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Original Article

Efficacy and safety of rituximab in children with steroid- and calcineurin inhibitor-dependent nephrotic syndrome: a systematic review of randomized controlled trials

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Abstract

Background Iron deficiency (ID) is a common micronutrient problem, especially in pregnant women in developing countries such as Indonesia. Moreover, vitamin D deficiency is also a major concern in worldwide public health. A correlation between anemia, ID, and vitamin D deficiency in children has been identified, but investigations in pregnant women and their newborn babies are still limited.

Objective To assess association between iron status and vitamin D levels in umbilical cord blood and maternal anemia.

Methods This cross-sectional study involved 109 pregnant women and their newborns. They were divided into two groups, with and without maternal anemia. Collected cord blood (2 mL) was placed in tubes with ethylenediaminetetraacetic acid (EDTA). Plasma ferritin and vitamin D (25-hydroxyvitamin D, 25(OH)D) levels were measured by enzyme-linked immunosorbent assay (ELISA).

Results Maternal anemia was found in 60 mothers (55% subjects). The mean cord blood hemoglobin levels for the anemic and non-anemic groups were 15.19 (SD 2.25) g/dL and 15.12 (SD 1.98) g/dL, respectively (P=0.87). Median cord blood ferritin levels were slightly lower in anemic [12.95 (range 0.42-17.69) μg/L] than in non-anemic mothers[13.45 (range 7.10-22.12) μg/L], but were not significantly different (P=0.555). Median cord blood 25(OH)D levels were lower in the anemic group [12.24 (range 8.53-32.99) ng/dL] than in the non-anemic group [14.26 (range 9.84-61.44) ng/dL], but the difference was not significant (P=0.964).

Conclusion Maternal anemia was not significantly associated with cord blood hemoglobin, ferritin, or 25(OH)D levels. **[Paediatr Indones. 2024;64:490-500; DOI: https://doi.org/10.14238/pi64.6.2024.490-500].**

Keywords: *anaemic mother; hemoglobin, ferritin; vitamin D*

Nephrotic syndrome is the most prevalent glomerular disease in the pediatric population, affecting approximately 2.9 per 100,000 children annually on a global scale. Southeast Asian populations are particularly susceptible, with an incidence rate of 6.1 per 100,000 children.[1] This disorder, characterized by the triad of proteinuria, hypoalbuminemia, and edema, poses a substantial threat to the well-being of affected children, elevating the risks of infection, thromboembolism, and renal failure.[2]

Traditionally, steroids have served as the primary treatment for pediatric nephrotic syndrome. However, the long-term risks associated with steroid use, including obesity, osteoporosis, cataracts, glaucoma,

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and metabolic syndrome, underscore the need to minimize steroid exposure. Consequently, there is a growing emphasis on replacing steroids with alternative agents such as mycophenolate mofetil (MMF) or calcineurin inhibitors (CNIs) when feasible.[1] Nevertheless, the prolonged use of CNIs, such as cyclosporine A or tacrolimus, has led to reported cases of steroid- and CNI-dependent nephrotic syndrome (CNI-SDNS).[3] Furthermore, CNI utilization is associated with severe nephrotoxicity, imposing limitations on its application in pediatric populations. In response to these challenges, various alternative steroid-sparing agents, including mycophenolate mofetil (MMF) and rituximab, have been proposed for the management of these conditions.[1]

Rituximab, a chimeric anti-CD20 monoclonal antibody, has been used to treat frequently-relapsing nephrotic syndrome (FRNS) or steroid-resistant nephrotic syndrome (SRNS) since 2004.[1] A previous study demonstrated rituximab's superiority over MMF in maintaining remission for SDNS, showcasing comparable efficacy to CNIs.[4] While the effectiveness of rituximab in FRNS/SRNS has been well-established, there is limited evidence on its use in CNI-SDNS.[1-3] Therefore, we performed this systematic review to investigate the efficacy and safety of rituximab for treating children with CNI-SDNS.

Methods

This systematic review adhered to the guidelines outlined in the *Cochrane Handbook for Systematic Reviews of Interventions v6.4*[5] and was reported in accordance with the *Preferred Reporting Items for Systematic Review and Meta-analysis* (PRISMA) 2020 statement.[6] We conducted a thorough systematic search across both peer-reviewed and grey-literature databases, including *PubMed, Scopus, the Cochrane Central Register of Controlled Trials* (CENTRAL), and *Google Scholar*, to identify RCTs focusing on the effectiveness and safety of rituximab for treating children with CNI-SDNS, using the keywords listed in **Table 1**. The exclusion criteria were: (a) editorials, reviews, conference proceedings, or ongoing trials lacking published data, (b) inaccessible full-text articles, or (c) articles not in English or Indonesian. Two investigators independently conducted searches, with any disparities resolved through the blinded evaluation by a third reviewer. Additionally, we manually examined the references of the included studies and relevant prior systematic reviews to identify potentially eligible articles.

