Rituximab therapy in adults with steroid-dependent nephrotic syndrome

Hongzhen Zhong[1], Hong-Yan Li[2], Tianbiao Zhou[1], Wenjuan Weng[1]

[1]Department of Nephrology, the Second Affiliated Hospital of Shantou University Medical College, Shantou, China
[2]Department of Nephrology, Huadu District People's Hospital of Guangzhou, Southern Medical University, Guangzhou, China

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Corresponding author:
Tianbiao Zhou
Department
of Nephrology
the Second Affiliated
Hospital of Shantou
University Medical
College
Shantou, China
E-mail: zhoutb@aliyun.com

Abstract

Introduction: Patients with steroid-dependent nephrotic syndrome (SDNS) suffer frequent relapse with adverse effects caused by long-term prednisolone treatment. Recently, the chimeric monoclonal antibody against the protein CD20 (rituximab – RTX) was observed to be efficacious and safe in the treatment of patients with SDNS. We summarized the scientific literature to evaluate RTX therapy in the clinical management of SDNS.
Material and methods: PubMed, EMBASE, and Cochrane Library databases were investigated from interception to 2019-6-6, without language limitation. The analysis was restricted to adults ≥ 19 years of age. Data were administered and analyzed through the Review manager 5.3 software.
Results: After RTX treatment, relapse times, prednisolone dose, and proteinuria decreased, whereas serum albumin was increased. The clinical parameters blood pressure and total cholesterol diminished also, whereas bone mineral density was improved. Overall, RTX ameliorated the adverse effects of prednisolone. Moreover, the Th1/Th2 ratio was changed except for the CD19 and CD20 cell counts. Additionally, most of the adverse effects of RTX were mild and well tolerated.
Conclusions: In the studies that we considered, we concluded that RTX treatment was effective and safe in the therapy of patients with SDNS. Nevertheless, more randomized controlled trials are required to explore the mechanism of RTX action and verify its efficacy.

Key words: steroid-dependent nephrotic syndrome, rituximab, efficacy, safety.

Introduction

Steroid-dependent nephrotic syndrome (SDNS) is a class of refractory nephrotic syndrome. A patient with SDNS relapses during steroid taper or withdrawal. Moreover, maintaining high-dose treatment for long term causes severe immunosuppressive effects [1, 2], and increases morbidity and mortality [3, 4]. Other side effects caused by steroid treatment such as cushingoid features, hypertension, growth failure, and emotional problems are also reported [5].

Severe proteinuria and hypoproteinemia characterize the nephrotic syndrome, which is common in children and adults [6]. Rituximab (RTX), a chimeric monoclonal anti-CD20 antibody, is used in the treatment of

several immune diseases [7–9], and recently it was observed to be efficacious in the treatment of pediatric and adult SDNS [10–15].

To explore the efficacy and safety of RTX treatment in patients with SDNS, we reviewed the literature regarding its therapeutic use in SDNS.

Material and methods

Literature search

Search terms were "rituximab" or "anti-CD20 antibodies" and "steroid-dependent nephrotic syndrome" or "SDNS" or "frequently relapsing nephrotic syndrome" or "FRNS". Currently, RTX is permitted only in children with SDNS, so Clinical Trials were waived, and keyword searches were conducted in PubMed, EMBASE and Cochrane Library from interception to 2019-6-6, without language limitation. We considered only adult cases (age ≥ 19). Reference lists of every relevant trial or review article were also searched. Disagreement was resolved through discussion.

Inclusion and exclusion criteria

Included articles met the following criteria: 1) Diseases: SDNS or FRNS. 2) Treatment: RTX. 3) Patients' age ≥ 19. Exclusion criteria: 1) Secondary treatment for other systemic diseases; 2) Combined treatment with other immunosuppressive drugs; 3) Patients' age < 19.

