Efficacy and safety of immunosuppressive medications for steroid-resistant nephrotic syndrome in children: a systematic review and network meta-analysis

Shaojun Li1,3, Haiping Yang2,5, Pengfei Guo1,3, Xiaoxiao Ao1,4, Junli Wan2,4, Qiu Li1,2,3 and Liping Tan1,4

1 Department of Emergency, Children’s Hospital of Chongqing Medical University, Chongqing, China
2 Department of Nephrology, Children’s Hospital of Chongqing Medical University, Chongqing, China
3 Ministry of Education Key Laboratory of Child Development and Disorders, Chongqing, China
4 Key Laboratory of Pediatrics in Chongqing, Chongqing, China
5 Chongqing International Science and Technology Cooperation Center for Child Development and Disorders, Chongqing, China

Correspondence to: Liping Tan, email: tanlp0825@hotmail.com

Keywords: immunosuppressant, SRNS, pediatrics, multiple-treatments meta-analysis

Received: June 21, 2017  Accepted: August 07, 2017  Published: August 21, 2017

ABSTRACT

Background: Conventional meta-analyses and randomized controlled trials have shown inconsistent results regarding the efficacy of immunosuppressants for pediatric steroid-resistant nephrotic syndrome (SRNS).

Objective: To conduct a network meta-analysis aimed at evaluating the efficacy and safety of available immunosuppressive agents in pediatric patients with SRNS.

Study methods: MEDLINE, the Cochrane Central Register of Controlled Trials, and EMBASE were searched on January 2017. Data from randomized controlled trials (RCTs) were included. The main outcomes analyzed were efficacy [number/portion with complete remission (CR), number/portion with partial remission (PR), and total number/portion in remission (TR)] and safety [adverse secondary event (ASE) rates].

Results: A meta-analysis of 18 RCTs showed that tacrolimus was more efficacious for achieving CR than intravenous (i.v.) cyclophosphamide, mycophenolate mofetil (MMF), oral cyclophosphamide, leflunomide, chlorambucil, azathioprine, and placebo/nontreatment (P/NT), and more efficacious than i.v. cyclophosphamide, oral cyclophosphamide, and P/NT in terms of TR outcomes. Cyclosporin was associated with a greater CR rate than i.v. cyclophosphamide, MMF, oral cyclophosphamide, chlorambucil, azathioprine, or P/NT, and associated with a greater TR rate than i.v. cyclophosphamide, oral cyclophosphamide, or P/NT. MMF was found to be more efficacious than i.v. cyclophosphamide and oral cyclophosphamide in terms of TR.

Conclusions: Tacrolimus and cyclosporine are preferred initial treatments for children with SRNS. MMF may be another option for this patient population. Further studies of the efficacy and safety of these three drugs in children with SRNS should be pursued.

INTRODUCTION

The incidence of pediatric primary nephrotic syndrome (NS) is about 1–3/100,000 children 16 years old or younger [1]. In most cases, clinical remission of primary NS can be achieved with corticosteroid therapy [2]. The approximately 10–20% for whom complete remission is not achieved following corticosteroid therapy are classified as having steroid-resistant nephrotic syndrome (SRNS) [1]. SRNS patients are a heterogenous population...
with related diagnoses of minimal-change disease (MCD), mesangial proliferative glomerulonephritis (MesPGN), focal segmental glomerulosclerosis (FSGS), or other histopathologies [1].

Treating SRNS, which should be done under the care of a pediatric nephrologist, can be challenging because there is a paucity of strong evidence to inform SRNS treatment decisions due to the lack of large-scale randomized controlled trials (RCTs). Children with SRNS may be treated with immunosuppressive agents, such as cyclosporin, cyclophosphamide, or tacrolimus [3]. Remission rates obtained with combinations of cyclophosphamide and intravenous (i.v.) methylprednisolone have reached 50–60% in observational studies and individual treatment groups in RCTs [4–7]. Meanwhile, complete remission (CR) and partial remission (PR) rates with calcineurin inhibitors (cyclosporine and tacrolimus) have been in the range of 30–80% in observational studies and RCTs [8–10]. If there is a failure to achieve at least PR, SRNS progresses to end-stage kidney disease [11, 12].

