Systematic Review and Meta-Analysis

Medicine®

OPEN

Efficacy and acceptability of immunosuppressive agents for pediatric frequently-relapsing and steroid-dependent nephrotic syndrome

A network meta-analysis of randomized controlled trials

Liping Tan, MD[a,e], Shaojun Li, MD[a,d], Haiping Yang, MD[b,d], Qing Zou, MS[a,c], Junli Wan, MS[b,c], Qiu Li, MD[b,e,*]

Abstract

Introduction: A network meta-analysis was conducted to regard the effects of available immunosuppressive medications in pediatric frequently-relapsing nephrotic syndrome (FRNS) and steroid-dependent nephrotic syndrome (SDNS).

Methods: We reviewed systematically 26 randomized controlled trials (1311 patients) that compared any of the following immunosuppressive agents to placebo/nontreatment (P/NT) or another drug for FRNS/SDNS treatment in children.

Results: The main outcomes were efficacy and acceptability. At the 6-month, cyclophosphamide, chlorambucil, levamisole, and rituximab had better efficacy than P/NT (odds ratio [OR]: 0.09, 0.03, 0.28, and 0.07, respectively); cyclophosphamide was significantly more effective than azathioprine and chlorambucil. At 12 months, cyclophosphamide, chlorambucil, cyclosporine, levamisole, and rituximab had better efficacy than P/NT (0.10, 0.03, 0.10, 0.23, and 0.07, respectively); Chlorambucil were found to be more efficacious than levamisole and MMF (0.12 and 0.09, respectively). At 24 months, cyclophosphamide, chlorambucil, and levamisole had better efficacy than P/NT (0.09, 0.04, and 0.03, respectively); cyclophosphamide had better efficacy than cyclosporine and vincristine (0.17 and 0.39, respectively).

Conclusion: No significant differences in acceptability were found. Our results suggest that cyclophosphamide may be preferred initially in children with FRSN/SDNS, chlorambucil, and rituximab may be acceptable medications for patients with FRSN/SDNS. Long-term follow-up trials focused on gonadal toxicity and limitation of maximum dosage of cyclophosphamide should been carried out.

Abbreviations: CIs = confidence intervals, FRNS = frequently-relapsing nephrotic syndrome, INS = idiopathic nephrotic syndrome, MMF = mycophenolate mofetil, OR = odds ratio, P/NT = placebo/nontreatment, SDNS = steroid-dependent nephrotic syndrome, SUCRA = surface under the cumulative ranking curve.

Keywords: FRNS, immunosuppressant, multiple-treatments meta-analysis, pediatrics, SDNS

1. Introduction

In most of cases, clinical remission of pediatric idiopathic nephrotic syndrome (INS) can be reached with corticoid (e.g., prednisolone) therapy.[1] However, 80% of children treated for PNS suffer from edema and proteinuria recurrence, and up to 50% of these children go on to develop frequently relapsing nephrotic syndrome (FRNS) or steroid-dependent nephrotic syndrome (SDNS) during corticosteroid dose reduction or within a few weeks after steroid withdrawal.[2,3] It has been suggested that immunosuppressive medications may help extend the

Editor: Muhammed Mubarak.

Funding: This research was supported by the projects of basic and frontier research, Chongqing Science and Technology Commission (Fund number: cstc2014jcyjA10032).

Contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission. LT and QL conceived and designed the study. SL and LT wrote the protocol. HY designed and implemented the search strategies. LT and QZ selected studies, assessed validity, and extracted data. JW entered and analyzed the data. All authors interpreted the data, prepared the full review and contributed to its revision, interpretation of results, and approval.

The authors declare that they have no conflict of interests.

Supplemental Digital Content is available for this article.

[a] Emergency Department, [b] Nephrology Department, Children's Hospital Affiliated to Chongqing Medical University, [c] Key Laboratory of Pediatrics in Chongqing, [d] Chongqing International Science and Technology Cooperation Center for Child Development and Disorders, [e] Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing, China.

[*] Correspondence: Qiu Li, Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing, China (e-mail: liqiu809@126.com).

Medicine (2019) 98:22(e15927)

Received: 6 November 2018 / Received in final form: 2 April 2019 / Accepted: 10 May 2019

http://dx.doi.org/10.1097/MD.0000000000015927

duration of remission in PNS patients, particularly during the corticosteroid withdrawal process.[4]

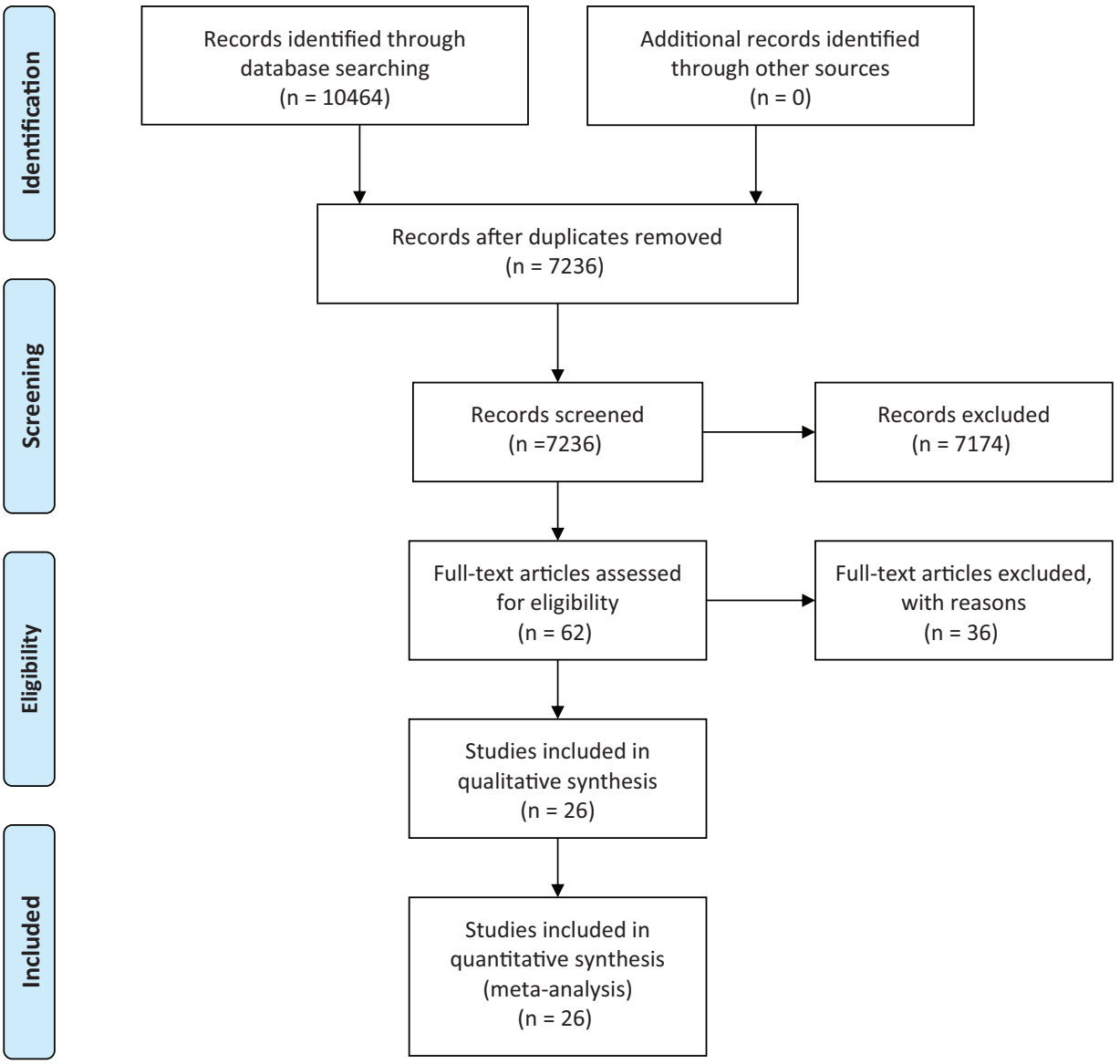
Some kinds of new hypotoxic immunosuppressive agents have been presented in recent decades for the intervention of pediatric FRNS/SDNS recovering from INS.[5] But, these emerging agents may be lesser efficacious for prolonged remission when corticoid withdrawal than conventional immunosuppressant medications. Consequently, there is still no consensus on which immunosuppressive agents are most effective for pediatric FRNS/SDNS. Factors that may be related to treating efficiency have been identified by conventional meta analyses estimating the efficiency of emerging immunosuppressive drugs and system reviews demonstrated different efficacy among non-steroidal immunosuppressive agents.[6–9] Nevertheless, conclusions of previous evidences are inconsistent because indirect comparisons could not be conducted. Furthermore, the degree to which effectiveness and acceptability differentiates across available FRNS/SDNS medications is not clear.[6,7,10,11]

In view of the above, a network meta-analysis[12] is reported in which comparisons of eight non-steroidal immunosuppressive medications were made with regard to effectiveness and acceptability in pediatric FRNS/SDNS. The purpose of this study was to defined a better pediatric FRNS/SDNS therapeutic regimen.