Data extraction

Data from eligible studies were divided into two parts: 1) Basic information: the first author, publication year, PMID in PubMed, database identification number, number of patients, age of patients, administration of RTX, follow-up; 2) Outcomes data: clinical characterization (relapse, prednisolone dose, serum albumin, proteinuria and serum creatinine), immunological characterization (IgG, CD19 cell count, CD20 cell count, CD4/8 ratio, Th1/2 ratio). Adverse effect (AE) of prednisolone (body mass index (BMI), total cholesterol, diastolic blood pressure (DBP), systolic blood pressure (SBP), bone mineral density (BMD), and T-score of BMD), and AE of RTX.

Statistical analysis

Hypoalbuminemia, severe proteinuria, prednisolone dose and frequent relapse were characteristics of SDNS. So, relapse times, prednisolone dose and those laboratory indexes were extracted to estimate the efficacy of RTX in SDNS. Heavy and long-term treatment with prednisolone causes obesity, hyperlipidemia, hypertension and osteoporosis. Thus, we compared the BMI, blood total cholesterol, SBP, DBP, BMD and *T*-score to assess whether RTX reduced the adverse effect of prednisolone in patients with SDNS. RTX is a monoclonal antibody targeting CD20 positive cells. We reported the data regarding the level of IgG, CD19 cell count, CD4/8 cell ratio and Th1/2 cell ratio except CD20 cells to explore the immunological influence of RTX in patients.

Data were extracted to compare the pre- with the post-RTX treatment and management with the Review manager 5.3 software to calculate the mean differences. Data were continuous variables and were expressed as mean ± standard deviation (SD). Standardized mean difference (SMD) with 95% confidence intervals were used. We calculated I^2 to estimate the heterogeneity of the included studies. When $I^2 < 50\%$, we used a fixed-effects model. In the case of $I^2 \geq 50\%$ to assume substantial variability, we used a random-effects model. We considered significant those differences with a p-value < 0.05.

Results

Search results and study characteristics

Among the 135 abstracts identified, 8 fitted our inclusion criteria with 209 patients and a male/female ratio of 143/66. The follow-up period was no less than 12 months. RTX was administered in a single dose of 375 mg/m^2 at 6-month intervals or 1000 mg (Table I).

Rituximab was effective in the treatment of SDNS

Four studies [16–19] (102 patients) were included to assess the influence of RTX on disease relapse. The I^2 was 0, so a fixed effects model was used. We found a statistically significant difference between pre- and post-RTX treatment relapse in SDNS patients after RTX was administered less frequently (SMD: –1.96 (–2.30, –1.62), $p < 0.00001$; Figure 1).

Four studies [16, 19–21] registered the influence of RTX on prednisolone dose. Since the I^2 was 50%, moderate heterogeneity existed, and a random effects model was conducted. Total impact was –2.23 (–2.69, –1.77) with $p < 0.00001$ on the dose of prednisolone, showing statistical significance. So, the dose of prednisolone required was reduced after RTX administration (Figure 1).

Six studies [17–22] (173 patients) were included to estimate the influence of RTX on the level of serum albumin. The value of I^2 was 97%, which showed substantial heterogeneity, then a random effects model was chosen. The SMD was 2.52 (0.95, 4.08) with $p = 0.002$, which showed that the level of serum albumin between baseline and post-RTX was statistically significant, and the level of serum albumin increased after RTX administration (Figure 1).

Table I. Basic characteristics of eligible studies

Author, year	PMID	Study type	Patient (*n*)	Male/female (*n*/*n*)	Age [years]	RTX administration	Follow-up period [months]
Miyabe 2016	26138356	Comparative study	54	41/13	28.2 ±10.4	A single dose of 375 mg/m^2 BSA at 6-month interval	24
Iwabuchi 2018	30334956	Comparative study; observational study	19	12/7	36.0 ±11.4	375 mg/m^2 of RTX at 6-month intervals	24
Takura 2017	28387313	Prospective study	30	21/9	29.1 ±11.4	375 mg/m^2 body surface area once weekly for 4 weeks	24
Takei 2013	23239834	Prospective study	25	19/6	30 ±12	375 mg/m^2 of RTX at 6-month intervals	12
Iwabuchi 2014	25546674	Prospective cohort study	25	21/4	30.1 ±11.9	375 mg/m^2 of RTX at 6-month intervals	24
DaSilva 2017	28534103	Retrospective study	28	16/12	37 ±15	Infusions of rituximab 1000 mg or 375 mg/m^2	31 ±26
Ruggenenti 2014	24480824	Multicenter clinical study	20	10/10	34.3 (22.7–47.4)	375 mg/m^2 of rituximab was infused according to circulating B cells	12
Katsuno 2019	30121802	Retrospective cohort study	8	3/5	40.8 ±11.5	1137.5 ±866.7 mg	13.9 (11.6–20.0)

RTX – rituximab.