In recent decades, several new lower-toxicity immunosuppressive medications have been introduced for the treatment of SRNS in children [13]. However, these new medications have been found to be less effective for prolonging remission after corticosteroid withdrawal than traditional immunosuppressant drugs. Because head-to-head comparison trials of these new agents with traditional ones have not been completed, however, there is not a consensus regarding which immunosuppressive drugs are most suitable for treating SRNS in children. Pairwise meta-analyses evaluating the efficacy of new immunosuppressive medications have identified factors that may be associated with therapeutic efficacy and previous systematic reviews have suggested efficacy differences among nonsteroidal immunosuppressive medications [14–16]. However, these studies are inconclusive because they could not provide direct comparisons. Moreover, the extent to which efficacy and safety varies across potential SRNS drugs is unclear.

Here, we report a network meta-analysis in which nine nonsteroidal immunosuppressive agents were compared with respect to efficacy and safety in children being treated for SRNS. The aim of this work was to identify a preferable SRNS therapy drug in children.

RESULTS

Study characteristics and evidence network

A total of 7,681 potentially relevant studies were retrieved, which included 6,146 non-repetitive potentially eligible articles. On the basis of our eligibility criteria (parallel RCTs whose subjects were children with initial SRNS and children with delayed SRNS and that were examining immunosuppressive medications), 6,102 articles were excluded during the title/abstract review process and, subsequently, 26 articles were excluded consequent to a full-text review. Finally, 18 articles published from 1970 to 2015 were included in our network meta-analysis. The 18 selected studies involved a total of 790 individuals who were assigned randomly to an immunosuppressive medication or placebo/nontreatment (P/NT) group. The trial selection process is summarized in Figure 1.

Study characteristics

The characteristics of the 18 included trials are summarized in Table 1 [4, 6–9, 17–29]. Briefly, trial durations ranged from 3 months to 24 months and the enrolled patients ranged in age from 1 year to 18 years old. A majority (61%) of the participants were male. The distribution of histopathologic diagnoses in each trial are shown in Figure 2. Most (14/17, 82%) of the studies included patients with MCD, MesPGN, and FSGS, three studies included only patients with FSGS, and one study included only patients with MCD. Data from 790 individuals were included in the efficacy and safety analyses. The mean sample size was 44 individuals per group (range, 8–138). Most (17/18, 94%) of the studies had two arms; one study had three arms. Regarding study quality, 67% of the trials were outcome-blinded, 56% were allocation-concealed, 50% had incomplete outcome data, and 17% were patient-blinded. Generally, the risk of bias in the reviewed trials was medium (see Supplementary Figure 1).

Evidence network

Our efficacy analyses included 730 patients with a CR in 17 trials examining a total of ten treatments (Figure 3A), 569 patients with a PR in 12 trials examining a total of seven treatments (Figure 3B), and 605 TR patients in 12 trials examining a total of seven treatments (Figure 3C). Our safety analyses based on the incidence of ASEs included 730 patients in 11 trials examining a total of seven treatments (Figure 3D). Ultimately, the following nine treatments were analyzed relative to P/NT in the present meta-analysis: cyclosporin (7 trials), i.v. cyclophosphamide (3 trials), tacrolimus (4 trials), MMF (3 trials), oral cyclophosphamide (5 trials), leflunomide (1 trial), chlorambucil (1 trial), azathioprine (1 trials), and rituximab-cyclosporin dual therapy (1 trial).
have significantly better efficacy for achieving both CR and PR (both, I² = 0%). Cyclosporin also showed better efficacy than i.v. cyclophosphamide for both PR and TR outcomes (both I² = 0%), as well as greater efficacy than MMF for TR (I² = 0%), though in the latter case the benefits were less clear (95% CI for OR slightly more than 1). Additionally, tacrolimus was more efficacious than i.v. cyclophosphamide for TR (I² = 0%) and i.v. cyclophosphamide was more efficacious than oral cyclophosphamide for CR (I² = 37.8%).