2. Methods

2.1. Trials identification

Prepared for this multiple-treatments meta-analysis, a study protocol had been drafted and published on the prospero website



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Figure 1. Study selection process.

Table 1

Descriptive characteristics of studies included in the meta-analysis.

Study	Country	Study design	Time frame	Cases (N)	Age (years)	Sex (M/F)	Patients	Interventions	Study outcomes	Duration of follow-up	Attrition (%)
Abeyagunawardena 2006	Sri Lanka	RCT	2002–2005	76	1.7–13.4	45/31	SD SSNS	Oral LEV 2.5 mg/kg on alternate days × 1 year vs no treatment	Relapse rate at 12 months, adverse effects	12 months	0
Abeyagunawardena 2007	Sri Lanka	RCT	over 3 years	39	1–15	26/13	SD SSNS	IV CPA 500 mg/m^2/dose monthly 6 months vs VIN 1.5 mg/m^2/dose weekly × 4 doses then monthly × 4 doses for 4 months	Relapse rate at 12 months and 24 months, adverse effects	24 months	0
Abramowicz 1970	International	RCT	1967–1969	36	1–15.9	NR	FR SSNS	Oral AZA 60 mg/m^2/dose for 26 weeks vs placebo	Relapse rate at 6 months	6 months	4
Al-saran 2006	Saudi Arabia	RCT	2001–2003	56	<14 years	35/21	SD or FR SSNS	LEV 2.5 mg/kg on alternate days for 1 year vs no treatment	relapse rate at 12 months, adverse effects	12 months	0
Alatas 1978	Indonesia	RCT	NR	20	4–10	15/5	FR SSNS	Oral CHL 0.3 mg/kg/dose for 8 weeks vs placebo	Relapse rate at 6 months and 12 months	12 months	50
APN 1982	Germany	RCT	1977–1981	50	2–16	31/19	FR or SD SSNS	Oral CPA 2mg/kg/dose for 8 weeks (total dose 112 mg/kg) vs oral CHL 0.15 mg/kg/dose for 8 weeks (total dose 8.4 mg/kg)	Relapse rate at 12 months and 24 months, adverse effects	24 months	0
BAPN 1991	UK/Ireland	RCT	NR	61	4.7–12.5	41/20	SD SSNS	Oral LEV 2.5 mg/kg on alternate days for 16 weeks vs placebo on alternate days for 16 weeks	Relapse at 6 months and 12 months, adverse effects	6 months	0
Barratt 1970	UK	RCT	NR	30	1.9–12.9	NR	FR SSNS	Oral CPA 3 mg/kg/dose for 8 weeks vs no treatment	Relapse at 6 months, 12 months and 2 years	24 months	13
Barratt 1977	UK	RCT	NR	24	<14 years	NR	FR SSNS	Oral AZA 2 mg/kg/dose for 8 weeks vs no treatment	Relapse rate at 6 months	6 months	0
Chiu 1973	Canada	RCT	1967–1971	23	2–15	11/12	FR SSNS	Oral CPA 75 mg/m^2/dose for 16 weeks (total dose 280 mg/kg) vs no treatment	Relapse rate at 6 months, 12 months and 24 months, adverse effect	24 months	0
Dayal 1994	India	RCT	1988–1990	37	2–9	29/8	relapsing SSNS	Oral LEV 2–3 mg/kg twice a week for 52 weeks vs no treatment	Relapse rate at 12 months, adverse effects	12 months	3
Donia 2005	Egypt	RCT	NR	40	4–10	31/9	SD SSNS	Oral LEV 2.5 mg/kg on alternate days for 6 months vs IV CPA 500 mg/m^2/dose monthly for 6 months (total dose 132 mg/kg)	Relapse rate 6 months, 12 months and 24months, adverse effects	24 months	0
Dorresteijn 2008	Netherlands	RCT	2003–2005	24	3.7–17.5	21/3	FR or SD SSNS	Oral MMF 1200 mg/m^2/dose in 2 divided doses for 1-year vs CSA 4–5 mg/kg/dose in 2 divided doses for 1-year	Relapse rate at 12 months, adverse effects	12 months	22.50
Gellermann 2013	Germany	RCT	2003–2008	60	3–17	NR	FR SSNS	Oral MMF starting dosage 1000–1200 mg/m^2/dose for 1-year vs oral CSA target trough level 80–100 ng/mL for 1 year	Relapse rate at 12 months, adverse event	24 months	0
Grupe 1976	USA	RCT	NR	21	3–15.5	13/8	FR or SD SSNS	Oral CHL started at 0.1–0.2 mg/kg/dose and increased every 2 weeks, total average dose at 16.9 mg/kg vs placebo	Relapse rate at 6 months and 12 months, adverse effects	20 months	0
Iijima 2014	Japan	RCT	2008–2010	48	2–18	34/14	FR or SD SSNS		Relapse rate at 12 months, adverse effects	12 months	0

Study	Country	Study design	Time frame	Cases (N)	Age (years)	Sex (M/F)	Patients	Interventions	Study outcomes	Duration of follow-up	Attrition (%)
								RTX intravenous dose of 375 mg/m^2 (maximum 500 mg) once weekly for 4 weeks vs placebo			
ISKDC 1974	International	RCT	1970–1972	53	aged < 16	NR	FR SSNS	Oral CPA 5 mg/kg/dose and then 1–3 mg/kg/dose total duration 6 weeks vs no treatment	Relapse rate at 6 months, adverse effects	20 months	0
Niaudet 1992	France	RCT	1985–1989	40	children, NR	NR	SD SSNS	Oral CSA 6 mg/kg/dose for 3 months then tapered over 3 months vs oral CHL 0.2 mg/kg/dose for 40 days	Relapse rate at 6 months, 12 months and 24 months, adverse effect	24 months	0
Ponticelli 1993	Italy	RCT	NR	66	2–15	48/18	FR or SD SSNS	Oral CSA 6mg/kg/dose for 9 months then reducing over next 3 months vs oral CPA 2.5 mg/kg/dose for 8 weeks then reducing over next 3 months	Number in relapse rate at 12 months and 24 months, adverse effects	24 months	6
Rashid 1996	Bangladesh	RCT	NR	40	1–15	27/13	FR or SD SSNS	Oral LEV 2.5 mg/kg on alternate days for 24 weeks vs placebo	Relapse rate at 6 months and 12 months, adverse effects	12 months	0
Ravan 2011	Italy	RCT	2007–2008	54	6–15	43/11	SDNS	RTX 375 mg/m^2 vs placebo	Relapse rate at 6 months, adverse effects	12 months	4
Ravani 2015	Italy	RCT	2009 and 2012	30	3–11	21/9	SDNS	RTX 375 mg/m^2 vs placebo	Relapse rate at 6 months, 12 months and 24 months, adverse effects	24 months	0
Sural 2001	India	RCT	NR	85	2–16	NR	FR SSNS	Oral LEV 2.5 mg/kg on alternate days for 24 weeks vs CPA 2 mg/kg/dose for 12 weeks vs no treatment	Relapse rate at 6 months and 12 months, adverse effects	12 months	0
Weiss 1993	USA	RCT	NR	49	3–12	38/11	FR or SD SSNS	LEV oral 2.5 mg/kg orally twice weekly for 6 months vs placebo	Relapse rate at 6 months and 12 months	12 months	10
Mariken 2017	Netherlands	RCT	2007–2012	100	2–16	70/30	FR or SD SSNS	LEV 2.5 mg/kg on alternate Days for 12 months vs placebo	Relapse rate at 12 months, adverse effects	12 months	8
Aditi 2018	India	RCT	2012–2016	149	6–18	125/24	FR or SD SSNS	LEV 2.5 mg/kg on alternate days for 12 months vs MMF 750 to 1000 mg/m^2 in 2 divided doses daily	Relapse rate at 3 months and 12 months, adverse effects	12 months	19

AZA = azathioprine, CHL = chlorambucil, CPA = cyclophosphamide, CSA = cyclosporine, FR = frequent relapsing, LEV – levamisole, MMF = mycophenolate mofetil, NR = not reported, NS = nephrotic syndrome, RCT = randomised controlled trial, RTX = rituximab, SD = steroid-dependent, SSNS = steroid-sensitive nephrotic syndrome, VIN = vincristine.