Four studies [17, 19–21] (134 patients) were considered to investigate the effect of RTX on proteinuria. Since proteinuria disappeared after RTX treatment in two studies [17, 19], these data could not be pooled for analysis. Proteinuria was ≤ 0.5 g/day, which was defined as a complete response in the treatment of nephrotic syndrome, and the level of proteinuria met the criteria in the other two studies [20, 21]. So, proteinuria was lower after RTX treatment (Figure 1).

Six studies [17–22] could evaluate the role of RTX in the change of serum creatinine. The value of I^2 = 0% indicates no heterogeneity, so a fixed effects model was used. The SMD was –0.13 (–0.34, 0.09) with p = 0.25, which was more than 0.5. No statistically significant difference was detected, so the level of serum creatinine was undifferentiated between post-RTX and baseline (Figure 1).

Rituximab reduced the adverse effect of prednisolone

Three [18, 20, 22] of the eight quality studies were associated with BMI. Since no heterogeneity was found (I^2 = 0%), we applied a fixed-effects model. The BMI after RTX treatment was similar to baseline (SMD = 0.01 (–0.29, 0.32); p = 0.93) (Figure 2).

Five studies [17, 18, 20–22] assessed the effect of RTX in the SBP and DBP. Both I^2 = 0%, no obvious heterogeneity was shown, so a fixed effects model was conducted. The SMDs were –0.54 (–0.79, –0.29) with p < 0.0001 and –0.48 (–0.73, –0.24) with p = 0.0001 for SBP and DBP, respectively. Both had statistical significance, so after RTX administration, SBP and DBP were lower than baseline (Figure 2).

The influence of RTX on the total cholesterol was assessed in five studies [17, 19–22]. Large heterogeneity was observed in the included studies (I^2 = 67%), so a random effects model was used. There was a statistically significant difference between post-RTX and baseline (SMD was –0.97 (–1.40, –0.54) with p < 0.00001), showing that total cholesterol was lower after RTX administration (Figure 2).

The impact of RTX administration was assessed by BMD [17, 19, 20] and *T*-score of BMD [18–20] in three studies. Both heterogeneities were large, for I^2 = 92% and I^2 = 98% in BMD and *T*-score of BMD, and random effects models were used. The SMDs were 1.26 (0.19, 2.34), p = 0.02 and 1.26 (–0.94, 3.46), p = 0.26 respectively. Statistical significance was observed in BMD but not *T*-score of BMD; the level of BMD increased after RTX was administered but not T-score of BMD (Figure 2).

Some immunological indexes were changed after RTX was administered

Four studies [17–20] evaluated the change of IgG. Overall, the I^2 was 97%, which showed substantial heterogeneity, so a random effects model was conducted. The result of pooled data was 2.54 (0.53, 4.55) with p = 0.01, showing statistical significance for IgG levels (Figure 3).