In terms of ASEs, oral cyclophosphamide was found to be safer than i.v. cyclophosphamide (95% CI for OR slightly more than 1) and tacrolimus was found to be safer than both cyclosporin and i.v. cyclophosphamide (I² = 15.1%). There were no significant differences in safety revealed by other direct comparisons between

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**Table 1: Descriptive characteristics of studies included in the meta-analysis**

| Study          | Country | Study design | Time frame | Cases (N) | Age (y) | Sex (M/F) | Patients       | Interventions | Study outcomes | Follow-up duration | Attrition (%) |
|----------------|---------|--------------|------------|-----------|---------|-----------|----------------|---------------|----------------|-------------------|---------------|
| Abramowicz 1970 | International | Multicenter RCT | 1967–1969 | 38 | NR | NR | Initial SRNS | AZA vs P/NT | CR and PR at 90 d, | 3 mos. | 18% |
| Choudhry 2009 | India   | Single center RCT | 2005–2007 | 41 | 3.5–6.0 | 25/16 | Initial and late SRNS | TAC vs CSA | CR and PR at 12 mos., adverse effects | 12 mos. | 0% |
| D’Agati 2013 | USA     | Multicenter RCT | 2004–2009 | 138 | NR | 73/65 | Initial SRNS | CSA vs MMF | CR and PR at 12 mos., adverse effects | 12 mos. | 1% |
| Elhence 1994 | India   | Single center RCT | 1990–1991 | 13 | 3–16 | 11/2 | Initial and late SRNS | OCPA vs ICPA | CR at 6 mos., adverse effects | 6 mos. | 15% |
| Gaur 1988 | USA     | Single center RCT | NR | 8 | 3–18 | 6/2 | SRNS | CSA vs P/NT | CR at 3 mos. | 3 mos. | 0% |
| Gulati 2012 | India   | Multicenter RCT | 2008–2010 | 131 | 2–16 | 86/45 | Initial and late SRNS | TAC vs ICPA | CR and PR at 12 mos., adverse effects | 12 mos. | 5% |
| ISKDC 1974 | International | Multicenter RCT | 1970–1972 | 31 | NR | NR | Initial SRNS | OCPA vs P/NT | CR and PR at 12 mos., adverse effects | 24 mos. | 0% |
| Kleinknecht 1980 | France | Single center RCT | NR | 30 | NR | NR | SRNS | CHL vs P/NT | CR at 6 mos. | 6 mos. | 0% |
| Lieberman 1996 | USA     | Multicenter RCT | NR | 31 | 7–16 | 21/9 | Initial SRNS | CSA vs P/NT | CR and PR at 6 mos., adverse effects | 6 mos. | 23% |
| Magnasco 2012 | Italy   | Single center RCT | 2007–2010 | 31 | <16 | 19/12 | Initial and late SRNS | RTCA vs P/NT | CR at 12 mos., adverse effects | 12 mos. | 0% |
| Munan 2008 | India   | Single center RCT | 2001–2003 | 52 | 1–18 | 35/17 | Initial and late SRNS | ICPA vs OCPA | CR and PR at 6 mos., adverse effects | 18 mos. | 6% |
| Ohri 2010 | India   | Single center RCT | NR | 35 | 1–12 | 17/18 | Initial SRNS | ICPA vs OCPA | CR and PR at 6 mos., adverse effects | 6 mos. | 0% |
| Plank 2008 | International | Multicenter RCT | 2001–2004 | 32 | 1–13 | 19/13 | Initial SRNS | CSA vs CPA | CR and PR at 3 mos., adverse effects | 12 mos. | 33% |
| Ponticelli 1993 | Italy   | Multicenter RCT | NR | 20 | 2–18 | NR | Initial SRNS | CSA vs P/NT | CR and PR at 12 mos., adverse effects | 12 mos. | 0% |
| Sinha 2015 | India   | Multicenter RCT | NR | 60 | 1–18 | NR | SRNS | TAC vs MMF | Complete or PR at 12 mos. | 12 mos. | 0% |
| Tarshish 1996 | International | Multicenter RCT | NR | 60 | 1–16 | NR | Initial SRNS | OCPA vs P/NT | CR and PR at 6 mos., adverse effects | 12 mos. | 11% |
| Vallverde 2010 | Mexico | Single center RCT | NR | 17 | 1–18 | NR | SRNS | CSA vs TAC | CR and PR at 12 mos., adverse effects | 12 mos. | 0% |
| Wu 2015 | China   | Single center RCT | 2008–2012 | 18 | 2–18 | 11/7 | SRNS | CPA vs MMF vs LEF | CR at 6 mos. | 18 mos. | 18% |

