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ORIGINAL ARTICLE

Corticosteroids combined with doublet or single-agent immunosuppressive therapy for active proliferative lupus nephritis

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Abstract

Objectives We performed a meta-analysis to assess whether corticosteroids (C) plus (+) doublet immunosuppressive therapy (IT) is superior to the classical combination of C with single-agent IT in active proliferative lupus nephritis (LN).

Method Randomized trials evaluating the benefits and risks of C+doublet versus single-agent IT in active proliferative LN were obtained by searching PubMed, EMBASE, and Cochrane Central Register. The primary outcome was overall response rate (ORR). The secondary outcomes were the change from baseline in Systemic Lupus Erythematosus Disease Activity Index (SLE-DAI) score, negative conversion ratio of anti-double-stranded DNA (anti-dsDNA), and adverse events. The PROSPERO registry number is CRD42017068491.

Results Eleven trials with 1855 patients were included. Compared with C+single-agent IT, C+doublet IT had a significantly higher ORR (relative risk [RR], 1.22; 95% confidence interval [CI], 1.09 to 1.35; $P < 0.01$). In a subgroup analysis, C+doublet IT without biologics had a significantly higher ORR than C+single-agent IT (RR, 1.30; 95% CI, 1.13 to 1.50; $P < 0.01$), while C+doublet IT including biologics improved ORR only for refractory severe LN (RR, 1.46; 95% CI, 1.09 to 1.96; $P = 0.012$). A larger change from baseline in SLE-DAI scores (standardized mean difference, − 0.49; 95% CI, − 0.68 to − 0.30; $P < 0.01$) and a higher negative conversion ratio of anti-dsDNA (RR, 1.34; 95% CI, 1.06 to 1.69; $P = 0.014$) were observed with C+doublet IT than with C+single-agent IT. The rates of adverse events were similar between the two regimens.

Conclusions Compared with single-agent IT, the combination of C and doublet IT without biologics improved clinical outcomes in active proliferative LN.

Key Points

- *Compared with corticosteroids + single-agent immunosuppressive therapy, corticosteroids + doublet immunosuppressive therapy without biologics had a significantly higher overall response rate in active proliferative lupus nephritis.*
- *Compared with corticosteroids + single-agent immunosuppressive therapy, corticosteroids + doublet immunosuppressive therapy including biologics improved overall response rate only for refractory severe lupus nephritis.*
- *A larger change from baseline in SLE-DAI scores and a higher negative conversion ratio of anti-dsDNA were observed with corticosteroids + doublet immunosuppressive therapy than with corticosteroids + single-agent immunosuppressive therapy.*

Keywords Active proliferative lupus nephritis · Biologics · Corticosteroids · Doublet immunosuppressive therapy · Meta-analysis · Single-agent immunosuppressive therapy

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that involves multiple organs. Lupus nephritis (LN) is one of its most common and severe manifestations and usually has greater mortality. The prevalence of chronic kidney disease in patients with LN is high, with approximately 20% of biopsy-proven LN patients reaching end-stage renal disease (ESRD) by 8.5 years [1]. During a median follow-up of 4.4 years, 42.6% of patients with ESRD from lupus

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nephritis (ESLN) died and the mortality for ESLN was 7.9 (95% CI, 7.8 to 8.1) per 100 person-years in the USA [2].

In LN, survival is significantly better in patients who achieve complete or partial remission during initial therapy than in those with no remission [3]. With the increasing use of immunosuppressive agents, including cyclophosphamide, mycophenolate mofetil (MMF), and calcineurin inhibitors (CNIs), the risk of ESRD in LN patients has steeply declined; however, the probability of renal remission is only 50% or lower at 6 months in patients who receive a combined treatment regimen involving corticosteroids and one immunosuppressive drug to treat active proliferative LN, and this rate remains unsatisfactory [4, 5]. Therefore, deeper investigations into more effective methods to treat active proliferative LN are a key task for nephrologists and rheumatologists around the world.

In recent years, a novel multitarget therapy involving corticosteroids and two immunosuppressive drugs (i.e., tacrolimus and MMF) was proposed by the Chinese nephrologist Leishi Li and has been demonstrated to be well tolerated and superior to pulse monthly intravenous cyclophosphamide plus oral corticosteroids in inducing complete remission of class V+IV LN [6]. Conversely, the LUNAR study [7] published in 2012 failed to show that adding rituximab to glucocorticoids plus MMF was superior over glucocorticoids plus MMF alone in achieving a renal response. Moreover, guidelines regarding corticosteroids plus doublet immunosuppressive therapy for active proliferative LN are lacking [8–10]. As was previously noted, whether corticosteroids (C) plus (+) doublet immunosuppressive therapy (IT) outperform the classical combination of C with single-agent IT for active proliferative LN remains controversial. Here, we designed a meta-analysis of randomized clinical trials (RCTs) to assess whether the efficacy and safety of C + doublet IT is superior to that of C + single-agent IT in active proliferative LN.