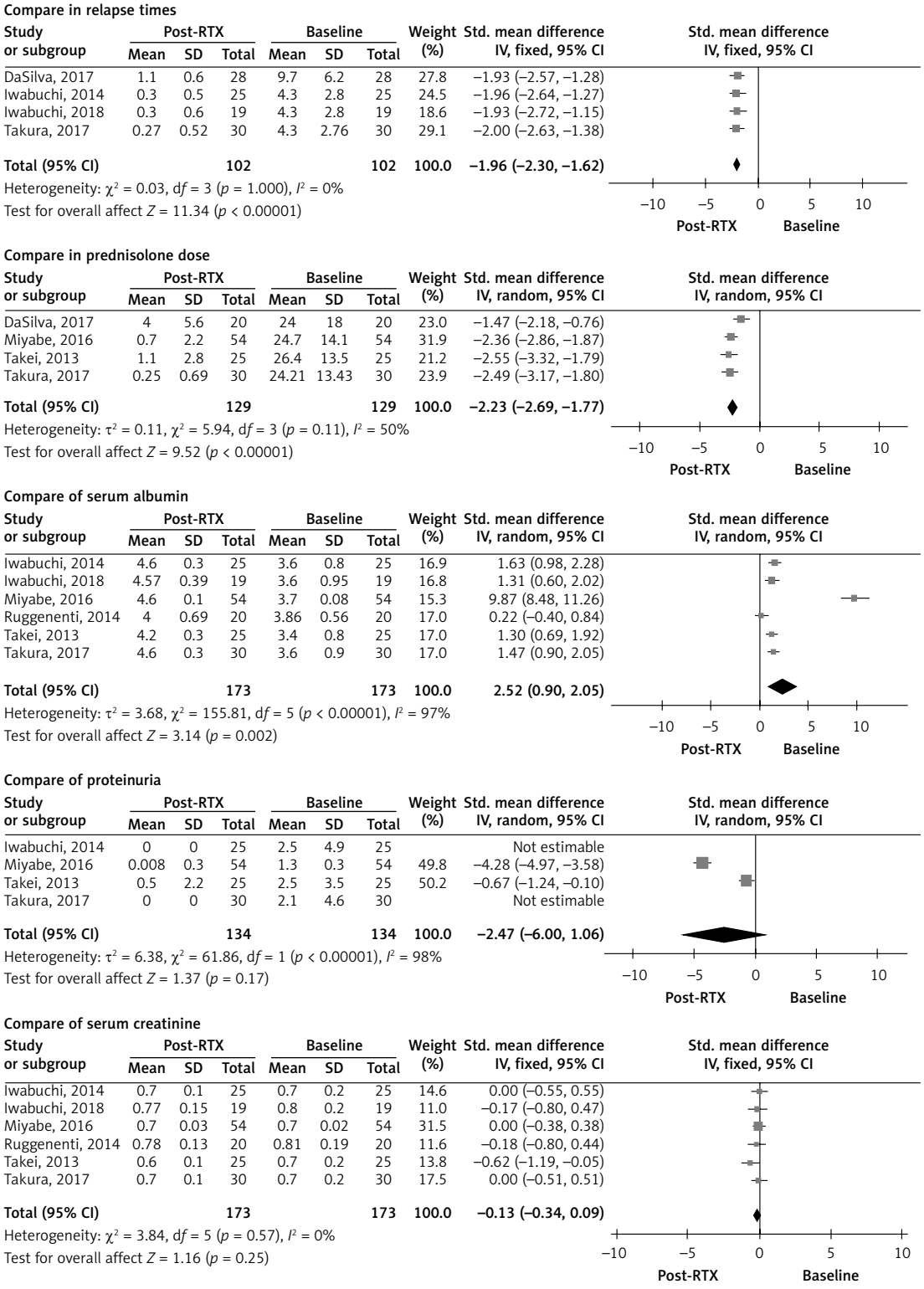


Figure 1. Efficacy of rituximab in SDNS

Three studies [17, 19, 20] were included to analyze the change of CD20 and CD19 cells. Both I^2 values (99%) justify the random-effects model. The pooled results were –4.90 (–8.88, –0.93) with p =0.02 and –4.52 (–8.42, –0.63) with p = 0.02 respectively, showing statistically significant differences, and CD20 and CD19 cell counts were lower than baseline, as expected (Figure 3).