(CRD 42016048032). There are no ethical conflicts involved in the article. A literature search for relevant studies was performed in Medline (from 1950 to March 2019), the Central (Cochrane Central Register of Controlled Trials, Issue 3, 2019), and Embase (1974 to March 2019) using the following terms: "alkylating agents," "immunosuppressive agents," "cyclosporine," "azathioprine" or "mycophenolic acid," "cyclophosphamide," "tacrolimus," "chlorambucil," "levamisole," "rituximab"; and "nephrotic syndrome," "nephrosis lipoid," "focal segment glomerulosclerosis," "glomerulonephritis membranoproliferative," "minimal change nephrotic syndrome," "membranoproliferative glomerulonephritis," "IgM nephrothay." We restricted the search results to papers reporting clinical trials on children. In addition, we screened the reference lists of eligible articles and correlative reviews and searched ClinicalTrials.gov for ongoing studies to identify other potentially germane studies.

2.2. Selection criteria

We included randomized controlled trials compared with any of the following interventions and in which children with FRNS/SDNS were the subjects: cyclosporine, azathioprine, MMF, tacrolimus, chlorambucil, cyclophosphamide, levamisole, and rituximab. The experience group might be compared to a P/NT and/or another agent. FRNS was defined as at least two recurrences within 6 months or at least four recurrences within 12 months of an initial remission. SDNS was defined as two consecutive relapses during corticosteroid reduction or within 14 days of corticosteroid withdrawal.[13]

We excluded trials involving patients experiencing their first bout of steroid sensitive nephrotic syndrome, steroid resistant nephrotic syndrome, congenital nephrotic syndrome, and other renal/ systemic forms of nephrotic syndrome. We also excluded trials in which only abstracts were published with no available data available from other ways. Language restrictions were not applied.

2.3. Outcome measures

The primary efficacy outcome was relapse rate and the primary acceptability outcomes were dropout rate and adverse effects. We extracted primary outcome data for the following timepoints (±1 month): 6 months, 12 months, 24 months, and the final follow-up examination reported. We defined relapse as urinalysis results of ≥3+ (300 mg/dL) protein level in early morning urine samples for three consecutive days.[13] We defined adverse effects (acceptability outcome) as sequelae happening in the initial 6 ± 1 months post-treatment period. Dropout for any reason (acceptability outcome) included patients who withdrew before the end of the study follow-up period.

2.4. Extraction of data and assessment of bias risk

Two researcher (LT and SL) evaluated references and abstracts, reviewed quality of trials and rated the integrity of abstracted data respectively. Emails were sent to the writer of papers with inadequate data who were required to provide supplemental material. We used Cochrane risk of bias tool to assessed the quality of methodology and bias risk.

2.5. Statistics analysis

First, traditional pairwise comparisons of random-effects were conducted using the metan command with Knapp–Hartung method,[14] from which odds ratios (ORs) with 95% confidence intervals (CIs) were reported. We used the Haldane method to add 0.5 to each arm when trial reported a zero event. We performed conventional meta-analyses with the DerSimonian-Laird random effects model. We used the I^2 statistic as heterogeneity index.

Secondly, we performed network meta-analyses using the network suite based on a frequentist framework.[15] Based on the assumption that all treatment-contrasts had the same heterogeneity variance, we performed the network meta-analysis with a multivariable meta-analysis of random-effects using mvmeta command. Netleague command was used to report relative effects of treatment for all pairwise comparisons obtained by the multiple-treatments meta-analysis. We considered that $P < .05$ was significant. For population difference magnitude, a plausible range was looked at. The network rank option was used to estimate the probability which agent might be the most, second most, third most, etc efficacious intervention. We determined the

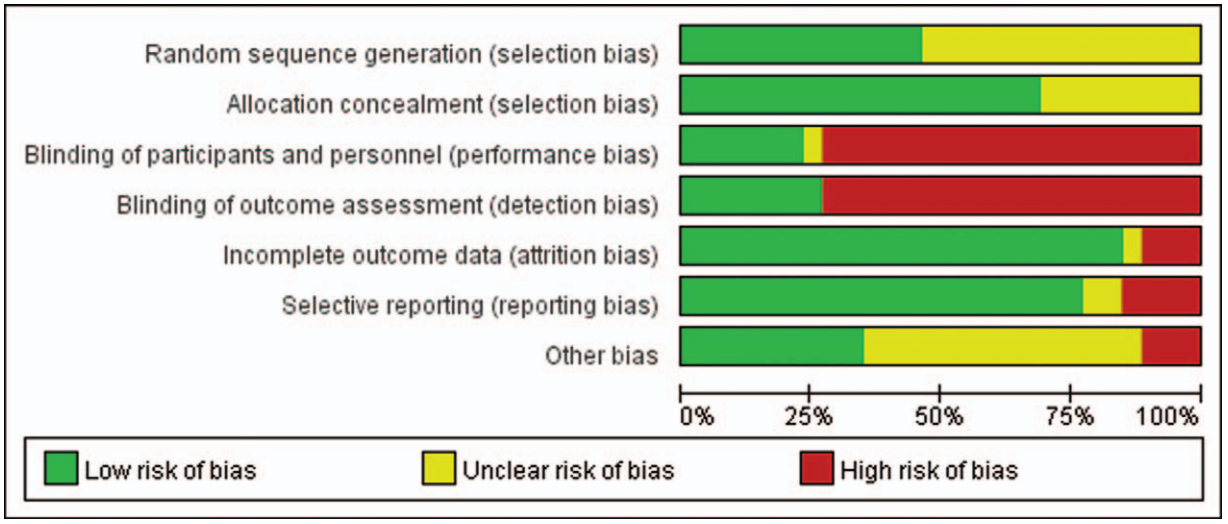


Figure 2. Risk of bias graph.

surface under the cumulative ranking curve (SUCRA)[16] as an evaluation of the ranking probability for each medication to obtain a treatment hierarchy. We ranked the agents' acceptability using the same method. Consistency within the networks was assessed between direct and indirect comparison using interaction model of the design-by-treatment.[17] We applied a loop-specific approach to check local inconsistency in network meta-analysis models when information was adequately similar among combined data. For a specific comparison, we calculated inconsistency factor with 95% CIs between indirect and direct evaluations as a method of within-loop inconsistency.[18] The definition of inconsistency was disagreement between indirect and direct comparison (95% CIs excluding 0). We conducted all data analyses in Stata 14.0 (Stata Corp, College Station, TX).

3. Results

3.1. Characteristics of study and network of evidence

Total number of 10,464 possibly correlative articles was included identified by literature searches, which identified 7236 unique qualified studies. We excluded 7174 reports during the review process based on our eligibility criteria. Ultimately, 26 studies reported from 1970 to 2018 were selected for inclusion in ultimate analysis. The 26 eligible trials included 1311 participants who were randomly assigned to a treatment group or placebo/nontreatment (P/NT) group. The summary of study screening process is shown in Fig. 1.

3.2. Characteristics of study

Table 1 summarizes the characteristics of 26 included studies.[3,19–43] In brief, study time of duration varied from 6 to 24 months and the age of included participants ranged from 1 to 17 years old. Most (71%) of the individuals were male. Data from 1311 participants were processed in ours study. The average sample number was 50 participants each group with range from 20 to 149. Majority (25/26; 96%) of the trials were two-arms (one experimental medication and one P/NT); one study had three arms (two experimental medications and one P/NT).[28] On the quality of trials, 23% of the studies were patient-blinded, 27% were outcome-blinded, 69% were allocation-concealed, and 15% were incomplete outcome. In general, low risk of bias was showed in the included studies (see Fig. 2 and Fig. 3).