The following data were extracted from each study: (a) the last name of the first author and year of publication; (b) study characteristics, such as recruitment period, study design (blinding and clinical trial phase), geographical location, population, details on intervention and comparators, and duration of follow-up; (c) participant characteristics, including sample sizes, age, and sex; and (d) outcomes related to the efficacy and safety of rituximab. The included studies were further assessed for risk of bias using the revised Cochrane risk-of-bias tool for randomized trials (*RoB 2.0*), in which the overall risk of bias was categorized as low, moderate, or high.[7] Data extraction and risk of bias assessments were initially carried out by a single reviewer and subsequently validated by a second investigator. The extracted data were tabulated and discussed narratively. Due to the limited number of eligible studies and the heterogeneous outcomes and follow-up periods between the included studies, we were unable to perform a quantitative meta-analysis. Instead, we performed an effect-direction vote counting method to summarize the observed findings and trends.[8]

Results

The initial database search yielded 457 studies, 107 of which were duplicates, 249 were excluded following title and abstract screening, and 2 full-texts were not retrieved i.e., conference proceedings. Among the 99 studies retrieved for full-text screening, 46 studies with non-randomized design were excluded, followed by 31 studies not investigating CNI-SDNS, 12 studies with non-pediatric populations, and five study protocols, resulting in the inclusion of five RCTs with a total of 299 children [mean age 7.4 (SD 5.4) years, 71.2% boys] in this systematic review. Additional search methods by snowballing reference lists from previous systematic reviews and reference lists (n=327) failed to identify additional eligible studies (**Figure 1**). Among the included RCTs, all but one was open labeled (4 RCTs, 80.0%), and

Table 1. Search strategy and hits (up to 23 January 2024)

No	Database	Keyword	Hits
1	PubMed	(("rituximab"[MeSH Terms]) OR "Rituxan" OR "mabthera" OR ("antibodies, monoclonal"[MeSH Terms])) AND (("nephrotic syndrome"[MeSH Terms]) OR ("nephrosis, lipoid"[MeSH Terms]) OR "nephrotic syndrome" OR "lipoid nephrosis") AND (("child"[MeSH Terms]) OR ("infant"[MeSH Terms]) OR ("pediatrics"[MeSH Terms])) AND (("randomized controlled trial"[Publication Type]) OR ("controlled clinical trial"[Publication Type]) OR randomized OR placebo OR randomly OR "drug therapy" OR trial)	236
2	Scopus	(TITLE-ABS-KEY(rituximab) OR TITLE-ABS-KEY(Rituxan) OR TITLE-ABS-KEY(mabthera) OR TITLE-ABS-KEY(anti-cd20)) AND (TITLE-ABS-KEY("nephrotic syndrome") OR TITLE-ABS-KEY("lipoid nephrosis")) AND (TITLE-ABS-KEY(child*) OR TITLE-ABS-KEY(infant) OR TITLE-ABS-KEY(pediatric*)) AND (TITLE-ABS-KEY(randomized controlled trial) OR TITLE-ABS-KEY(randomized clinical trial) OR TITLE-ABS-KEY("controlled clinical trial") OR TITLE-ABS-KEY(placebo) OR TITLE-ABS-KEY(randomized) OR TITLE-ABS-KEY("drug therapy") OR TITLE-ABS-KEY(randomly) OR TITLE-ABS-KEY(RCT))	189
3	Google Scholar	(rituximab OR Rituxan OR mabthera OR anti-CD20 OR "monoclonal antibody") AND ("nephrotic syndrome" OR "lipoid nephrosis") AND (children OR infant OR pediatric) AND ("randomized controlled trial" OR "controlled clinical trial" OR "randomized clinical trial" OR placebo OR randomized OR drug therapy OR randomly OR trial OR RCT) [Search in Abstract]	4
4	CENTRAL	#1 MeSH descriptor: [Rituximab] explode all trees #2 MeSH descriptor: [Antibodies, Monoclonal] explode all trees #3 "rituximab" OR "Rituxan" OR "mabthera" #4 #1 OR #2 OR #3 #5 MeSH descriptor: [Nephrotic Syndrome] explode all trees #6 MeSH descriptor: [Nephrosis, Lipoid] explode all trees #7 "lipoid nephrosis" OR "nephrotic syndrome" #8 #5 OR #6 OR #7 #9 MeSH descriptor: [Child] explode all trees #10 MeSH descriptor: [Infant] explode all trees #11 MeSH descriptor: [Pediatrics] explode all trees #12 #9 OR #10 OR #11 #13 MeSH descriptor: [Randomized Controlled Trial] explode all trees #14 MeSH descriptor: [Controlled Clinical Trial] explode all trees #15 randomized OR placebo OR randomly OR "drug therapy" OR trial #16 animals NOT humans #17 (#13 OR #14 OR #15) NOT #16 #18 #4 AND #8 AND #12 AND #17	28