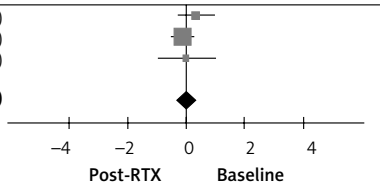
Four studies [17–20] were about the change of CD4/8 after RTX was administered. The I^2 was 97%, which means substantial heterogeneity, and a random-effects model was applicable. The

Change in BMI

Study or subgroup	Post-RTX Mean	SD	Total	Baseline Mean	SD	Total	Weight (%)	Std. mean difference IV, fixed, 95% CI
Iwabuchi, 2018	23	3	19	21.9	3.3	19	23.2	0.34 (–0.30, 0.98)
Miyabe, 2016	21.9	11	54	23	11.9	54	66.9	–0.10 (–0.47, 0.28)
Ruggenenti, 2014	25.6	6.9	8	25.7	5.7	8	9.9	–0.01 (–0.99, 0.97)
Total (95% CI)			**81**			**81**	**100.0**	**0.01 (–0.29, 0.32)**

Heterogeneity: $\chi^2 = 1.33$, d$f = 2$ ($p = 0.51$), $I^2 = 0\%$

Test for overall affect $Z = 0.09$ ($p = 0.93$)

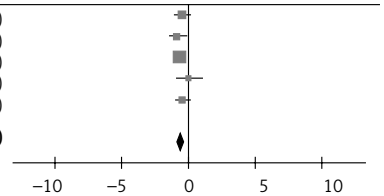


Change in SBP

Study or subgroup	Post-RTX Mean	SD	Total	Baseline Mean	SD	Total	Weight (%)	Std. mean difference IV, fixed, 95% CI
Iwabuchi, 2014	117	14	25	123	13	25	19.4	–0.44 (–1.08, 0.12)
Iwabuchi, 2018	111	12.4	19	121	12.7	19	14.0	–0.78 (–1.44, –0.12)
Miyabe, 2016	111.8	13.8	54	120.9	14.1	54	40.8	–0.65 (–1.03, –0.26)
Ruggenenti, 2014	123.4	13.1	8	122	11.9	8	6.4	0.11 (–0.88, 1.09)
Takei, 2013	113	13	25	119	13	25	19.4	–0.45 (–1.02, 0.11)
Total (95% CI)			**131**			**131**	**100.0**	**–0.54 (–0.79, –0.29)**

Heterogeneity: $\chi^2 = 2.68$, d$f = 4$ ($p = 0.61$), $I^2 = 0\%$

Test for overall affect $Z = 4.27$ ($p < 0.0001$)

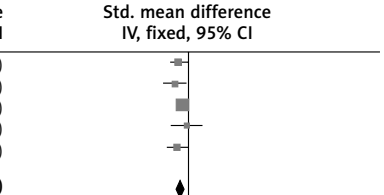


Change in DBP

Study or subgroup	Post-RTX Mean	SD	Total	Baseline Mean	SD	Total	Weight (%)	Std. mean difference IV, fixed, 95% CI
Iwabuchi, 2014	69	14	25	76	11	25	19.0	–0.55 (–1.11, 0.02)
Iwabuchi, 2018	65.8	10.5	19	74.1	9.8	19	13.8	–0.80 (–1.46, –0.14)
Miyabe, 2016	70.3	11.6	54	74.4	12.9	54	42.1	–0.33 (–0.71, 0.05)
Ruggenenti, 2014	73.8	10.3	8	75	9.1	8	6.3	–0.12 (–1.10, 0.86)
Takei, 2013	67	9	25	74	12	25	18.7	–0.65 (–1.22, 0.08)
Total (95% CI)			**131**			**131**	**100.0**	**–0.48 (–0.73, –0.24)**

Heterogeneity: $\chi^2 = 2.40$, d$f = 4$ ($p = 0.66$), $I^2 = 0\%$

Test for overall affect $Z = 3.84$ ($p = 0.0001$)

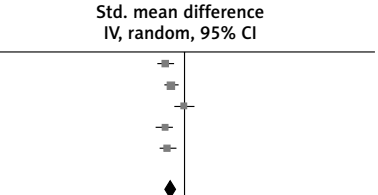


Change in total cholesterol

Study or subgroup	Post-RTX Mean	SD	Total	Baseline Mean	SD	Total	Weight (%)	Std. mean difference IV, random, 95% CI
Iwabuchi, 2014	179	41	25	262	79	25	18.7	–1.30 (–1.91, –0.68)
Miyabe, 2016	178.6	154	54	282.5	12.4	54	24.1	–0.94 (–1.34, –0.55)
Ruggenenti, 2014	212	83	20	215	68	20	18.6	–0.04 (–0.66, 0.58)
Takei, 2013	188	48	25	285	86	25	18.5	–1.37 (–1.99, –0.75)
Takura, 2017	185.3	38.7	30	287	112.1	30	20.2	–1.20 (–1.75, –0.64)
Total (95% CI)			**154**			**154**	**100.0**	**–0.97 (–1.40, –0.54)**