Materials and methods

Search strategy

Our study was registered with PROSPERO under the registration number CRD42017068491. This study was conducted and reported according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines [11]. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology was used to estimate the overall quality of the evidence [12]. RCTs comparing the benefits and risks of C + doublet versus single-agent IT in active proliferative LN were searched for electronically. The PubMed, EMBASE, and Cochrane Central Register of Controlled Trials databases were searched to identify relevant RCTs published prior to March 2019, using a highly sensitive search strategy. Randomized trials were limited to human studies published in English. The following main keywords or corresponding terms were used to search the databases: "immunosuppressive drugs", which includes all types of conventional and novel immunosuppressive drugs, "lupus nephritis", and "randomized trials." The search strategy is shown in the supplement.

Inclusion criteria

Trials meeting the following criteria were included in this study: (1) randomized trials that compared the efficacy of C + doublet and single-agent IT in active proliferative LN and reported endpoints for a renal response to the treatment; (2) LN patients in whom there was a histologically (renal biopsy) confirmed diagnosis according to the World Health Organization (WHO) 1982 classification [13] or the International Society of Nephrology/Renal Pathology Society 2003 classification [14] regardless of whether they were adults or children; and (3) the number of patients in each group was at least 5.

Selection of trials and data extraction

We screened the titles and abstracts of the retrieved search records to determine potential eligibility. For all potential articles, the full text was retrieved when possible. The data were independently abstracted by three investigators (Bo Liu, Qiyun Ou, and Ying Tang), cross-checked, and discussed to identify any discrepancies and to reach a consensus between the authors. Data retrieved from trial publications included publication details, sample size, interventions, histological and clinical characteristics, duration of follow-up, criteria for complete and partial renal responses, and outcomes. The primary outcome of interest was the overall response rate (ORR, including the complete response rate (CRR) and the partial response rate (PRR)). The second outcomes were the change from baseline in SLE Disease Activity Index (SLE-DAI) scores, the negative conversion ratio of anti-double-stranded DNA (anti-dsDNA), all-cause mortality, total adverse events (AEs), serious AEs, infections, urinary tract infection, varicella zoster virus infection, upper respiratory tract infection, leukopenia, menstrual disorder, and infusion-related AEs. Efficacy was evaluated in a subgroup analysis in which patients were classified by the type of immunosuppressive agent used and the duration of IT.

Trial sequential analysis

A trial sequential analysis (TSA) was used to calculate the required information size for our meta-analysis. This analysis provided trial sequential monitoring boundaries that could be used to decide whether a trial could be terminated at an early

date. The TSA can reduce the repetitive testing of accumulated data and control the risks of type I and type II errors due to sparse data. The TSA was conducted using TSA version 0.9 beta [15–20].

Statistical analysis

The meta-analysis was performed using a random effects model to estimate the treatment effects according to relative risks with 95% confidence intervals (95% CIs), and pooled standardized mean differences (SMDs) with 95% CIs were estimated for continuous outcomes. Heterogeneity was evaluated using the I^2 statistic [21]. $P < 0.05$ was considered statistically significant, and all P values were two-sided. Potential publication bias was visually evaluated using funnel plots and quantified using funnel plots and the Copas selection model [22] to visually evaluate the extent of symmetry of the plots (Egger et al.'s test [23] and Begg's test [24]). $P < 0.05$ indicated publication bias. Two authors (Zhenjian Xu and Yongjian Chen) independently uploaded the data to ensure the reliability and accuracy of the results. The statistical analyses were conducted in R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics

Eleven randomized trials were eligible (Fig. 1). These trials involved 1855 participants. Ten RCTs were evaluated as full-text articles. Two trials (402 participants) evaluated C combined with tacrolimus (4 mg daily) and MMF (1000 mg daily) [6, 25]. One trial (265 participants) evaluated C combined with voclosporin (23.7 mg or 39.5 mg twice a day) and MMF (2000 mg daily for some participants) [26]. One trial (82 participants) evaluated C combined with cyclophosphamide (0.4 g/m^2 monthly) and MMF (1000 mg daily) [27]. One trial (46 participants) evaluated C combined with laquinimod and MMF [28]. Six trials evaluated C combined with biologics and MMF or cyclophosphamide, including 3 trials (247 participants) for rituximab (RTX) [7, 29, 30], 2 trials (432 participants) for abatacept [31, 32], and 1 trial (381 participants) for ocrelizumab [33]. The details related to these 11 RCTs are shown in Table 1. The other disease-modifying antirheumatic drugs (DMARDs) administered concomitantly in the trials are shown in Table S1. Most of the participants had active proliferative LN except for patients in one trial that enrolled refractory LN patients. Four trials [6, 7, 25, 33] in

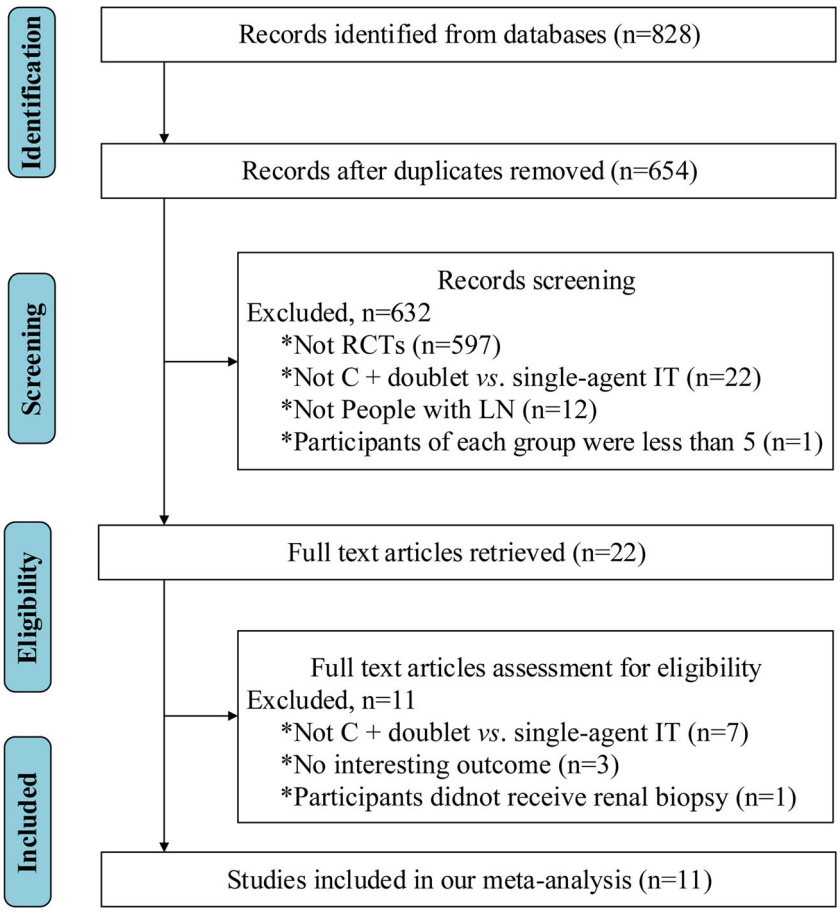

Fig. 1 PRISMA flow diagram. LN, lupus nephritis; C, corticosteroids; IT, immunosuppressive therapy; RCTs, randomized clinical trials