CENTRAL=Cochrane Central Register of Controlled Trial

most were performed in European centers (4 RCTs, 80.0%). Three of five RCTs (80.0%) recruited more children with minimal change disease (MCD), while one study (20.0%) recruited more children with focal segmental glomerulosclerosis (FSGS), and one did not perform renal biopsies on the enrolled children. With regards to the interventions, four RCTs (80.0%) compared rituximab infusion (a dose of 375 mg/m^2 with or without conventional therapy) to placebo or conventional therapy, the latter consisting of both oral steroids and CNIs (cyclosporine or tacrolimus); while the other study compared rituximab (375 mg/m^2) to ofatumumab (1500 mg/1.73 m^2) (**Table 2**).

Compared to conventional therapy regimens involving steroids and calcineurin inhibitors (CNIs), three RCTs reported that the addition of rituximab infusion (375 mg/m^2) to the conventional regimen resulted in a lower rate of relapse,[10,11,13] while a study reported no significant differences in the remission rate (18.8% [3/16] in the rituximab group and 20.0% [3/15] in the control group).[12] (**Table 3**). The crude relapse rate between CNI-SDNS children treated with rituximab and conventional therapy and those treated only with conventional therapy was 20.8% (15/72) *vs.* 66.1% (37/56) overall, 18.5% (5/27) vs. 48.1% (13/27) at 3 months [odds ratio (OR) 0.25; 95%CI 0.07-0.84; P=0.029]13, and 22.2% (10/45) *vs.* 82.8% (24/29) at 6 months10,11. The duration of remission was also longer in those treated with rituximab infusion and conventional therapy compared to conventional therapy alone (median 9.0 *vs.* 2.9 months; P=0.004).10 Moreover, children concurrently treated with rituximab and conventional therapy had longer steroid-free [mean difference (MD) 60.3 days; 95%CI 10.3 to 110.3; P=0.02] and CNIs-free periods (MD 93.0 days;