Notes: SRNS, steroid-resistant nephrotic syndrome; NR, not reported; RCT, randomized controlled trial; CSA, cyclosporin; ICPA, intravenous cyclophosphamide; TAC, tacrolimus, MMF, mycophenolate mofetil; OCPA, oral cyclophosphamide; LEF, leflunomide; CHL, chlorambucil; AZA, azathioprine; RTCA, rituximab-cyclosporin dual therapy; P/NT, placebo/nontreatment; CR, complete response; PR, partial response.
immunosuppressants. However, it should be noted that the 95% CIs obtained for most of the comparisons were reflective of either high or no heterogeneity due to the small number of studies included in the pairwise comparisons; overall, heterogeneity was moderate.

**Network meta-analysis of individual medications**

Our network meta-analysis results for immunosuppressive medications, active comparators, and P/NT are presented in Figure 4. Tacrolimus was found to be more efficacious for achieving CR than i.v. cyclophosphamide, MMF, oral cyclophosphamide, leflunomide, chlorambucil, and azathioprine, as well as P/NT. Tacrolimus was also found to be more efficacious for achieving TR than i.v. cyclophosphamide, oral cyclophosphamide, azathioprine, and P/NT. Meanwhile, cyclosporin therapy was associated with a better CR rate than i.v. cyclophosphamide, MMF, oral cyclophosphamide, chlorambucil, azathioprine, or P/NT. Cyclosporin was more likely to yield more TR outcomes than i.v. cyclophosphamide, oral cyclophosphamide,

![Flowchart of included studies](image-url)

**Figure 1: Flowchart of included studies.**
Figure 2: Distribution of histopathologic diagnoses in included RCTs.

Figure 3: Network of eligible efficacy and safety comparisons. (A–D) The thickness of the lines reflects the number of studies being compared, and node size reflects the number of individuals treated with each pharmacotherapy.
Figure 4: Comparison of efficacy across drugs. OR with 95% CI of network meta-analysis for CR (A), PR (B), TR (C) and ASE (D).

**A. OR with 95% CI of network meta-analysis for CR**

| Drug | OR (95% CI) |
|------|-------------|
| N.A. | 0.28 (0.01, 6.83) |
| CSA  | 0.15 (0.03, 0.91) |
| NA   | 0.89 (0.41, 1.93) |
| N.A. | 1.08 (0.04, 21.80) |
| N.A. | 2.77 (0.82, 9.40) |

**B. OR with 95% CI of network meta-analysis for PR**

| Drug | OR (95% CI) |
|------|-------------|
| N.A. | 0.17 (0.02, 1.48) |
| CSA  | 0.14 (0.03, 0.72) |
| N.A. | 0.59 (0.30, 1.18) |
| N.A. | 0.86 (0.35, 2.08) |
| N.A. | 1.14 (0.01, 1.68) |
| N.A. | 1.74 (0.40, 7.63) |

**C. OR with 95% CI of network meta-analysis for TR**

| Drug | OR (95% CI) |
|------|-------------|
| N.A. | 1.15 (0.28, 9.19) |
| N.A. | 0.89 (0.89, 1.33) |
| N.A. | 0.32 (0.08, 1.34) |
| N.A. | 0.15 (0.02, 1.30) |

**D. OR with 95% CI of network meta-analysis for ASE rate**

Note: The treatments are reported in alphabetical order. The results of direct comparisons and network-a-analysis are reported above and below the diagonal, respectively. For direct comparisons, ORs > 1 favor the column-defining treatment. For network meta-analyses, ORs > 1 favor the first drug in alphabetical order. Significant comparisons are underscored and bolded. CSA, cyclosporin; ICPA, intravenous cyclophosphamide; TAC, tacrolimus; MMF, mycophenolate mofetil; OCPA, oral cyclophosphamide; LEF, leflunomide; CHL, chlorambucil; AZA, azathioprine; RTCA, rituximab-cyclosporin dual therapy; and P/NT, placebo/nontreatment.