3.3. Network of evidence

Our efficacy and acceptability analyses at the 6-, 12-, and 24-month follow-up time points included 566 participants in 14 studies of total six drugs (Fig. 4A), 1008 participants in 21 studies of total eight drugs (Fig. 4B), and 318 participants in 8 studies of total six drugs (Fig. 4C), respectively. Altogether, the following eight drugs were analyzed compared with P/NT in the presenting analysis: cyclophosphamide (7 trials), cyclosporine (5 trials), azathioprine (2 trials), chlorambucil (4 trials), levamisole (10 trials), rituximab (3 trials), vincristine (1 trials), and mycophenolate mofetil (3 trials).

3.4. Direct pairwise pooled-analyses of single-drugs

Table 2 shows the efficacy and acceptability analysis results from single immunosuppressive agents at 6, 12, and 24 months follow up as obtained by conventional meta-analyses. Cyclophosphamide, chlorambucil, and rituximab were found to be associated with a significantly better efficacy (reduced relapse rate) compared with P/NT at both the 6- and 12-month follow-up

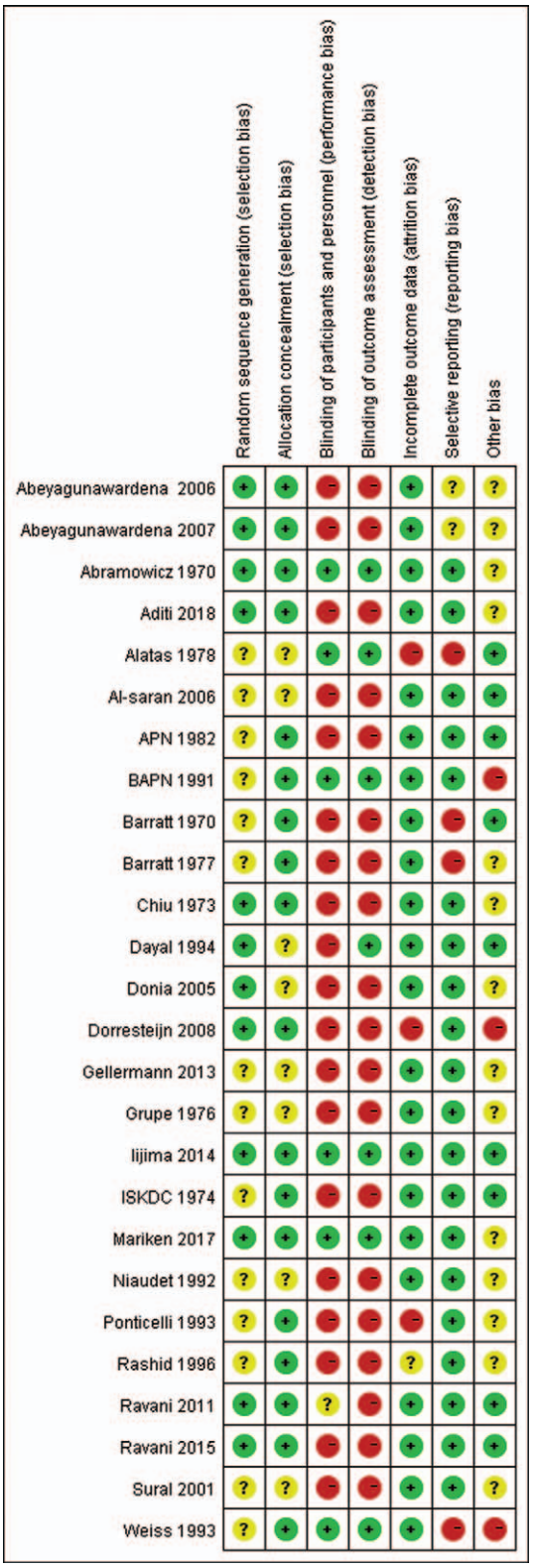


Figure 3. Risk of bias summary.

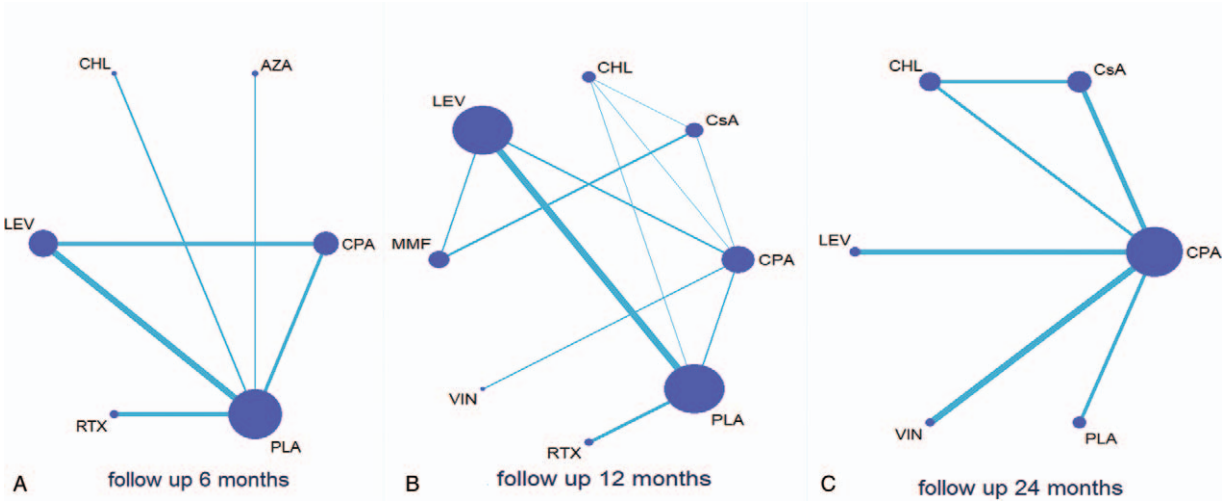


Figure 4. Network of eligible efficacy and acceptability comparisons. The thickness of the lines reflects the number of studies being compared, and node size reflects the number of randomized individuals.

time points (Table 2, Fig. S3, http://links.lww.com/MD/D20). Additionally, chlorambucil had better efficacy than cyclosporine, cyclosporine had better efficacy than MMF, and levamisole better than P/NT at 12-month follow-up time points (Table 2, Fig. S3, http://links.lww.com/MD/D20). At the 24-month follow-up time point, cyclophosphamide was more efficacious than cyclosporine and P/NT and chlorambucil was more efficacious than cyclosporine (Table 2).

There were no significant differences in acceptability between any of the eight experimental drugs versus P/NT nor between one another. But, it is noteworthy that most of the 95% CIs obtained from the comparisons were reflective of high or no heterogeneity as result of a small amount of included trials in direct comparisons; in general, there was moderate heterogeneity.

3.5. Network meta-analysis of single-drugs

Our network meta-analysis results for immunosuppressive medications, active comparators, and P/NT are presented in Fig. 5 presents network meta-analysis outcomes for immunosuppressive agents and P/NT. At the 6-month follow-up time point (Fig. 5A), cyclophosphamide, chlorambucil, levamisole, and rituximab had significant associations with relapse reduction compared with P/NT. Chlorambucil was associated with reduced relapse rates compared with azathioprine, while cyclophosphamide versus azathioprine, cyclophosphamide versus levamisole and chlorambucil versus levamisole were noted with the 95% CI for OR slightly more than 1. At the 12-month follow-up time point (Fig. 5B), cyclophosphamide, chlorambucil, cyclosporine, levamisole, and rituximab were associated with reduced relapse rates compared with P/NT. Chlorambucil were found to be more efficacious than levamisole and MMF while cyclophosphamide was not found to be more efficacious than levamisole with 95% CIs for ORs slightly more than 1. Meanwhile, chlorambucil was found to be more efficacious than vincristine. At the 24-month follow-up time point (Fig. 5C), cyclophosphamide, chlorambucil, and levamisole were associated with reduced relapse rates compared with P/NT, cyclophosphamide was more efficacious than cyclosporine. Cyclophosphamide and chlorambucil was not more efficacious than vincristine with 95% CIs for ORs slightly more than 1. No significant differences in acceptability were found.

3.6. Medications ranking

The relative rankings of efficacy and acceptability of the drugs evolved over time. At the 6-month follow-up time point, chlorambucil, rituximab, and cyclophosphamide were among the most efficacious treatments, while P/NT, levamisole, and azathioprine were better tolerated than the remaining immunosuppressive medications (Fig. 6A). The accumulative chances of efficacy for the testing agents at 6 months were: chlorambucil (68.7%), rituximab (21.2%), cyclophosphamide (9.9%), azathioprine (0.1%), levamisole (0.1%), and nontreatment/placebo (0%). The cumulative acceptability rates for the examined medications were: nontreatment/placebo (37.0%), levamisole (23.5%), azathioprine (15.1%), cyclophosphamide (13.0%), chlorambucil (10.7%), and rituximab (0.7%).