Table 1 Basic characteristics of the included randomized clinical trials

Study	Follow up (mo)	The type of LN	Regimen (drug dose)	No. of Pts	Age (yr)	F (*n*)	Duration of LN	SCr (μmol/L)	Urinary protein (g/day)/UPCR (g/g)	SLE-DAI score	Anti-dsDNA positive (%)
AURA-LV Study [26]	6	Class III, IV, V, V+III/IV	C + VCS (39.5 mg bid) + MMF	88	30.6[a]	81	3.2[a] yr	–	4.48[a,d]	–	–
			C + VCS (23.7 mg bid) + MMF	89	31.4 [a]	76	4.2 [a] yr	–	5.16[a,d]	–	–
			C + placebo + MMF	88	33.1[a]	73	3.5[a] yr	–	4.43[a,d]	–	–
Sun et al. [27]	6	Class IV	C + IVCY + MMF	42	31.9[a]	38	0.5–24 mo	128.0 [a]	2.04[a,c]	14.1[a]	–
			C + IVCY	40	33.3[a]	37	0.5–24 mo	118.0[a]	2.45[a,c]	13.8[a]	–
Liu et al. [25]	6	Class III, IV, V, V+III/IV	C + MMF + tacrolimus	181	30.3[b]	168	2[b] mo	69.0[b]	3.44[b,c]	16.0[b]	59.2
			C + IVCY	181	33.6[b]	161	3[b] mo	72.5[b]	3.68[b,c]	15.0[b]	63.1
Zhang et al. [30]	12	Refractory Class V+III/IV	C + RTX + IVCY	42	38.7[a]	31	–	115.08[a]	4.82[a,c]	14.90[a]	–
			C + IVCY	42	39.1[a]	29	–	116.39[a]	4.91[a,c]	14.48[a]	–
The ACCESS Trial Group [32]	6	Class III, IV, V+III/IV	C + abatacept + (IVCY-AZA)	66	32.0[a]	58	Time from onset of LN <1 yr (*n*) 47	106.1[a]	3.8[a,c]	–	75
			C + placebo + (IVCY-AZA)	68	32.7[a]	64	Time from onset of LN <1 yr (*n*) 48	114.9[a]	4.5[a,c]	–	75
Furie et al. [31]	12	Class III, IV, V+III/IV	C + abatacept (30/10)[e] + MMF	99	31.0[a]	84	–	79.6[b]	3.9[a,d]	–	–
			C + abatacept (10/10)[f] + MMF	99	30.5[a]	86	–	70.7[b]	4.3[a,d]	–	–
			C + placebo + MMF	100	31.8[a]	81	–	70.7[b]	3.6[a,d]	–	–
Mysler et al. [33]	12	Class III, IV, V+III/IV	C + ocrelizumab (1000 mg) + (IVCY-AZA)/MMF	128	30.6[a]	110	0.7[b] yr	88.4[a]	2.9[b,d]	–	–
			C + ocrelizumab (400 mg) + (IVCY-AZA)/MMF	127	31.9[a]	115	0.8[b] yr	88.4[a]	3.0[b,d]	–	–
			C + placebo + (IVCY-AZA)/MMF	126	31.3[a]	107	0.6[b] yr	79.6[a]	2.7[b,d]	–	–
Jayne et al. [28]	6	Active	C + laquinimod + MMF	31	–	–	–	–	–	–	–
			C + placebo + MMF	15	–	–	–	–	–	–	–
Rovin et al. [7]	12	Class III, IV, V+III/IV	C + RTX + MMF	72	31.8[a]	63	11.1[b] mo	88.4[a]	3.8[a,d]	–	–
			C + placebo + MMF	72	29.4[a]	67	5.4[b] mo	88.4[a]	4.2[a,d]	–	–
Li et al. [29]	12	Class III, IV, V+III/IV	C + RTX + IVCY	10	39.6[a]	9	9.9[a] yr	134.8[a]	3.8[a,c]	10.3[a]	–
			C + RTX	9	40.3[a]	9	6.9[a] yr	99.8[a]	4.1[a,c]	8.5[a]	–
Bao et al. [6]	9	Class IV+V	C + MMF + tacrolimus	20	27.2[a]	16	30.0[b] mo	76.9[a]	4.41[a,c]	14.9[a]	60
			C + IVCY	20	30.6[a]	18	26.0[b] mo	78.7[a]	4.10[a,c]	14.0[a]	60

mo, months; *LN*, lupus nephritis; *Pts*, patients; *yr*, years; *F*, female; *SCr*, serum creatinine; *UPCR*, urine protein-to-creatinine ratio; *SLE-DAI*, Systemic Lupus Erythematosus Disease Activity Index; *Anti-dsDNA*, anti-double-stranded DNA; *C*, corticosteroids; *VCS*, voclosporin; *bid*, twice a day; *MMF*, mycophenolate mofetil; *IVCY*, intravenous cyclophosphamide; *RTX*, rituximab; *AZA*, azathioprine

[a] Expressed as mean values

[b] Expressed as median values

[c] The values of urinary protein (g/day)

[d] The values of UPCR (g/g)

[e] Abatacept administered at 30 mg/kg on days 1, 15, 29, and 57 followed by abatacept administered at approximately 10 mg/kg on days 85, 113, 141, 169, 197, 225, 253, 281, 309, and 337

[f] Abatacept administered at approximately 10 mg/kg on all infusion days

which the dosage of the administered corticosteroids was compared between doublet and single-agent immunosuppressive therapy showed that was similar. The patients were followed up for half a year in 5 trials, 9 months in 1 trial, and 1 year in 5 trials. The abstract for this study was published in the EULAR 2018 Annual European Congress of Rheumatology [34].