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or P/NT. Additionally, rituximab-cyclosporin dual therapy was more efficacious for obtaining CR than oral cyclophosphamide or P/NT, and MMF more efficacious in terms of TR than either i.v. cyclophosphamide or oral cyclophosphamide. However, in terms of safety, tacrolimus use was less likely to result in ASEs than i.v. cyclophosphamide or rituximab-cyclosporin dual therapy. Meanwhile, rituximab-cyclosporin dual therapy was associated with a greater likelihood of ASEs than oral cyclophosphamide, cyclosporin, or P/NT (95% CI for OR slightly more than 1).

**Ranking of medications**

The relative efficacy and safety rankings of the interventions are shown in Figure 5. Cyclosporin, tacrolimus, rituximab-cyclosporin dual therapy, and MMF were among the most efficacious treatments for achieving CR (Figure 5A). The cumulative probabilities of CR for the examined medications were: cyclosporin (88.7%), tacrolimus (86.4%), rituximab-cyclosporin (82.8%), MMF (59.8%), i.v. cyclophosphamide (44.8%), leflunomide (31.5%), chlorambucil (28.6%), azathioprine (28.6%), P/NT (24.5%), and oral cyclophosphamide (24.2%). Tacrolimus, cyclosporin, and MMF were the most efficacious treatments for achieving PR (Figure 5B), and the cumulative probabilities of the analyzed pharamcotherapies being the most efficacious medication were: tacrolimus (74.1%), cyclosporin (71.7%), MMF (65.9%), oral cyclophosphamide (41.1%), i.v. cyclophosphamide (37.6%), azathioprine (33.5%), and P/NT (26.1%). Finally, for TR, tacrolimus, cyclosporin, and MMF were the most efficacious treatments (Figure 5C), and the cumulative probabilities of each treatment being the most efficacious medication were: tacrolimus (91.5%), cyclosporin (87.8%), MMF (65.7%), P/NT (29.2%), i.v. cyclophosphamide (28.1%), azathioprine (28.1%) and oral cyclophosphamide (19.6%). In terms of safety, rituximab-cyclosporin dual therapy was the treatment that was most likely to produce ASEs (Figure 5D), and the cumulative probabilities of being the most adverse medication were: rituximab-cyclosporin (96.8%), MMF (62.8%), intravenous cyclophosphamide (58.3%), cyclosporin (52.4%), P/NT (44.8%), oral cyclophosphamide (27.8%), and tacrolimus (7.3%).

**Figure 5: Efficacy and safety outcome rankings.** CR (A), PR (B), TR (C) and ASE (D) rankings reflect the probability of being the best, second best, etc., treatment among the treatments compared.
Inconsistency and publication bias

Inconsistency between direct and indirect comparisons of recurrence rates was low (Figure 6). Most loops (networks of three or four comparisons that arise when collating studies involving different treatments) were consistent, with the 95% CIs for the inconsistency factor (including 0) indicating similar effect estimations for

**Figure 6:** Inconsistency in closed loops at CR (A) PR (B) and TR (C). Graph shows estimates of differences between direct and indirect estimates as represented by 95% CIs.
direct and indirect comparisons. Hence, the network meta-analysis results can be considered robust. Comparison-adjusted funnel plots for CR outcomes show no evidence of asymmetry (Figure 7).