At 12 months (Fig. 6B), chlorambucil, rituximab, cyclophosphamide, and cyclosporine were the most efficacious treatments, and rituximab, levamisole, nontreatment/placebo, and vincristine were better tolerated than the other medications. The accumulative chances of being the most efficacious agent were: chlorambucil (74.8%), rituximab (18.7%), cyclosporine (3.7%), MMF (0.1%), vincristine (1.2%), cyclophosphamide (1.5%), levamisole (0.1%), and nontreatment/placebo (0%). The probabilities for being the most acceptable at 12 months were: rituximab (43.1%), vincristine (31.3%), levamisole (1.0%), cyclosporine (11.1%), MMF (3.6%), nontreatment/placebo (4.7%), chlorambucil (3.1%), and cyclophosphamide (2.1%).

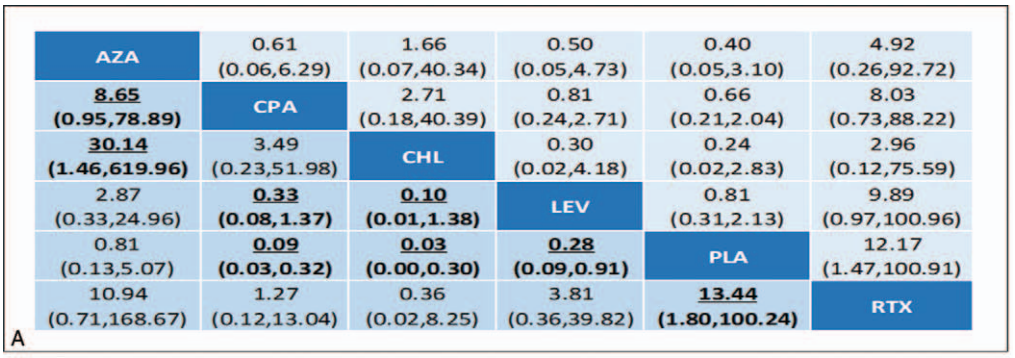
At 24 months (Fig. 6C), levamisole, chlorambucil, and cyclophosphamide were the most efficacious treatments, while vincristine, levamisole, and chlorambucil were the best tolerated. The accumulative chances of the most efficacious agent at 24 months were: levamisole (64.0%), chlorambucil (33.5%), cyclophosphamide (1.6%), vincristine (0.9%), cyclosporine (0%), and nontreatment/placebo (0%). The probabilities for being the most acceptable at 24 months were: vincristine

Table 2

Efficacy and acceptability in meta-analyses of direct comparisons between each pair of immunosuppressive medications.

			Efficacy		Acceptability	
Follow_up 6 months	**Number of studies**	**Number of patients**	**Response rate (responders /total randomised)**	**OR (95% CI)**	**adverse event (presence /total randomised)**	**OR (95% CI)**
Cyclophosphamide vs						
Levamisole	2	97	16/47 vs 23/50	1.989 (0.604–6.554)	4/47 vs 6/50	0.869 (0.173–4.371)
Nontreatment/Placebo	4	161	17/54 vs 24/42	**14.18 (5.735–35.044)**	4/54 vs 3/42	0.544 (0.143–2.070)
Cyclosporin vs						
Chlorambucil	1	40	8/20 vs 8/20	1.00 (0.282–3.544)	1/20 vs 0/20	0.317 (0.012–8.260)
Azathioprine vs						
Nontreatment/Placebo	2	60	15/30 vs 17/30	1.389 (0.444–4.349)	4/30 vs 1/30	0.404 (0.053–3.098)
Chlorambucil vs						
Nontreatment/Placebo	2	41	3/21 vs 17/20	**35.14 (5.029–245.644)**	3/21 vs 0/20	0.243 (0.021–2.831)
Levamisole vs						
Nontreatment/Placebo	4	207	62/104 vs 85/104	3.139 (0.746–13.209)	9/104 vs 8/104	0.810 (0.287–2.287)
Rituximab vs						
Nontreatment/Placebo	2	84	6/42 vs 27/42	**7.451 (2.406–23.077)**	9/54 vs 0/54	**0.082 (0.010–0.681)**
			Efficacy		Acceptability	
Follow_up 12 months	Number of studies	Number of patients	Response rate (responders/total randomized)	OR (95% CI)	Dropout rate (dropouts /total randomised)	OR (95% CI)
Cyclophosphamide vs						
Cyclosporin	1	66	8/25 vs 9/30	0.917 (0.303–2.771)	5/30 vs 6/36	1.000 (0.273–3.670)
Chlorambucil	1	50	15/26 vs 12/24	0.733 (0.240–2.239)	0/26 vs 0/24	1.082 (0.021–56.639)
Levamisole	2	97	29/47 vs 33/50	1.323 (0.531–3.295)	0/47 vs 0/50	0.949 (0.058–15.620)
Vincristine	1	39	6/18 vs 13/21	3.250 (0.870–12.137)	0/18 vs 0/21	0.860 (0.016–45.541)
Nontreatment/Placebo	3	108	14/48 vs 41/49	**9.785 (3.785–25.187)**	6/54 vs 5/54	0.840 (0.228–3.089)
Cyclosporine vs						
Chlorambucil	1	40	18/20 vs 9/20	**0.091 (0.017–0.501)**	0/20 vs 0/20	1.000 (0.019–52.849)
Mycophenolate mofetil	2	84	5/42 vs 16/40	**4.463 (1.443–13.804)**	0/42 vs 2/42	2.865 (0.250–32.854)
Chlorambucil vs						
Nontreatment/Placebo	2	41	1/15 vs 17/17	**48.272 (5.862–397.547)**	6/21 vs 3/20	0.477 (0.091–2.509)
Levamisole vs						
Mycophenolate mofetil	1	149	48/73 vs 45/76	0.756 (0.389–1.471)	8/73 vs 7/76	0.824 (0.283–2.402)
Nontreatment/Placebo	7	449	94/235 vs 151/214	**3.403 (2.191–5.287)**	17/236 vs 9/214	0.660 (0.267–1.631)
Rituximab vs						
Nontreatment/Placebo	2	79	18/39 vs 37/39	**13.961 (3.651–53.390)**	0/39 vs 1/40	1.934 (0.156–23.980)
			Efficacy		Acceptability	
Follow_up 24 months	Number of studies	Number of patients	Response rate (responders /totalrandomised)	OR (95% CI)	Dropout rate (dropouts /total randomised)	OR (95% CI)
Cyclophosphamide vs						
Cyclosporine	1	66	8/25 vs 24/30	**5.500 (1.895–15.960)**	5/30 vs 6/36	1.000 (0.273–3.670)
Chlorambucil	1	50	17/26 vs 12/24	0.529 (0.170–1.651)	0/26 vs 0/24	1.082 (0.021–56.639)
Levamisole	1	40	19/20 vs 17/20	0.298 (0.028–3.146)	0/20 vs 0/20	1.000 (0.019–52.849)
Vincristine	1	39	10/18 vs 16/21	2.560 (0.652–10.059)	0/18 vs 0/21	0.860 (0.016–45.541)
Nontreatment/Placebo	2	53	11/12 vs 10/10	**11.415 (1.781–73.159)**	15/27 vs 16/26	1.268 (0.415–3.878)
Cyclosporine vs						
Chlorambucil	1	40	19/20 vs 11/20	**0.064 (0.007–0.578)**	0/20 vs 0/20	1.000 (0.019–52.849)
Rituximab vs						
Nontreatment/Placebo	1	30	9/15 vs 14/15	9.333 (0.958–90.940)	0/15 vs 0/15	1.000 (0.019–53.770)

CI = confidence interval, OR = odds ratio, Vs = versus.



