed to an improvement of growth retardation and the obesity index.

According to reports by Foote et al. [15] and Rüth et al. [16], most patients with steroid-sensitive nephrotic syndrome (SSNS) have a decreasing relapse rate as they grow older, with the final height not significantly affected. Leroy et al. reported

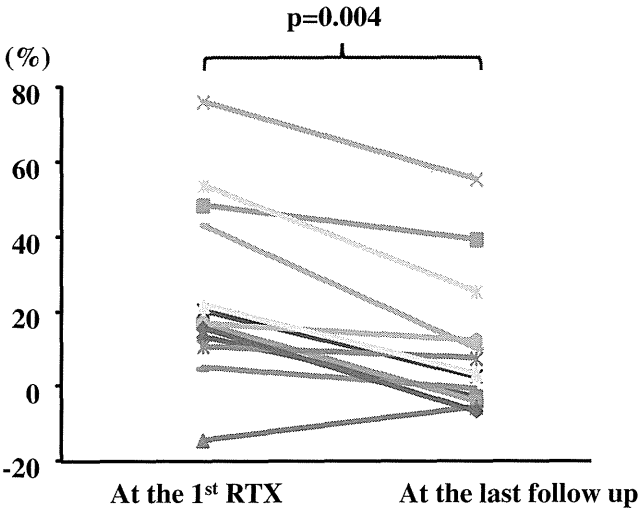

Fig. 4 Changes in the obesity index before and after rituximab (RTX) therapy. The obesity index of 12 of the 13 patients (92.3 %) improved significantly after RTX therapy (n=13; 16.9 vs. 3.1 %; paired t test, p=0.026)

that 25 % of children with SDNS experience severe growth retardation during the course of their disease but that most can achieve catch-up growth during late puberty [17]. In contrast, Kashtan et al. reported that mean final height SDS in five patients with SDNS was −1.2 SDS [5]. A total of 23 patients with FRNS or SDNS reported by Emma et al. had an average loss of 0.9 SDS in height from the onset of nephrotic syndrome when they reached their final height [6]. Furthermore, Kitamura et al. reported that the final height in 30 % of 17 patients with FRNS was below −2.0 of the height SDS [7]. Another study reported that combined administration of the immunosuppressive agents CPA and CsA significantly reduced growth impairment caused by steroids [18]. In our study, the children had a median height of −1.6 SDS prior to receiving RTX infusions, and after the RTX infusions, their median height SDS improved to −0.8 SDS (Fig. 2). Overall, height improvement was seen in ten of the 13 patients (77 %), of whom seven displayed growth retardation prior to RTX treatment.

The five patients who did not show growth retardation before RTX treatment were resistant to multiple immunosuppressive therapy. Hence these patients were treated with RTX to prevent relapses and reduce the PSL dose. Compared to growth-retarded patients at the first RTX infusion, non-growth retarded patients did not achieve a significant improvement in growth after RTX therapy (Fig. 2). However, the median duration from onset of NS to the first RTX infusion between these two groups was significantly different (growth-retarded patients vs. non-growth retarded patients: 7.7 vs 3.0 years; p= 0.02), suggesting that non-growth-retarded patients might have experienced growth retardation if SDNS had persisted. Based on these results, we hypothesize that RTX would prevent future loss of height SDS in some non-growth retarded patients.

It has been demonstrated that children who continue to receive steroids after the age of 9 years (for girls) and 11 years (for boys) may be at a higher risk of growth retardation due to the loss of the growth spurt in adolescence [5]. On the other hand, a late pubertal growth spurt allows a certain degree of catch-up growth even at an older age [16, 17]. In our study, the five patients who had their bone age measured before RTX treatment showed a marked delayed bone age (median age difference between chronologic age and bone age was 2.5 years, range 0.5–7.4 years). In particular, patients No. 7 and No. 12 showed excellent catch-up growth after RTX treatment, as indicated by their improved height SDS (Fig. 2; Table 1). This result indicates that RTX in older children may contribute to growth if their bone age is delayed but the epiphyseal line is still open. We have shown that RTX improved the height of three patients who were older than 16 years at the first RTX infusion (median improvement of height SDS: 0.9 SDS, range 0.6–1.4 SDS; Table 1; Fig. 3). Among these, the LHRH analog was used for one patient

(patient No.12) to delay his puberty so as to prolong his growing period. However, with the records available, we were unable to evaluate how the LHRH analog affected growth in this particular patient.

The body shape resulting from long-term exogenous exposure to glucocorticoids is described as cushingoid, in reference to the body shape observed in Cushing's disease. Cushing's disease is classically characterized by obesity, with redistribution of fat from the limbs to the trunk, decreased lean mass and proximal muscle wasting. According to reports by Elzouki et al. [19] and Meritt et al. [20], 35–43 % children with SSNS are obese. Foster et al. reported that obesity is a common complication among children with SSNS; in their study, 41 % of children with SSNS were obese compared with 16 % of the 186 community-based reference subjects [21]. In our study, the obesity index was 16.9 % before RTX therapy, improving to 3.1 % after RTX (Fig. 4).