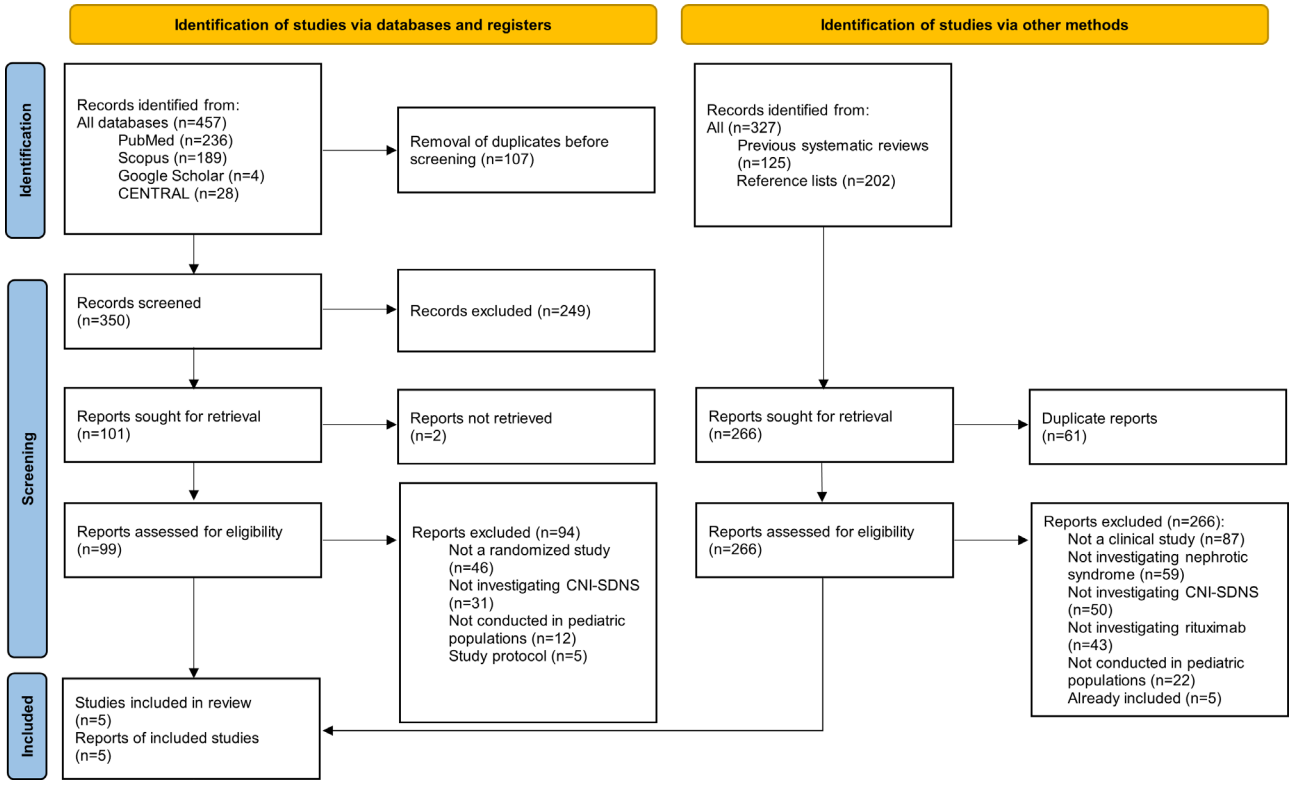

Figure 1. PRISMA flow diagram of study selection

95%CI 40.4 to 145.6; P<0.001), and were able to maintain a lower steroid dosage (-0.221 mg/kg/d; P<0.001) compared to control, cyclosporine (-0.669 mg/kg/d; P<0.05), and tacrolimus doses (-0.027 mg/kg/d) throughout the study period. The rate of withdrawal of steroids (96.3%) and CNIs (55.6%) were also higher in children treated with rituximab.[12] The effect of rituximab infusion was also evident in long-term follow-ups, where the drug-free period for steroid and CNIs remained longer in children receiving rituximab after 12 months compared to those receiving conventional therapy only (MD 41.4 and 93.0 days, respectively; 95%CI 40.4 to 145.6; P<0.001).10 The relapse rate between rituximab and ofatumumab, a human anti-CD20 monoclonal antibody with a higher affinity to CD20 receptors and longer half-life, were also similar at 12 months (OR 0.62; 95%CI 0.49-1.82) and 24 months (OR 0.62; 95%CI 0.29-1.82; P=0.32).[9]

In terms of the reduction of proteinuria, the included RCTs showed conflicting findings. An open-label RCT conducted in 2011 involving 45 children with CNI-SDNS, demonstrated that rituximab successfully reduced proteinuria at 3 months post-infusion (-69.80%; 95%CI -86.04 to -34.68; P=0.003), with higher effects observed in those without toxicity (-83.59%; 95%CI -94.24 to -53.18; P=0.001). However, in children with toxicity, there was no significant reduction in proteinuria (-35.66%; 95%CI -78.62 to 93.66%; P=0.425).13 On the other hand, Magnasco et al. reported that the reduction in proteinuria at 3 months between the rituximab and control groups was not significant after adjusting for baseline proteinuria (-12%; 95%CI -73 to 110; P=0.77). The authors also stated that serum albumin and creatinine levels were similar between those treated with and without rituximab throughout the study period.[12]

Four RCTs reported data on the safety profile of rituximab infusion,[9,10,12,13] with a maximum safety assessment follow-up of 18 months.[12] Due to the heterogeneity in comparators and time of adverse events evaluation, a formal meta-analysis could not be performed. Rituximab was generally well-tolerated when administered to the affected children, with a similar rate of adverse events compared to placebo

Table 2. Characteristics of the included studies and participants

Author (year)	Study characteristics				
	Recruitment period	Study design	Location	Type of nephrotic syndrome	Duration of follow-up, months
Ravani *et al.*[9] (2021)	2015-2018	Open label	Italy	NS	24
Ahn *et al.*[10] (2018)	2012-2013	Open label	South Korea	60.8% MCD, 5.9% FSGS	12
Boumediene *et al.*[11] (2018)	2010-2014	Double-blind	France	87.0% MCD, 4.3% FSGS	6
Magnasco *et al.*[12] (2012)	2007-2010	Open label	Italy	61.3% FSGS, 22.6% MCD	3
Ravani *et al.*[13] (2011)	2007-2008	Open label	Italy	35.2% MCD, 31.5% FSGS	3

FSGS=focal segmental glomerulosclerosis; MCD=minimal change disease; NS=not stated

[mean 27 (72.2%) *vs.* 10 (55.6%); P=0.220]10 and ofatumumab [4 (5.7%) *vs.* 1 (1.4%); P=0.31]9 (**Table 3**). In addition, the incidence of serious adverse events with rituximab infusion was also relatively rare, ranging from 0.0% to 8.3%,[9,10,12] none of which resulted in death.[10] The most commonly reported infusion-related adverse events were infusion reaction (21/148 children; 14.2%),[10,12,13] skin rash (7/148; 4.7%),[9,12,13] abdominal pain (4/148; 2.7%),[12] dyspnea (4/148; 2.7%),[9,12] pruritus (3/148; 3.0%),[9] fever (2/148; 1.4%),[13] and cough (1/148; 0.7%).[9] All of these infusion-related adverse events were non-lethal, and most rapidly resolved by reducing the infusion rate or discontinuing the drug, in addition to symptomatic treatments. Meanwhile, other non-infusion-related adverse events included infections (13/148; 8.8%),10 articular pain (2/148; 2.7%),[9,13] and neutropenia (2/148; 1.4%).[9]