AZA	0.61 (0.06,6.29)	1.66 (0.07,40.34)	0.50 (0.05,4.73)	0.40 (0.05,3.10)	4.92 (0.26,92.72)
8.65 (0.95,78.89)	CPA	2.71 (0.18,40.39)	0.81 (0.24,2.71)	0.66 (0.21,2.04)	8.03 (0.73,88.22)
30.14 (1.46,619.96)	3.49 (0.23,51.98)	CHL	0.30 (0.02,4.18)	0.24 (0.02,2.83)	2.96 (0.12,75.59)
2.87 (0.33,24.96)	**0.33 (0.08,1.37)**	**0.10 (0.01,1.38)**	LEV	0.81 (0.31,2.13)	9.89 (0.97,100.96)
0.81 (0.13,5.07)	**0.09 (0.03,0.32)**	**0.03 (0.00,0.30)**	**0.28 (0.09,0.91)**	PLA	12.17 (1.47,100.91)
10.94 (0.71,168.67)	1.27 (0.12,13.04)	0.36 (0.02,8.25)	3.81 (0.36,39.82)	**13.44 (1.80,100.24)**	RTX

A

Note: Agents are reported in alphabetical order. ORs in the column-defining drug are compared to ORs in the row-defining drug. For efficacy, ORs > 1 favor the column-defining treatment. For acceptability, ORs < 1 favor the first drug in alphabetical order. Significant comparisons are underscored and bolded. AZA=azathioprine. CPA=cyclophosphamide. CHL=chlorambucil. LEV=levamisole. PLA=nontreatment/placebo. RTX=rituximab.

CPA	0.88 (0.28,2.81)	1.53 (0.29,8.10)	1.39 (0.40,4.87)	1.30 (0.30,5.72)	0.86 (0.29,2.56)	0.44 (0.03,6.90)	0.86 (0.02,45.54)
0.99 (0.26,3.76)	CsA	1.74 (0.28,10.99)	1.58 (0.35,7.04)	1.48 (0.30,7.26)	0.97 (0.23,4.06)	0.50 (0.03,9.10)	0.98 (0.02,61.12)
3.62 (0.94,13.99)	3.64 (0.78,17.02)	CHL	0.91 (0.17,4.75)	0.85 (0.13,5.52)	0.56 (0.13,2.40)	0.29 (0.02,5.30)	0.56 (0.01,41.52)
0.42 (0.15,1.18)	0.42 (0.10,1.77)	**0.12 (0.03,0.52)**	LEV	0.94 (0.34,2.57)	0.62 (0.26,1.45)	0.32 (0.02,4.55)	0.62 (0.01,39.75)
0.34 (0.08,1.50)	0.34 (0.09,1.31)	**0.09 (0.02,0.55)**	0.80 (0.20,3.15)	MMF	0.66 (0.19,2.33)	0.34 (0.02,5.70)	0.66 (0.01,45.72)
0.10 (0.03,0.27)	**0.10 (0.02,0.42)**	**0.03 (0.01,0.12)**	**0.23 (0.11,0.48)**	0.29 (0.07,1.25)	PLA	0.52 (0.04,6.41)	1.00 (0.02,61.68)
1.44 (0.19,10.69)	1.45 (0.15,13.91)	0.40 (0.04,3.82)	3.43 (0.53,22.24)	4.28 (0.45,41.19)	**14.82 (2.63,83.39)**	RTX	1.94 (0.02,242.32)
0.31 (0.04,2.25)	0.31 (0.03,3.39)	**0.09 (0.01,0.94)**	0.73 (0.08,6.89)	0.91 (0.08,11.04)	3.17 (0.34,29.66)	0.21 (0.01,3.60)	VIN

B

Note: Agents are reported in alphabetical order. ORs in the column-defining drug are compared to ORs in the row-defining drug. For efficacy, ORs > 1 favor the column-defining treatment. For acceptability, ORs < 1 favor the first drug in alphabetical order. Significant comparisons are underscored and bolded.CPA=cyclophosphamide. CsA=cyclosporine. CHL=chlorambucil. LEV=levamisole. MMF= mycophenolate mofetil. PLA=nontreatment/placebo. RTX=rituximab. VIN=vincristine.

CPA	1.00 (0.28,3.56)	1.04 (0.06,18.43)	1.00 (0.02,52.85)	1.27 (0.41,3.88)	0.86 (0.02,45.54)
0.17 (0.06,0.45)	CsA	1.04 (0.06,18.36)	1.00 (0.02,64.11)	1.26 (0.23,6.84)	0.86 (0.01,55.24)
2.03 (0.72,5.69)	11.89 (3.34,42.37)	CHL	0.96 (0.01,128.61)	1.22 (0.06,26.54)	0.83 (0.01,110.80)
3.35 (0.32,35.36)	19.64 (1.53,251.80)	1.65 (0.13,21.62)	LEV	1.27 (0.02,78.22)	0.86 (0.00,235.46)
0.39 (0.10,1.53)	2.29 (0.43,12.31)	**0.19 (0.03,1.07)**	0.12 (0.01,1.78)	PLA	0.68 (0.01,41.90)
0.09 (0.01,0.56)	0.51 (0.06,4.19)	**0.04 (0.01,0.36)**	**0.03 (0.00,0.52)**	4.46 (0.44,44.80)	VIN

C

Note: Agents are reported in alphabetical order. ORs in the column-defining drug are compared to ORs in the row-defining drug. For efficacy, ORs > 1 favor the column-defining treatment. For acceptability, ORs < 1 favor the first drug in alphabetical order. Significant comparisons are underscored and bolded. CPA=cyclophosphamide. CsA=cyclosporine. CHL=chlorambucil. LEV=levamisole. PLA=nontreatment/placebo. VIN=vincristine.

Figure 5. Efficacy and acceptability of agents at 6-month (A), 12-month (B), and 24-month (C) follow-up time points. Agents are reported in alphabetical order. ORs in the column-defining drug are compared to ORs in the row-defining drug. For efficacy, ORs > 1 favor the column-defining treatment. For acceptability, ORs < 1 favor the first drug in alphabetical order. Significant comparisons are underscored and bolded. AZA = azathioprine, CHL= chlorambucil, CPA = cyclophosphamide, CsA = cyclosporine, LEV = levamisole, MMF = mycophenolate mofetil, PLA= nontreatment/placebo, RTX = rituximab.