Heterogeneity: $\tau^2 = 0.16$, $\chi^2 = 12.03$, d$f = 4$ ($p = 0.02$), $I^2 = 67\%$

Test for overall affect $Z = 4.46$ ($p < 0.00001$)

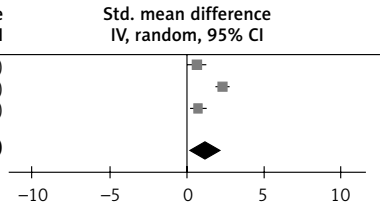


Change in BMD

Study or subgroup	Post-RTX Mean	SD	Total	Baseline Mean	SD	Total	Weight (%)	Std. mean difference IV, random, 95% CI
Iwabuchi, 2014	0.95	0.1	25	0.84	0.2	25	32.9	0.68 (0.11, 1.26)
Miyabe, 2016	0.9	0.03	54	0.83	0.03	54	33.7	2.32 (1.83, 2.81)
Takura, 2017	0.94	0.13	30	0.83	0.15	30	33.4	0.77 (0.25, 1.30)
Total (95% CI)			**109**			**109**	**100.0**	**1.26 0.19, 2.34)**

Heterogeneity: $\tau^2 = 0.83$, $\chi^2 = 24.69$, d$f = 2$ ($p < 0.00001$), $I^2 = 92\%$

Test for overall affect $Z = 2.31$ ($p = 0.02$)



***T*-score of BMD**

Study or subgroup	Post-RTX Mean	SD	Total	Baseline Mean	SD	Total	Weight (%)	Std. mean difference IV, random, 95% CI
Iwabuchi, 2014	0.85	1.08	19	1.56	1.6	19	33.2	–0.51 (–1.16, 0.14)
Miyabe, 2016	–1.1	0.2	54	–1.8	0.2	54	33.3	3.48 (2.87, 4.08)
Takura, 2017	–0.73	0.78	30	–1.65	1.38	30	33.5	0.81 (0.28, 1.34)
Total (95% CI)			**103**			**103**	**100.0**	**1.26 (–0.94, 3.46)**

Heterogeneity: $\tau^2 = 3.69$, $\chi^2 = 83.08$, d$f = 2$ ($p < 0.00001$), $I^2 = 98\%$

Test for overall affect $Z = 1.12$ ($p = 0.26$)

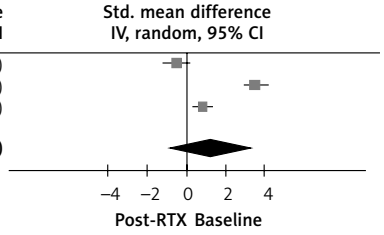


Figure 2. Impact of RTX on the adverse effects of prednisolone

BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, BMD – bone mineral density.