Renal response

Ten trials [6, 7, 25–27, 29–33] comprising 1651 participants and 10 trials [6, 7, 25, 27–33] involving 1432 participants were included in the current meta-analysis performed to estimate the CRR and ORR, respectively. Compared with C + single-agent IT, C + doublet IT had a significantly higher CRR and ORR (RRs of 1.40 [95% CI, 1.09 to 1.79], $P < 0.01$, and 1.22 [95% CI, 1.09 to 1.35], $P < 0.01$, respectively; Table 2 and Fig. 2). Moreover, we performed TSA on ORR with the settings and data and calculated that the information size was 1160. The cumulative *Z*-curve of ORR crossed above the TSA monitoring boundaries, demonstrating an a priori anticipated intervention effect indicating a 20% relative risk increment on the basis of a comparator event proportion of 54.8%. Further trials are unnecessary and are unlikely to change the outcomes (Fig. S1). No evidence of publication bias related to ORR was observed according to the results of Egger's test ($P = 0.427$), Begg's test ($P = 0.721$), and the Copas selection model (Fig. S2).

In a subgroup analysis, C + doublet IT without biologics resulted in significantly higher CRR and ORR than were found for C + single-agent IT (RRs of 1.66 [95% CI, 1.21 to 2.29], $P < 0.01$, and 1.30 [95% CI, 1.13 to 1.50], $P < 0.01$, respectively; Table 3), while C + doublet IT including biologics improved CRR and ORR only in refractory severe LN (RRs of 3.00 [95% CI, 1.61 to 5.58], $P < 0.01$, and 1.46 [95% CI, 1.09 to 1.96], $P = 0.012$, respectively; Table 3). Among patients who received biologics in six trials [7, 29–33] (902 participants), the type of accompanying immunosuppressive agent (i.e., cyclophosphamide or MMF) and the treatment duration did not influence the renal response (all $P > 0.05$; Table 3).

The activity of SLE

The change from baseline in SLE-DAI scores and the negative conversion ratio of anti-dsDNA were reported in 2 trials [25, 30] (446 participants) and 4 trials [6, 25, 32, 33] (437 participants), respectively. The change from baseline in SLE-DAI scores was larger (standardized mean difference, −0.49; 95% CI, −0.68 to −0.30; $P < 0.01$; Table 2), and the negative conversion ratio of anti-dsDNA was higher (RR, 1.34; 95% CI, 1.06 to 1.69; $P = 0.014$; Table 2) for C + doublet IT than for C + single-agent IT.

Table 2 Efficacies of the two treatments

Outcomes	No. of trials	No. of participants	Relative effect			GRADE
			Ratio (95% CI)	*P* value	I^2, %	
Complete response rate	10	1651	RR 1.40 (1.09 to 1.79)	< 0.01**	57	⊕⊕⊕O Moderate[a]
Partial response rate	9	1386	RR 1.03 (0.87 to 1.23)	0.716	26.3	⊕⊕⊕O Moderate[b]
Overall response rate	10	1432	RR 1.22 (1.09 to 1.35)	< 0.01**	30.5	⊕⊕⊕⊕ High
Change from baseline in SLE-DAI scores	2	446	SMD −0.49 (−0.68 to −0.30)	< 0.01**	19.9	⊕⊕⊕O Moderate[c]
Negative conversion ratio of anti-dsDNA	4	437	RR 1.34 (1.06 to 1.69)	0.014*	0	⊕⊕⊕O Moderate[c]

C, corticosteroids; *IT*, immunosuppressive therapy; *CI*, confidence interval; *RR*, risk ratio; *SLE-DAI*, Systemic Lupus Erythematosus Disease Activity Index; *SMD*, standardized mean difference; *anti-dsDNA*, anti-double-stranded DNA

*Significant *P* value < 0.05

**Significant *P* value < 0.01

GRADE Working Group grades for evidence quality:

⊕⊕⊕⊕ High quality: further research is very unlikely to change our confidence in the estimated effect

⊕⊕⊕O Moderate quality: further research is likely to have an important impact on our confidence in the estimated effect and might change the estimate

⊕⊕OO Low quality: further research is very likely to have an important impact on our confidence in the estimated effect and might change the estimate

⊕OOO Very low quality: We are very uncertain about the estimate

[a] Downgraded (− 1) for inconsistency: substantial heterogeneity ($I^2 > 50\%$) was found among the trials