DISCUSSION

In the present meta-analysis of 18 trials, with 790 individuals diagnosed with SRNS assigned randomly to one of nine immunosuppressive medication groups or a P/NT group, we found that tacrolimus was more efficacious for achieving CR or TR than i.v. cyclophosphamide, MMF, oral cyclophosphamide, leflunomide, chlorambucil, azathioprine, and P/NT, with a lower ASE risk than i.v. cyclophosphamide or rituximab-cyclosporin dual therapy. Cyclosporin also fared well, being associated with greater likelihood of CR or TR than intravenous cyclophosphamide, MMF, oral cyclophosphamide, chlorambucil, azathioprine, or P/NT. Hence, of the nine immunosuppressive pharmacotherapies analyzed, tacrolimus and cyclosporin emerged as the two most efficacious agents while maintaining relatively low ASE risk levels. A practical implication of our results is that tacrolimus and cyclosporin should be favored as first-line treatments for pediatric patients experiencing SRNS owing to their high efficacy and generally good, albeit not superior, safety. Given that tacrolimus had a similar efficacy but lower ASE likelihood than cyclosporin, further well designed RCTs are needed to evaluate the relative benefits and harms of tacrolimus versus cyclosporin for the treatment of SRNS in children.

Although MMF ranked favorably in efficacy and safety, the MMF data lacked power in the network meta-analysis indicating that there is a need for additional studies of the efficacy and safety of MMF in children with SRNS. The efficacy and safety outcomes for cyclophosphamide therapies were mediocre. Notwithstanding, it is worth noting that our analysis showed greater efficacy, but lesser safety, for i.v. cyclophosphamide relative to oral cyclophosphamide. Hence, the present results do not support the use of cyclophosphamide as a first-line treatment for SRNS. Finally, although rituximab-cyclosporin dual therapy was found to have a somewhat favorable CR outcome likelihood, especially compared
with oral cyclophosphamide, it had the poorest safety outcome of all of the regimens examined.

Our findings, which indicate clinically important differences in efficacy and safety among the examined drugs, provide reference information that can be used in immunosuppressive medication selection for treatment of SRNS in pediatric patients. Previous conventional pairwise meta-analyses of the efficacy of immunosuppressive medications for SRNS in children were inconclusive due to limitations in treatment effect information and failures to demonstrate clear relative efficacy benefits of particular drugs [15, 16, 30, 31]. Notwithstanding, a previous systematic review contributed by Hodson et al. indicated that calcineurin inhibitors yield better rates of CR or PR than P/NT or cyclophosphamide in children with SRNS [30]. The present study provides much needed direct comparisons between immunosuppressive agents in patients recovering from primary NS. The 2015 clinical guidelines for pediatric idiopathic NS recommended cyclosporine as a first-line treatment for SRNS (recommendation grade A). The guidelines suggested that tacrolimus be considered as a treatment option for patients with SRNS when cyclosporine is counter-indicated due to cosmetic side effects (recommendation grade C1), and that cyclophosphamide not be considered for induction therapy in children with SRNS (recommendation grade C2) [32]. The most problematic ASE of long-term cyclosporine use is chronic nephrotoxicity, an increased risk for which has been associated with cyclosporine treatment for ≥ 2 years [33–35]. The number of serious AEs of immunosuppressive agents reported here may be an underestimate because the analyzed studies were not designed primarily to evaluate harm. Additionally, because we did not exclude trials with combined corticosteroid regimens, our findings related to immunosuppressive agents cannot be considered independent of potential corticosteroid effects. Our results should not be generalized to patients who exhibit corticosteroid dependence because we did not include trials with that patient population.

The results of this analysis apply to treatment periods of 2 years or less. Longer term clinical efficacy and safety beyond 2 years may differ substantially from outcomes recorded within 2 years [35]. Additionally, the quality of our analysis may be limited by the quality of the original data. Many of the studies included in our review did not report adequate information on allocation concealment and randomization, which could influence the overall validity of the data [36]. Only 17% of the examined studies had low performance risk. We did not conduct publication bias or subgroup analyses due to the small numbers of studies examining each medication. The small number and small sample sizes of the included studies could also be of concern for the generalizability of our results. Finally, none of the included studies addressed fertility-related complications of alkylating agent therapy.