Discussion

Rituximab is widely used to treat malignancies, e.g., chronic lymphocytic leukemia and CD20+ B-cell non-Hodgkin's lymphoma; autoimmune diseases, e.g., rheumatoid arthritis, granulomatosis with polyangiitis, and microscopic polyangiitis; and pemphigus vulgaris. Its mechanism involves binding to CD20+ cells, inducing cell death through cell-mediated and complement-mediated cytotoxicity, as well as apoptosis and antibody-dependent phagocytosis.[14] In recent years, the potential utility of rituximab against childhood idiopathic nephrotic syndrome has garnered attention. While studies on children with FRNS/SRNS have shown favorable results, its use in CNI-SDNS has been rarely investigated, despite the potential severe adverse events associated with long-term steroid and CNI use.[15] Our findings suggest that rituximab successfully induced waning of steroid- and CNI-dependence in affected children, with a lower rate of relapse.

In this review, all but one trial demonstrated that rituximab was superior to conventional therapy

Table 2. Characteristics of the included studies and participants (continued)

Subject characteristics								Overall risk of bias
Intervention				Control				
Details	N	Age, years	Males (%)	Details	N	Age, years	Males (%)	
Ofatumumab 1500 mg/1.73m^2 single dose + conventional therapy	70	3 (2-4)*	44 (62.9)	Rituximab 375 mg/m2 single dose + conventional therapy	70	3 (2-5)*	52 (74.3)	Low
Rituximab 375 mg/m^2 single dose 1-2x/ month + conventional therapy	35	13.5 (5.0)**	26 (74.3)	Conventional therapy	16	12.5 (4.2)**	13 (81.3)	Moderate
Rituximab 375 mg/m2 2-4x/ month	10	11.1 (3.5)**	10 (100)	Placebo	13	12.3 (3.4)**	6 (46.2)	High
Rituximab 375 mg/m^2 1-2x/ month + conventional therapy	16	8.5 (4.4)**	10 (62.5)	Conventional therapy	15	7.3 (3.7)**	9 (60.0)	Low
Rituximab 375 mg/m^2 1-2x/ month + conventional therapy	27	10.2 (4.0)**	24 (88.9)	Conventional therapy	27	11.3 (4.3)**	19 (70.4)	Low

FSGS=focal segmental glomerulosclerosis; MCD=minimal change disease; NS=not stated;*median (range); **mean (SD)

in steroid and CNI dependence among children with idiopathic nephrotic syndrome, as shown by the lower relapse rate, the higher steroid and CNI withdrawal rate, and the longer duration of remission. This heterogeneity may be explained by the fact that the majority of subjects in the study by Magnasco et al. had FSGS (61.3%),[12] unlike the other three studies which enrolled more children with MCD.[10,11,13] A prior systematic review found that the rate of remission following rituximab infusion was higher in children with MCD compared to those with FSGS (80.3%; 95%CI 68.5-88.5% *vs.* 53.6%; 95%CI 15.8-87.6%; P=0.678).[16] In addition, the rate of relapse was also slightly lower for those with MCD than FSGS, although the difference was not significant (35.9%; 95%CI 25.1-48.4% *vs.* 47.3% 95%CI 25.4-70.2%; P=0.401). Nonetheless, it is worth noting that the lack of statistical significance might stem from the small number of studies and study sizes in the FSGS subgroup rather than real-world findings.[16] To date, no studies have directly compared the efficacy of rituximab between children with MCD and FSGS. However, existing evidence suggests decreased efficacy of rituximab in patients with FSGS.[17]

All of the included trials employed a similar rituximab dose of 375 mg/m^2, with varying infusion frequencies ranging from a single dose,[9,10,13] bimonthly,[11-13] to weekly.[11] Currently, there is no universal consensus on the specific number of rituximab doses needed to treat children with idiopathic nephrotic syndrome.[18] While our findings indicate that rituximab is effective irrespective of the administration frequency, studies have shown that remission may be prolonged after two to four doses of rituximab.[19-21] Furthermore, the terminal half-life of rituximab is 2.7-fold longer following administration of the fourth dose compared to the first dose, suggesting a potentially extended therapeutic effect.[19] Nonetheless, more recent studies have argued that lower doses may be have similar efficacy to repeated rituximab administration. For instance, a single rituximab dose of 375 mg/m^2 was shown to have similar efficacy to two doses of 750 mg/m^2 ,[22] while a rituximab dose of 100 mg/m^2 was associated with a shorter duration of B cell depletion, potentially increasing the risk of earlier relapse.[21] To mitigate