Several studies have demonstrated behavioral and psychological difficulties in children with nephrotic syndrome which are likely to affect the overall outcome of the disease in an adverse manner. Rüth et al. evaluated the health-related quality of life and psychosocial adjustment in patients with SSNS and showed that the quality of life subscale "social functioning" was significantly impaired [22]. A number of other studies have reported a significant correlation between treatments with high doses of corticosteroids and behavioral problems [23–25]. As growth retardation, obesity, hypertrichosis, acne and cutaneous striae can have a negative effect on the patient's self-esteem and quality of life, RTX may have great value in preventing these negative outcomes by reducing the patient's dependency on steroids.

Our study is limited by several factors: the small number of patients, the heterogeneity of the patient population and a relatively short observation period. At the same time, the cumulative dose, duration of continuous versus alternate-day steroid therapy before RTX, variability in pharmacokinetics and/or susceptibility to steroids between individuals, hypoproteinemia and pubertal status could all influence growth. We were unable to evaluate the effect of these factors on growth in our patients due to the retrospective nature of the study.

While RTX is generally well tolerated, it does occasionally cause severe or life-threatening adverse events, including progressive multifocal leukoencephalopathy, interstitial pneumonia and ulcerative colitis [26]. As such, to evaluate the potential side effects of RTX, a larger number of patients together with a longer follow-up are necessary for future studies. Nonetheless, our study has shown that RTX may have a significant steroid-sparing effect that improves growth and reduces obesity in a group of children with SDNS who suffered from severe steroid side effects.

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Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial

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Summary

Background Rituximab could be an effective treatment for childhood-onset, complicated, frequently relapsing nephrotic syndrome (FRNS) and steroid-dependent nephrotic syndrome (SDNS). We investigated the efficacy and safety of rituximab in patients with high disease activity.

Methods We did a multicentre, double-blind, randomised, placebo-controlled trial at nine centres in Japan. We screened patients aged 2 years or older experiencing a relapse of FRNS or SDNS, which had originally been diagnosed as nephrotic syndrome when aged 1–18 years. Patients with complicated FRNS or SDNS who met all other criteria were eligible for inclusion after remission of the relapse at screening. We used a computer-generated sequence to randomly assign patients (1:1) to receive rituximab (375 mg/m^2) or placebo once weekly for 4 weeks, with age, institution, treatment history, and the intervals between the previous three relapses as adjustment factors. Patients, guardians, caregivers, physicians, and individuals assessing outcomes were masked to assignments. All patients received standard steroid treatment for the relapse at screening and stopped taking immunosuppressive agents by 169 days after randomisation. Patients were followed up for 1 year. The primary endpoint was the relapse-free period. Safety endpoints were frequency and severity of adverse events. Patients who received their assigned intervention were included in analyses. This trial is registered with the University Hospital Medical Information Network clinical trials registry, number UMIN000001405.

Findings Patients were centrally registered between Nov 13, 2008, and May 19, 2010. Of 52 patients who underwent randomisation, 48 received the assigned intervention (24 were given rituximab and 24 placebo). The median relapse-free period was significantly longer in the rituximab group (267 days, 95% CI 223–374) than in the placebo group (101 days, 70–155; hazard ratio: 0·27, 0·14–0·53; p<0·0001). Ten patients (42%) in the rituximab group and six (25%) in the placebo group had at least one serious adverse event (p=0·36).

Interpretation Rituximab is an effective and safe treatment for childhood-onset, complicated FRNS and SDNS.

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Introduction

Childhood nephrotic syndrome is a disorder affecting the kidneys in which a large amount of protein passes through the glomerular filter, resulting in hypoproteinaemia and generalised oedema. Idiopathic nephrotic syndrome occurs in two or more of every 100 000 children[1] and is the most common chronic glomerular disease in paediatric nephrology practice. Minimal change nephrotic syndrome is the most common form of the disorder, for which steroid therapy is effective for most patients.[2] Those who respond well rarely progress to chronic renal failure, but up to half develop frequently relapsing nephrotic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS; table 1).[2] Moreover, 10–20% of patients with idiopathic nephrotic syndrome have steroid-resistant nephrotic syndrome (table 1).[2]

Standard treatments for FRNS, SDNS, and steroid-resistant nephrotic syndrome are immunosuppressive agents: cyclophosphamide, chlorambucil, ciclosporin, tacrolimus, and levamisole are used for paediatric FRNS or SDNS, and ciclosporin for paediatric steroid-resistant nephrotic syndrome.[3–5] Most children are effectively treated with these drugs; however, some have frequent relapses. In two studies,[6,7] 10–20% of children taking ciclosporin had frequent relapses, and in another study,[8] about 30% of the patients with steroid-resistant nephrotic syndrome after ciclosporin had steroid-sensitive, frequent relapses after complete remission. In addition to being ineffective in some patients, ciclosporin can cause side-effects—the most common of which is chronic nephrotoxicity[9,10]—suggesting that it should be discontinued within 24 months. However, discontinuation of ciclosporin almost always results in frequent relapses requiring long-term steroid treatment,[11]

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which also poses a long-term risk to children. Therefore, a new treatment that does not involve steroids or immunosuppressive agents is urgently needed.