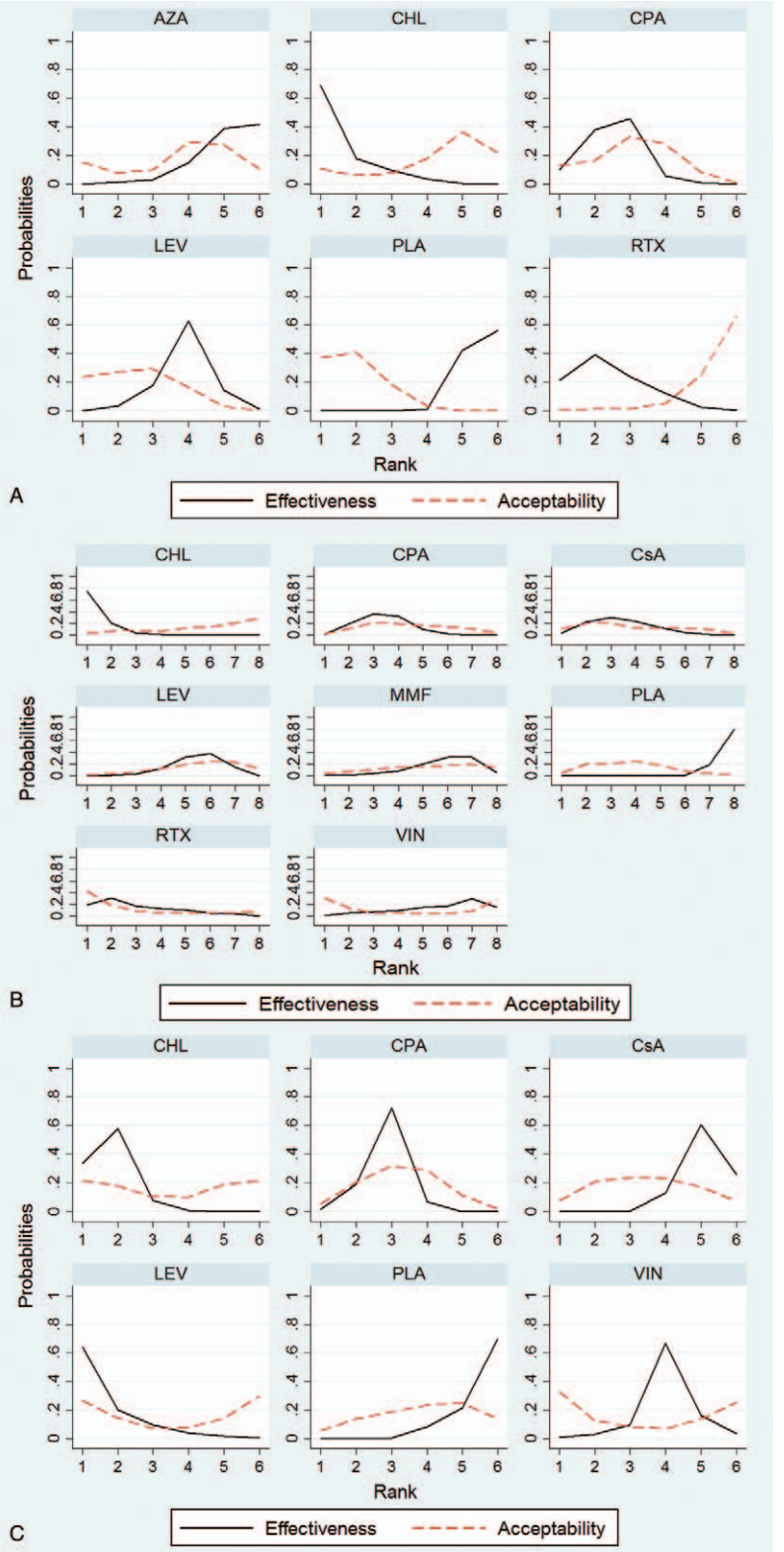


Figure 6. Efficacy (real line) and acceptability (dashed line) rankings at 6 months (A), 12 months (B), and 24-month (C) follow-up time points. Ranking reflects the probability of being the best, second best etc agent among the eight tested medications.

(32.8%), levamisole (36.8%), chlorambucil (21.5%), cyclosporine (7.8%), nontreatment/placebo (5.6%), and cyclophosphamide (5.5%).

Cluster ranking (Fig. S1, http://links.lww.com/MD/D20) indicated that chlorambucil, cyclophosphamide, and rituximab may have the best efficacy and acceptability profiles, relative to the other examined drugs, at 6 months. Cluster ranking indicated that chlorambucil, cyclosporine, cyclophosphamide, and rituximab may have the best efficacy and acceptability profiles, relative to the other examined drugs, at 12 months. And, finally, cluster ranking indicated that cyclophosphamide, levamisole, and chlorambucil may have the best efficacy and acceptability profiles at 24 months.

3.7. Inconsistency and publication bias

Figure S2, http://links.lww.com/MD/D20 shows low inconsistency of indirect and direct comparisons of rates of relapse. It was consistent in the most of loops, with the 95% CIs (contained 0) illustrating similar evaluations of effects between indirect and direct comparisons. Therefore, the results of network meta-analysis were robust. No asymmetry evidence was showed in comparison adjusted funnel plots for 12 months efficacy (Fig. S4, http://links.lww.com/MD/D20).

4. Discussion

Our analysis included 24 trials, with 1062 participants who were randomly allocated to either one of eight immunosuppressive agent groups or P/NT group. Chlorambucil, rituximab, and cyclophosphamide were more efficacious than azathioprine, levamisole, and P/NT at all examined time points. However, P/NT, levamisole, and azathioprine were better tolerated than cyclophosphamide, chlorambucil, and rituximab at 6 months. Chlorambucil, rituximab, cyclophosphamide, and cyclosporine may control recurrence better than MMF, vincristine, levamisole, and nontreatment/placebo, whereas rituximab, vincristine, levamisole, and MMF appear to be tolerated better than cyclosporine, nontreatment/placebo, chlorambucil, and cyclophosphamide at 12 months. At 24 months, levamisole, chlorambucil, and cyclophosphamide were more efficacious than vincristine, cyclosporine, and nontreatment/placebo, while vincristine, levamisole, and chlorambucil were better tolerated than cyclosporine, nontreatment/placebo, and cyclophosphamide. Our results, which illustrate different efficacy amongst the tested agents may provide useful information useful for the selection of immunosuppressive medications for FRSN/SDNS treatment in pediatric patients. Although prior research has produced apparently favorable efficacy and safety results for rituximab in pediatric FRSN/SDNS patients compared with other immunosuppressive agents, sufficient power was lacking to yield clinically significant differences in treatment effects.[6]

A clinical significance of our findings is that chlorambucil, rituximab, and cyclophosphamide should be considered as preferred immunosuppressive medications for FRSN/SDNS in children due to their more effectiveness and overall good, although not preferable, acceptability. Among these three drugs, cyclophosphamide is more affordable than rituximab in most countries. However, without a formal cost-effectiveness analysis, this recommendation cannot be made unequivocally. Conversely, azathioprine, vincristine, and levamisole were less favorable options for FRSN/SDNS in terms of efficacy. Azathioprine and vincristine were also not ranked high for acceptability among the presently examined immunosuppressive medications. Hence, the present findings suggest that azathioprine, vincristine, and levamisole should not be first-line treatments for FRSN/SDNS.

Existing traditional head-to-head meta-analyses of the effectiveness of immunosuppressive agents for pediatric FRSN/SDNS were not conclusive owing to limited information of treating effects and failures to provide evidence of relative effect of eligible agents. But all, a published systematic review, reported by Nanthiya et al, demonstrated that 8-week courses of cyclophosphamide or chlorambucil and extended-term courses of cyclosporine and levamisole can reduce relapse risk in children with SSNS compared with corticosteroids.[7] The present research provides much necessary direct comparisons among immunosuppressive drugs in patients of primary nephrotic syndrome.

Rituximab, a monoclonal anti-CD-20 antibody, represents a new treatment strategy of B cell apoptosis induction.[20] Some studies have reported that rituximab treatment prolonged clinical remission and decreased glucocorticoid dose levels in children with FRSN/SDNS.[19,20] Clinical guidelines for pediatric idiopathic nephrotic syndrome recommend the immunosuppressive agents cyclosporine and cyclophosphamide (recommendation grade A) as well as mizoribine (recommendation grade C2), while suggesting rituximab only for refractory disease (recommendation grade C).[5]

The most problematic adverse secondary effect of cyclosporine is chronic renal toxicity, an rising risk for which has be related to cyclosporine treatment for more than 2 years.[44] The rates of associated side effect of immunosuppressive medications reported may be underestimated because the initial trials were designed primarily not to estimate adverse effect. In addition, because we included studies with combined corticoid treatment, related results of immunosuppressive medications should not be considered unrelated of possible corticoid effects. Moreover, our findings cannot be generalized to children who suffer from steroid-resistant nephrotic syndrome because we excluded studies with that patients.

The findings of our meta-analysis should be applied to duration of <2 years. Practice efficacy and acceptability >2 years might be quite different from results obtained within 2 years.[45] In addition, the quality of the initial trials may limit the quality of this review. Most eligible trials in this study reported insufficient information on randomization and allocation concealment, which may have an affect on the total validity of the data.[46] About 65% of the included trials had high performance bias and detection bias. The small sample-sizes and small number of the eligible trials might also be considered for the generalizability of findings. Lastly, all of the eligible trials did not address long-term fertility-related adverse effect of alkylating-agent.

In conclusion, on the basis of all obtainable indirect and direct evidences, our analyses suggest that cyclophosphamide may be preferred initially in children with FRSN/SDNS, chlorambucil, and rituximab may be acceptable medications for patients with FRSN/SDNS. Moreover, long-term follow-up trials focused on gonadal toxicity and limitation of maximum dosage of cyclophosphamide should be carried out. Additional evidences about the safety and efficacy of rituximab in children with FRSN/SDNS are also needed.

Author contributions

Conceptualization: Liping Tan, Qiu Li.
Investigation: Shaojun Li, Haiping Yang, Qing Zou.

Methodology: Shaojun Li, Haiping Yang.
Resources: Junli Wan.
Software: Junli Wan.
Writing – review & editing: Liping Tan, Shaojun Li, Qiu Li.