Table 3. Efficacy and safety of rituximab infusion therapy in children with (CNI-SDNS)

Author (year)	Outcomes	Effect direction
Ravani *et al.*[9] (2021)	Efficacy (rituximab *vs.* ofatumumab) • Relapse at 12 months: OR 0.62 (95%CI 0.49 to 1.82, 36 [51.4%] *vs.* 37 [52.8%]) overall, 0.73 (0.27-1.99; 17 [54.8%] *vs.* 20 [62.5%]) in children aged ≤9 years old, and 1.17 (0.48-2.88; 19 [48.7%] *vs.* 17 [44.7%]) in children aged >9 years. • Relapse at 24 months: OR 0.62 (95%CI 0.29 to 1.28, P=0.32; 46 [65.7%] *vs.* 53 [75.7%]) overall, 0.34 (0.10-1.12, P=0.09; 20 [64.5%] *vs.* 27/32 [84.4%]) in children aged ≤9 years old, and 0.92 (0.36-2.40; 26 [66.7%] *vs.* 26 [68.4%]) in children aged >9 years. • Time to relapse: median 5 (IQR 3-9) months *vs.* 6 (IQR 4-8.5) months at 12 months, and 16 (IQR 14-20.2) months *vs.* 15 (IQR 14-17) months at 24 months.	Non-significant positive effect
	Safety (rituximab *vs.* ofatumumab) Infusion-related AEs • Any AEs: 7 (10.0%) vs. 4 (5.7%), P=0.34. • Serious AEs (grade ≥3): 0 (0.0%) *vs.* 0 (0.0%), P=1.00. • Other AEs: erythema (2 [2.9%] *vs.* 2 [2.9%], P=1.00), pruritus (3 [4.3%] *vs.* 1 [1.4%], P=0.37), cough (1 [1.4%] *vs.* 1 [1.4%], P=1.00), and dyspnea (1 [1.4%] *vs.* 0 [0.0%], P=0.68). AEs within 6 months • Any AEs: 4 (5.7%) *vs.* 1 (1.4%), P=0.31. • Serious AEs: 0 (0.0%) *vs.* 0 (0.0%), P=1.00. Other AEs: neutropenia (2 [2.9%] vs. 1 [1.4%], P=0.68) and articular pain (2 [2.9%] *vs.* 0 [0.0%], P=0.58).	No difference
Ahn *et al.*[10] (2018)	Efficacy (rituximab *vs.* control) • Relapse at 6 months: 9 (25.7%) *vs.* 11 (68.7%), P=0.003. • Median duration of remission: 9.0 *vs.* 2.9 (P=0.004). • Relapse rate: 3.4 per person-year *vs.* 9.4 per person-years (P=0.006). • Lower steroid dose in rituximab compared to control (0.235±0.192 *vs.* 0.396±0.282 mg/kg/d, P=0.02). • Higher reduction of steroid (-0.221 [P<0.001] *vs.* 75 mg/kg/d), cyclosporine (-0.669 [P<0.05] *vs.* -0.157 mg/kg/d), and tacrolimus doses (-0.027 *vs.* -0.005 mg/kg/d) in rituximab than control. • Longer drug-free period for steroid (MD 60.3 days [95%CI 10.3, 110.3], P=0.02) and CNIs (46.2 days [-14.7, 107.1], P=0.14) in rituximab compared to control. • Increase drug-free period for steroid (MD 41.4 days) and CNIs (MD 93.0 days [40.4, 145.6], P<0.001) in the rituximab group after the study. • Reduced prevalence of hypertension (-25.6% *vs.* 11.0%, P=0.006).	Significant positive effect
	Safety (rituximab *vs.* control) • Any AEs: 26 (72.2%) *vs.* 10 (55.6%), P=0.22. • Serious AEs: 3 (8.3%) *vs.* 1 (5.6%), P=0.72. • Death: 0 (0.0%) *vs.* 0 (0.0%). Other AEs: 17 (47.2%) infusion reaction in the rituximab group, and 13 (36.1%) *vs.* 3 (16.7%) infection.	No difference
Boumediene *et al.*[11] (2018)	Efficacy (rituximab *vs.* placebo) • Relapse at 6 months: 1 (10.0%) *vs.* 13 (100%).	Significant positive effect

Table 3. Efficacy and safety of rituximab infusion therapy in children with (CNI-SDNS) (continued)