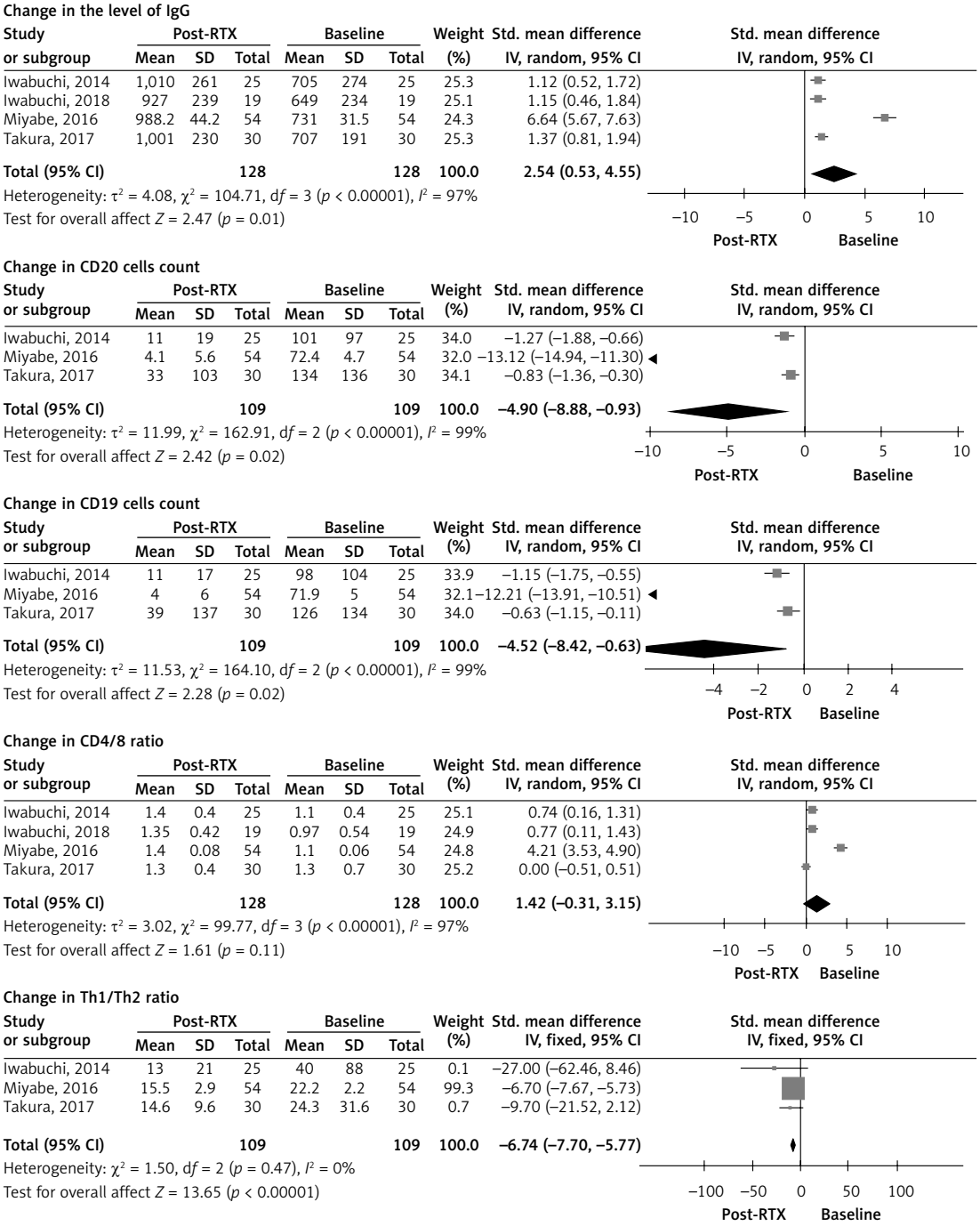


Figure 3. Change of immunological indexes after RTX was administered

pooled result was 1.42 (–0.31, 3.15) with $p = 0.11$, and no statistically significant difference was observed. CD4/8 ratio was similar to baseline after RTX treatment (Figure 3).

The effect of RTX on the change of Th1/Th2 ratio was favorable in three studies [17, 19, 20]. $I^2 = 0\%$, no obvious heterogeneity was detected, and a fixed-effects model was conducted. The result of pooled data was –6.74 (–7.70, –5.77) with $p < 0.00001$, and a statistically significant difference was observed between baseline and post-RTX. Th1/Th2 ratio was lower after RTX was administered (Figure 3).

Adverse effects of rituximab

The AEs [16–18, 21] of RTX are summarized in Table II. The most common adverse effect was infusion reaction, which occurs within 24 h after RTX administration. The long-term AEs were referable to hematologic reactions, such as leukopenia, neutropenia and agranulocytosis. Those AEs were mild, reversible or curable.