References

[1] Koskimies O, Vilska J, Rapola J, Hallman N. Long-term outcome of primary nephrotic syndrome. Arch Dis Child 1982;57:544–8.
[2] Tarshish P, Tobin JN, Bernstein JJr, E.C. Prognostic significance of the early course of minimal change nephrotic syndrome: report of the International Study of Kidney Disease in Children. J Am Soc Nephrol 1997;8:769–76.
[3] Listed N. Effect of cytotoxic drugs in frequently relapsing nephrotic syndrome with and without steroid dependence. N Engl J Med 1982;306:451–4.
[4] Habashy D, Hodson E, Craig J. Interventions for idiopathic steroid-resistant nephrotic syndrome in children. Cochrane Database Syst Rev 2004;Cd003594.
[5] Kaku Y, Ohtsuka Y, Komatsu Y, et al. Clinical practice guideline for pediatric idiopathic nephrotic syndrome 2013: general therapy. Clin Exp Nephrol 2015;19:34.
[6] Zhao Z, Liao G, Li Y, Zhou S, Zou H. The efficacy and safety of rituximab in treating childhood refractory nephrotic syndrome: a meta-analysis. Sci Rep 2015;5:8219.
[7] Pravitsitthikul N, Willis NS, Hodson EM, Craig JC. Non-corticosteroid immunosuppressive medications for steroid-sensitive nephrotic syndrome in children. Cochrane Datab System Rev 2013;10:CD002290.
[8] Hodson EM, Willis NS, Craig JC. Non-corticosteroid treatment for nephrotic syndrome in children. The Cochrane Library; 2008.
[9] Sun Q, Shen Y. A meta-analysis on the effect of cyclophosphamide in treatment of nephrotic syndrome in children. Zhonghua Er Ke Za Zhi Chin J Pediatr 2006;44:199–201.
[10] Metz DK, Kausman JY. Childhood nephrotic syndrome in the 21st century: what's new? J Paediatr Child Health 2014;51:497–504.
[11] Peco-Antić A. Management of idiopathic nephrotic syndrome in childhood. Srp Arh Celok Lek 2004;132:352–9.
[12] Salanti G, Higgins JP, Ades AE, Ioannidis JP. Evaluation of networks of randomized trials. Stat Methods Med Res 2008;17:279–301.
[13] Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of, diagnosis. A report of the International Study of Kidney Disease in, Children. Kidney Int 1978;13:159–65.
[14] Harbord RM, Higgins JPT. Meta-regression in Stata. Stata J 2008; 8:493–519.
[15] White IR. Multivariate random-effects meta-regression: updates to mvmeta. Stata J 2011;11:255–70.
[16] Salanti G, Ades AE, Ioannidis JP. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. J Clin Epidemiol 2011;64:163–71.
[17] Jackson D, Barrett JK, Rice S, et al. A design-bytreatment interaction model for network meta-analysis with random inconsistency effects. Stat Med 2014;33:3639–54.
[18] Song F, Altman DG, Glenny AM, Deeks JJ. Validity of indirect comparison for estimating efficacy of competing interventions: empirical evidence from published meta-analyses. BMJ 2003;326:472.
[19] Ravani P, Rossi R, Bonanni A, et al. Rituximab in children with steroid-dependent nephrotic syndrome: a multicenter, open-label, noninferiority, randomized controlled trial. J Am Soc Nephrol Jasn 2015;26:2259.
[20] Iijima K, Sako M, Nozu K, et al. Rituximab for childhood-onset, complicated, frequently relapsing nephrotic syndrome or steroid-dependent nephrotic syndrome: a multicentre, double-blind, randomised, placebo-controlled trial. Lancet 2014;384:1273.
[21] Gellermann J, Weber L, Pape L, et al. Mycophenolate mofetil versus cyclosporin A in children with frequently relapsing nephrotic syndrome. J Am Soc Nephrol 2013;24:1689–97.
[22] Ravani P, Magnasco A, Edefonti A, et al. Short-term effects of rituximab in children with steroid- and calcineurin-dependent nephrotic syndrome: a randomized controlled trial. Clin J Am Soc Nephrol 2011;6:1308–15.
[23] Dorresteijn EM, Kist-van Holthe JE, Levtchenko EN, et al. Mycophenolate mofetil versus cyclosporine for remission maintenance in nephrotic syndrome. Pediatr Nephrol 2008;23:2013–20.
[24] Abeyagunawardena A. Intravenous pulsed cyclophophamide versus vincristine therapy in steroid dependant nephrotic syndrome: a randomised controlled trial. Paper presented at Pediatric Nephrology; 2007.
[25] Al-Saran K, Mirza K, Al-Ghanam G, Abdelkarim M. Experience with levamisole in frequently relapsing, steroid-dependent nephrotic syndrome. Pediatr Nephrol 2006;21:201–5.
[26] Abeyagunawardena A, Trompeter R. Efficacy of Levamisole as a single agent in maintaining remission in steroid dependant nephrotic syndrome. Pediatr Nephrol 2006;21:1503.
[27] Donia AF, Ammar HM, El-Agroudy EB, Moustafa EH, Sobh AK. Long-term results of two unconventional agents in steroid-dependent nephrotic children. Pediatr Nephrol 2005;20:1420–5.
[28] Sural S, Pahari D, Mitra K, Bhattacharya S, Mondal S, Taraphder A. Efficacy of levamisole compared to cyclophosphamide and steroid in frequently relapsing (FR) minimal change nephrotic syndrome (MCNS). J Am Soc Nephrol 2001;12:126A.
[29] Rashid HU, Ahmed S, Fatima N, Khanam A. Levamisole in the treatment of steroid dependent or frequent relapsing nephrotic syndrome in children 1996.
[30] Dayal U, Dayal AK, Shastry JC, Raghupathy P. Use of levamisole in maintaining remission in steroid-sensitive nephrotic syndrome in children 1994;66:408–12.
[31] Weiss R. Randomized double-blind, placebo (p) controlled trial of levamisole (l) for children (ch) with frequently relapsing/steroid dependant (fr/sd) nephrotic syndrome (ns). [abstract]; 1993.
[32] Ponticelli C, Edefonti A, Ghio L, et al. Cyclosporin versus cyclophosphamide for patients with steroid-dependent and frequently relapsing idiopathic nephrotic syndrome: a multicentre randomized controlled trial. Nephrol Dial Transplant 1993;8:1326–32.
[33] Niaudet P. Comparison of cyclosporin and chlorambucil in the treatment of steroid-dependent idiopathic nephrotic syndrome: a multicentre randomized controlled trial. French Soc Paediatr Nephrol Pediatr Nephrol 1992;6:1–3.
[34] Nephrology BAFP. Levamisole for corticosteroid-dependent nephrotic syndrome in childhood. Lancet 1991;337:1555.
[35] Alatas H, Wirya IG, Tambunan T, et al. Controlled trial of chlorambucil in frequently relapsing nephrotic syndrome in children (a preliminary report). J Med Assoc Thai 1978;61(Suppl 1):222–8.
[36] Barratt TM, Cameron JS, Chantler C, et al. Controlled trial of azathioprine in treatment of steroid-responsive nephrotic syndrome of childhood. Arch Dis Child 1977;52:462.
[37] Grupe WE, Makker SP, Ingelfinger JR. Chlorambucil treatment of frequently relapsing nephrotic syndrome. N Engl J Med 1976;295: 746–9.
[38] Lancet T. Prospective controlled trial of cyclophosphamide therapy in children with the nephrotic syndrome. Lancet 1974;304:423–7.
[39] Chiu J, Mclaine PN, Drummond KN. A controlled prospective study of cyclophosphamide in relapsing, corticosteroid-responsive, minimal-lesion nephrotic syndrome in childhood. J Pediatr 1973;82:607–13.
[40] Barratt TM, Soothill JF. Controlled trial of cyclophosphamide in steroid-sensitive relapsing nephrotic syndrome of childhood. Lancet 1970; 2:479–82.
[41] Abramowicz M, Barnett HL, Edelmann CM JJr, et al. Controlled trial of azathioprine in children with nephrotic syndrome. A report for the international study of kidney disease in children. Lancet 1970;1: 959–61.
[42] Sinha A, Puraswani M, Kalaivani M, et al. Efficacy and safety of mycophenolate mofetil versus levamisole in frequently relapsing nephrotic syndrome: an open-label randomized controlled trial. Kidney Int 2019;95:210–8.
[43] Gruppen MP, Bouts AH, Jansen-van der Weide MC, et al. A randomized clinical trial indicates that levamisole increases the time to relapse in children with steroid-sensitive idiopathic nephrotic syndrome. Kidney Int 2018;93:510–8.
[44] Melocoton TL, Kamil ES, Cohen AH, et al. Long-term cyclosporine A treatment of steroid-resistant and steroid-dependent nephrotic syndrome. Am J Kidney Dis 1991;18:583–8.
[45] Latta K, Von SC, Ehrich JH. A meta-analysis of cytotoxic treatment for frequently relapsing nephrotic syndrome in children. Pediatr Nephrol 2001;16:271–82.
[46] Karin H-M, Peter J, Christoph J, et al. Quality of reporting of randomized trials as a measure of methodologic quality. JAMA 2002;287:2801–4.