This study focused on examining RCTs of available immunosuppressive agents in pediatric SRNS patients. Recently, ongoing or completed small sample case series of new biologics—including anti-CD20 ofatumumab, abatacept, adalimumab, fresolimumab, and saquinavir which target immune cell subsets or activation pathways selectively—have spurred a new direction of hypothesis-driven therapies that may improve outcomes of children with kidney disease [37, 38]. Further research should be conducted to determine the benefits and risks of these therapies in children with SRNS.

In conclusion, on the basis of all available direct and indirect evidence, our results suggest that tacrolimus and cyclosporine are preferable first-line medications for initial SRNS in children. MMF may be an acceptable option for patients with SRNS. Further studies are needed to evaluate the relative benefits and harms of tacrolimus versus cyclosporin for pediatric SRNS treatment. Additional information about the safety and efficacy of MMF in children with SRNS is also needed.

MATERIALS AND METHODS

Identification of trials

In preparation for this network meta-analysis, we drafted a study protocol and published it on the PROSPERO website (CRD42017062564). Clinical trials comparing at least two different treatments were searched in MEDLINE (1950 to January 2017), the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 7, 2017), and EMBASE (1974 to January 2017) with the following search terms: “immunosuppressive agents” or “alkylating agents” or “azathioprine” or “cyclosporine” or “cyclophosphamide” or “mycophenolic acid” or “rituximab” or “chlorambucil” or “levamisole” or “tacrolimus”; and “nephrotic syndrome” or “minimal change nephrotic syndrome” or “glomerulonephritis membranoproliferative” or “focal segment glomerulosclerosis” or “membranoproliferative glomerulonephritis”. The search results were restricted to articles reporting studies involving children. Additionally, the reference lists of all included publications and relevant reviews were screened and ClinicalTrials.gov was searched for trials in progress.

Selection criteria

Parallel RCTs in which children with initial SRNS and children with delayed SRNS were the subjects and comprehensive comparisons of any of the following agents were included: cyclophosphamide, cyclosporine,
that heterogeneity variance was consistent across treatment contrasts. We used the netleague command to report relative treatment effects for all pairwise comparisons estimated by the network meta-analysis. $P < 0.05$ was considered significant. We looked at a plausible range for population difference magnitude. We used the network rank option to evaluate the probability that each drug could be the most (or second most, third most, etc.) efficacious treatment. The surface under the cumulative ranking curve (SUCRA) was determined as an estimation of the ranking probability for each medication, and the resultant SUCRA estimates were used to rank the treatments in a hierarchy [41]. We ranked the medications’ safety with the same method. Within the networks, we assessed consistency between direct and indirect evidence using the design-by-treatment interaction model [42]. A loop-specific approach was applied to detect local inconsistencies within network meta-analysis models if information was sufficiently similar across sources to be combined. Difference (inconsistency factor) between direct and indirect estimations for a specific comparison was calculated with 95% CIs as a measure of within-loop inconsistency [43]. Inconsistency was defined as disagreement between direct and indirect evidence with a 95% CI excluding 0. Publication bias was estimated by comparison-adjusted funnel plots.

Author contributions

All the authors have accepted responsibility for the full contents of this submitted manuscript and approved submission. SL and LT conceived and designed the study. SL and LT wrote the protocol. HY and QL designed and implemented the search strategies. SL and XA selected studies, assessed validity, and extracted data. JW and PG entered and analyzed the data. All authors were involved in interpreting the results, contributed to the preparation of the full review and its revision, and approved the submission of this manuscript.

Abbreviations

SRNS: steroid-resistant nephrotic syndrome; RCT: randomized controlled trial; i.v.: intravenous; MCD: minimal-change disease; MesPGN: mesangial proliferative glomerulonephritis; FSGS: focal segmental glomerulosclerosis; P/NT: placebo/nontreatment; MMF: mycophenolate mofetil; CR: complete remission; PR: partial remission; TR: total number in remission; OR: odds ratio; NS: nephrotic syndrome; CI: confidence interval; UP/C: protein-creatinine ratio; ASE: adverse secondary effect; CR: complete remission; PR: partial remission; SUCRA: surface under the cumulative ranking curve.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest concerning this article.
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