Table II. Adverse effects of rituximab

Adverse effects	Clinical symptoms	Time to event	Treatment and results
Infusion reactions	Chills, cough, headache, hiccough, nausea, itching, pruritus, skin rash	Within 24 h after infusion	Disappeared without treatment or with a reduction of the infusion speed
Flu-like reactions	Chills, headache, nausea, pharyngalgia, pyrexia	Shortly after RTX infusion	Improved with betamethasone or reduction of the rate of RTX infusion
Exanthema	A fixed drug eruption on the trunk	Immediately after the start of administration of RTX	Improved with betamethasone
Cardiovascular reactions	Hypotension, sinus tachycardia, sinus bradycardia	During RTX infusion	Improved following treatment with betamethasone or reduction of the rate of rituximab infusion
Hematologic reactions	Leukopenia, neutropenia, agranulocytosis	1) Neutropenia and leukopenia occurred at 1 month or 9 months from the baseline 2) Agranulocytosis occurred at 11 months from the baseline	1) Neutropenia and leukopenia recovered without any treatment within 1 month or 3 months later 2) Agranulocytosis improved with G-CSF administration

RTX – rituximab, G-CSF – granulocyte colony-stimulating factor.

Discussion

Treatment of steroid-dependent nephrotic syndrome usually involves steroids accompanied by a broad array of immunosuppressants. The most commonly used immunosuppressive drugs are calcineurin inhibitors, alkylating agents, and anti-proliferative immunosuppressants. However, while alkylating agents and anti-proliferative immunosuppressants had compromised defense against viruses and malignancy [23], calcineurin inhibitors cause significant nephrotoxicity [24]. In our meta-analysis, we found RTX effective in the treatment of SDNS by reducing relapse, prednisolone dose, and proteinuria, increasing the level of albumin and having no impact on the serum creatinine. RTX was also able to reduce total cholesterol and blood pressure, and increase serum IgG. RTX alleviated some side-effects of prednisolone, by the reduction of prednisolone dose, and ameliorating the immune response and the lipid metabolism [18]. Ruggenenti *et al.* [22] also found that RTX treatment benefited blood pressure in pediatric cases. We confirmed some studies that found RTX able to improve patients' BMD [17, 20, 21]. However, the *T*-score of BMD failed to show any significant difference. Each diagnostic model had certain limitations, and better diagnostic criteria are required. Moreover, the heterogeneity we found in some studies prevented us from conducting a more robust analysis.

RTX reduced autoantibody levels [25] and ameliorated chronic inflammatory diseases mediated by T and B cells [26]. Kamburova *et al.* [27] found that RTX induces stronger T-cell proliferation (especially Th2-like cells) by B cell stimulation when compared to untreated patients. This partially explains our finding that the Th1/Th2 ratio was lower after RTX administration.

RTX depletes B cells through antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and apoptosis [28, 29], which determine the therapeutic use in malignant B-cell lymphoma [30], and the reduced auto-antibodies in various autoimmune disorders [31, 32]. Moreover, B cells had an additional role in producing permeability factors with T cells, which provided a rationale for RTX therapy [33]. Interestingly, Fornoni *et al.* [34] found that RTX prevents the disruption of podocyte apoptosis and actin cytoskeleton through the phosphodiesterase acid-like 3b. All of these data along with our results demonstrate the efficacy of RTX in the treatment of SDNS.

There are some limitations of our analysis. First, the studies included were not randomized controlled trials. Kamburova *et al.* [35] demonstrated the effect of RTX on the immune response not only through B cell depletion, but also through the cellular functions of the remaining B cells. Thus, the efficacy of RTX might not be as optimistic as we observed. Second, compared with baseline condition, it whittled down self-healing capacity, but it cab eliminate individual difference at the extreme. Third, Munyentwali *et al.* [15] observed that the relapse of steroid-dependent minimal change disease usually occurred after the reappearance of CD19 cells. Unfortunately, there are no further analyses of the temporal relations between relapse times and CD19 cell count.

In conclusion, so far, RTX has proved to be an effective and well-tolerated drug for the treatment of SDNS. However, more studies are needed to better evaluate its efficacy, long-term safety and mechanism of action.

Acknwoledgments

Hongzhen Zhong, Hong-Yan Li and Tianbiao Zhou should be regarded as joint first authors.

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Conflict of interest

The authors declare no conflict of interest.

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