Author (year)	Outcomes	Effect direction
Magnasco *et al.*[12] (2012)	Efficacy (rituximab *vs.* control) • Remission in early-resistant children (0 [0.0]% *vs.* 0 [0.0]%) and in delayed-resistant children (3 [42.9]% *vs.* 3 [37.5]%). • Percentage reduction of proteinuria at 3 months overall (-12% [95%CI -73 to 110], P=0.77), in early-resistant children (-3% [95%CI -67 to 179], P=0.95), or delayed-resistant children (-48% [95%CI -79 to 93], P=0.40), independent of baseline proteinuria. • Changes in proteinuria: -0.2 g/d/m^2 (2.7 [95%CI 1.6 to 7.8] *vs.* 2.9 [1.2-6.6]) *vs.* -2.1 (3.9 [1.2-7.1] *vs.* 6 [1.5-8.8]) in early-resistant children, and -0.5 (0.8 [0.1-1.7] *vs.* 1.3 [0.8-6.3]) *vs.* -1.6 (0.8 [0.1-4.6] *vs.* 2.4 [0.8-4.8]) in delayed-resistant children. • Changes in serum albumin level: 0.0 g/L (2.1 [SD 0.6] at 3 months *vs.* 2.1 [SD 0.5] at baseline) *vs.* -0.1 g/L (2.1 [SD 0.9] *vs.* 2.2 [SD 0.7]) in early-resistant children, and 0.7 g/L (3.3 [SD 0.3] *vs.*2.6 [SD 0.6]) *vs.* 0.5 mg/L (2.9 [SD 0.8] *vs.* 2.4 [SD 0.4]). • Changes in serum creatinine level: 0.1 mg/dL (0.7 [SD 0.3] at 3 months *vs.* 0.6 [SD 0.2] at baseline) *vs.* 0.0 mg/dL (0.7 [SD 0.4] *vs.* 0.7 [SD 0.4]) in early-resistant children, and 0.1 mg/dL (0.6 [SD 0.4] *vs.* 0.5 [SD 0.4]) *vs.* 0.0 mg/dL (0.5 [SD 0.3] *vs.* 0.5±0.3) in delayed-resistant children.	No difference
	Safety (in rituximab) • One (6.3%) AE requiring drug discontinuation due to severe reaction with bronchospasm and hypotension following the second rituximab infusion. • Other AEs with rapid resolution by reducing infusion rate: abdominal pain (4 children, 25.0%), skin rash (3, 18.8%), and mild dyspnea (3, 12.5%). No delayed adverse events following rituximab infusion at 18 months.	NA
Ravani *et al.*[13] (2011)	Efficacy (rituximab *vs.* control) • Relapse at 3 months: OR 0.25 (95%CI 0.07-0.84, P=0.029; 5 [18.5%] *vs.* 13 [48.1%]). • Percentage reduction of proteinuria at 3 months: -69.80% (95%CI -86.04 to -34.68; P=0.003) overall, -83.59% (-94.24, -53.18; P=0.001) without toxicity, and -35.66% (-78.62, 93.66%; P=0.425). • Probabilities of being prednisone-free and CNIs-free: 21 (77.8%) *vs.* 2 (7.4%, P<0.001), and 17 (62.9%) *vs.* 1 (3.7%, P<0.001) at 3 months, 13 (50.0%) at 6 months, and 7 (25.0%) at 12 months. • Withdrawal of steroid achieved 26 (96.3%) overall, and all but four children with toxicity. • Withdrawal of CNI achieved in 15 (55.6%) *vs.* 1 (3.7%; P<0.001).	Significant positive effect
	Safety (in rituximab) • Other AEs: 3 infusion reaction (11.1%), 2 fever with migrating skin rash and acute arthritis at day 2 and 6 post-infusion (7.4%). • Reduction of CD20 counts to <1% at the first month following rituximab infusion, and remained undetectable for 24 (88.9%) children after 3 months.	NA

AE=adverse event; CNI=calcineurin inhibitor; IQR=interquartile range; MD=mean difference; NA=not available; OR=odds ratio