In the past 10 years, rituximab has had some success in complicated FRNS and SDNS,[12,13] and several research groups have done single-arm or short-term studies of this drug.[14–16] The 2012 Kidney Disease: Improving Global Outcomes clinical practice guidelines[17] introduced rituximab as a treatment option for childhood-onset, complicated FRNS and SDNS. However, the efficacy and safety of rituximab for complicated FRNS and SDNS are yet to be established.[17] We aimed to assess the efficacy and safety of rituximab in patients with high disease activity.

Methods

Study design and participants

In a multicentre, double-blind, randomised, placebo-controlled trial, we enrolled patients at nine centres in Japan. Full eligibility criteria are listed in the appendix. Briefly, we screened patients aged 2 years or older experiencing a relapse of FRNS or SDNS, which had originally been diagnosed as nephrotic syndrome when aged 1–18 years (appendix). Patients with complicated FRNS or SDNS (table 1) who met all other criteria were eligible for inclusion after remission of the relapse they were experiencing at screening.

This study was approved by the institutional review boards at each centre and complied with the Declaration of Helsinki. Participants aged 20 years or older or parents of younger patients provided written informed consent.

Randomisation and masking

Once full eligibility was confirmed, patients were randomly assigned (1:1) to rituximab or placebo. We applied the minimisation method using a computer-generated sequence (SAS PROC PLAN), with age, institution, treatment history (whether a steroid or an immunosuppressive drug, or both, was given during the relapse immediately before randomisation), and the intervals between the previous three relapses as adjustment factors. Patients, patients' guardians, caregivers, treating physicians, and individuals assessing outcomes were masked to assignments. Investigators and patients (or their legal representatives) were masked to peripheral blood B-cell counts, which were centrally monitored. To maintain blinding, allocation codes were disclosed only after the entire clinical trial was completed and all data were locked. However, investigators could request the disclosure of a patient's allocation code urgently in the case of a serious adverse event that could lead to death or was life-threatening, a serious adverse event for which the information was essential to establish what treatment was necessary, or treatment failure.

Procedures

Patients received the first dose of their assigned drug within 2 weeks after randomisation. Patients assigned to rituximab received an intravenous dose of 375 mg/m² (maximum 500 mg) once weekly for 4 weeks. Because the optimum dose for paediatric FRNS and SDNS has not been established, we selected this dosing schedule on the basis of previous reports of rituximab's ability to prevent relapses in patients with immunosuppressant-resistant SDNS[12,13,18] and on the recommended dose for treating B-cell lymphoma, which has a known safety profile. Patients assigned to placebo received intravenous injections of a matched placebo at the same frequency. We used pretreatments to prevent infusion reaction (appendix). Patients could cease assigned treatment if they met discontinuation criteria (appendix).

Participants receiving prednisolone for the relapse at screening continued receiving the drug, taking 60 mg/m² orally three times a day (maximum of 80 mg per day) for 4 weeks. Participants not receiving prednisolone at screening received the same dose until 3 days after complete remission was achieved. After 4 weeks (in patients who received prednisolone at screening) or from 3 days after complete remission (in patients who did not receive prednisolone at screening), patients took 60 mg/m² prednisolone in the morning on alternate days (maximum

	Definition
FRNS	≥2 relapses of nephrotic syndrome within 6 months after initial remission, or ≥4 relapses within any 12-month period
SDNS	2 relapses of nephrotic syndrome during the reduction of steroid treatment or within 2 weeks of discontinuation of steroid treatment
SRNS	Persistent proteinuria after 60 mg/m² oral prednisolone per day for 4 weeks
Complicated FRNS or SDNS	Patients diagnosed with FRNS or SDNS when aged 2 years or older, who had ≥4 relapses in a 12-month period or steroid dependence at any point in the 2 years before relapse at screening, after completion of immunosuppressive drug treatment (eg, ciclosporin, cyclophosphamide, mizoribine, or mycophenolate mofetil); or patients diagnosed with FRNS or SDNS when aged 2 years or older, who had ≥4 relapses in a 12-month period or steroid dependence diagnosed at any point in the 2 years before relapse at screening, during immunosuppressive drug treatment (eg, ciclosporin, cyclophosphamide, mizoribine, or mycophenolate mofetil); or patients with a history of SRNS and diagnosed with FRNS or SDNS when aged 2 years or older, who had ≥4 relapses in a 12-month period or steroid dependence at any point in the 2 years before relapse at screening, during or after the completion of immunosuppressive drug treatment (eg, ciclosporin or a combination of ciclosporin and methylprednisolone)

FRNS=frequently relapsing nephrotic syndrome. SDNS=steroid-dependent nephrotic syndrome. SRNS=steroid-resistant nephrotic syndrome.

Table 1: **Definitions**