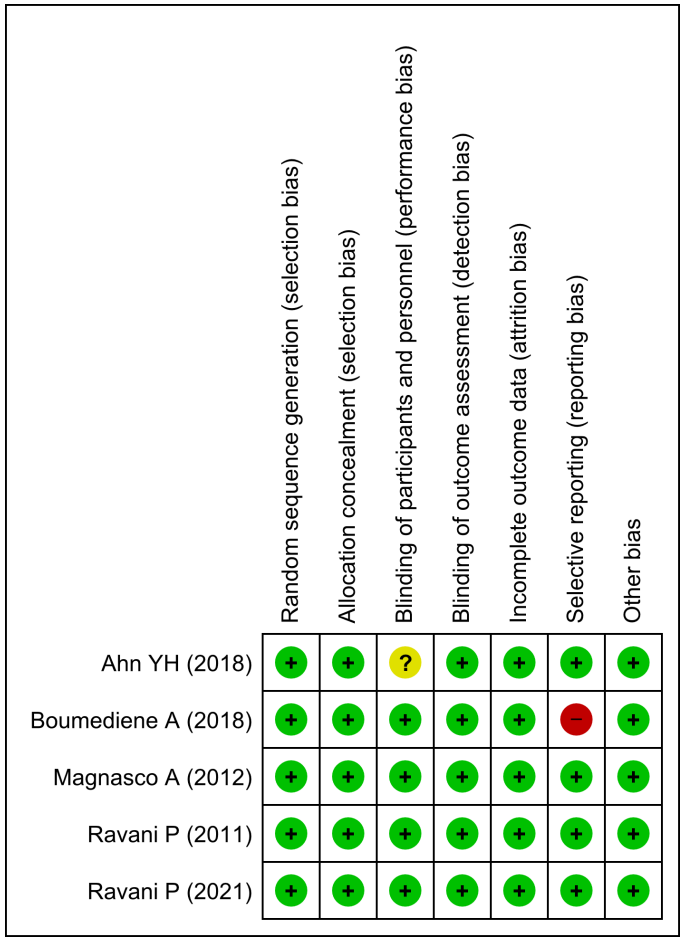

Figure 2. Results of risk of bias assessments among the individual studies

such relapse episodes, studies have indicated that adding MMF after rituximab infusion may increase the 2-year relapse-free survival rate by up to 58%.23 However, the long-term efficacy comparison between repeated doses of rituximab and a single rituximab dose followed by MMF requires further investigation.[24]

In general, a lower rituximab dose is preferred due to potential risks of infusion reactions with higher doses of rituximab such as flu-like symptoms, headache, skin rash, upper airway symptoms, arrythmia, or hypo-/hypertension.[19] These adverse events are generally well-tolerated,[19] as demonstrated in our systematic review. To minimize the risks of infusion reactions, a cautious approach should be adopted by initiating administration at a slow infusion rate and subsequently increasing it at 30-minute intervals. Additionally, pretreatment with antihistamines and/or steroids may also prevent the occurrence of these reactions. Another common adverse event linked to rituximab use is the risk of infection due to its immunosuppressive nature. Although cases of severe and fatal infections have been rarely reported, cotrimoxazole is recommended in patients receiving rituximab with concurrent immunosuppression.[19] Lastly, rituximab is contraindicated in patients with hepatitis B infection due to the risk of fulminant liver failure, in patients with cardiovascular diseases due to the risk of arrythmia and angina, and in patients with renal impairment.[25]

Overall, this systematic review highlights the potential utility of rituximab in children with CNI-SDNS. This is particularly important given the increasing incidence of children with CNI-SDNS, and the potential long-term risks of side effects associated with steroids and CNIs, including metabolic disorders, skeletal diseases, and irreversible kidney damage, all of which could lead to debilitating morbidity and a poor quality of life.[18,19,25] The *Kidney Disease:*

Improving Global Outcomes (KDIGO) currently recommends rituximab for children with frequently relapsing, steroid-sensitive nephrotic syndrome, despite receiving both steroids and glucocorticoid-sparing agents.[18] Similarly, the *National Health Service of England* advises rituximab administration only for children with persistent nephrotic syndrome despite more than 6 months of CNIs and more than 3 months of MMF therapy.[25] The addition of rituximab to the treatment regimen for these children may reduce steroid and CNI dependency, thereby preventing potential devastating complications with long-term use of both steroid and CNIs. Additionally, rituximab was also found to be acceptable and cost-effective in the treatment of children with nephrotic syndrome, potentially reducing healthcare-associated costs by a significant 56%.[26,27]

Our study was constrained by the small number of included trials and patients, which may reflect the rarity of CNI-SDNS in clinical settings.[3] Moreover, heterogeneity in the duration of follow up and outcomes prevented us from performing quantitative meta-analyses, thus limiting the interpretability of our findings. However, it is noteworthy that all studies employed the same rituximab infusion regimen in patients with relatively similar demographic characteristics, thereby facilitating a direct comparison of results between the trials. Additionally, the inclusion of only RCTs with predominantly low risk of bias enhances the quality of evidence synthesized in this review. To the best of our knowledge, this is the first systematic review investigating the efficacy and safety of rituximab in children with CNI-SDNS. Further studies with larger sample sizes and those comparing the efficacy of rituximab between children with FSGS and MCD are essential to further validate and strengthen our findings.

In conclusion, rituximab appears to be an effective and generally well-tolerated treatment for children with CNI-SDNS, showcasing superior efficacy compared to conventional therapy in sustaining remission and averting relapse. Rituximab administration may also contribute to a successful waning of steroid and CNI dependence among affected children, leading to extended drug-free periods and higher withdrawal rates for both steroids and CNIs. To substantiate and reinforce these findings, further investigations with larger sample sizes are warranted.

Conflict of interest

None declared.

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