[b] Downgraded (− 1) for inconsistency: the 95% confidence intervals were wide; the study included no effect and failed to exclude important benefits or serious harmful effects

[c] Downgraded (− 1) for imprecision: potential for small sample bias

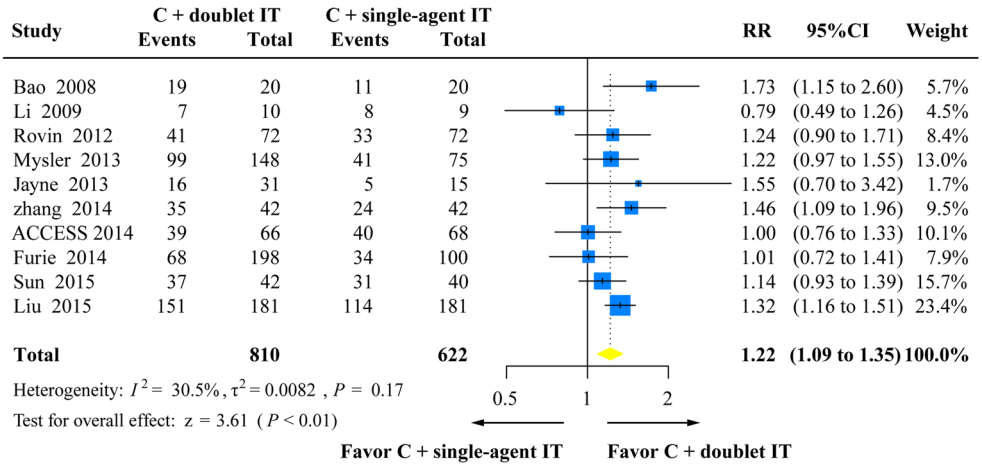

Fig. 2 Overall response rate of the two treatments. C, corticosteroids; IT, immunosuppressive therapy; RR, risk ratio; CI, confidence interval

Safety

We performed a pooled analysis of the 10 trials [6, 7, 25–29, 31–33] (1768 participants) that evaluated the safety of the treatment regimens. There was no significant difference in all-cause mortality between C + doublet and single-agent IT (RR, 0.89; 95% CI, 0.43 to 1.85; $P = 0.76$; Table S2). The risks for total AEs (RR, 1.01), serious AEs (RR, 1.08), infections (RR, 0.98), urinary tract infection (RR, 0.80), varicella zoster virus infection (RR, 1.37), upper respiratory tract infection (RR, 0.92), leucopenia (RR, 0.33), and infusion-related AEs (RR, 1.08) were similar between the two regimens (all $P > 0.05$; Table S2). Compared with C + single-agent IT, C + doublet IT had a lower risk of menstrual disorder (RR, 0.38; 95% CI, 0.17 to 0.87; $P = 0.022$; Table S2).

Study withdrawals

Nine trials [6, 7, 25–27, 29, 31–33] (1722participants) reported that 467 patients discontinued therapy. The reasons for withdrawal from treatment in the included RCTs are shown in Table S3. The pooled RR provided low-quality evidence indicating that there was no significant difference in the number of patients who discontinued therapy between the C + doublet and single-agent IT groups (RR, 0.91; 95% CI, 0.77 to 1.08; $P = 0.28$; $I^2 = 9\%$).

Discussion

To the best of our knowledge, this study constitutes the first meta-analysis to comprehensively and systematically evaluate the efficacy and safety of C + doublet versus single-agent IT in active proliferative LN. We found that there were significantly higher CRR and ORR in the group of C + doublet IT without biologics than in that of C + single-agent IT. C + doublet IT including biologics improved CRR and ORR only in refractory severe LN. The change from baseline in SLE-DAI scores was larger and the negative conversion ratio of anti-dsDNA was higher in the C + doublet IT group than in the C + single-agent IT group. The results of safety analyses showed that both groups tolerated the drug regimens well.

Our results indicate that C + doublet IT without biologics provided efficacy superior to that of C + single-agent IT (i.e., cyclophosphamide or MMF) when used to treat LN. Similarly, a 2017 network meta-analysis showed that MMF plus tacrolimus was more likely than MMF or cyclophosphamide alone (ORs of 1.87 [95% CI, 1.06–3.29], and 2.69 [95% CI, 1.74–4.16], respectively) to achieve complete renal remission during initial therapy for LN [35]. A multicenter study performed in China found that a multitarget therapy consisting of corticosteroids, MMF, and tacrolimus was also effective and safe as a maintenance treatment for LN [36]. Because most of these studies were conducted in Chinese patients, further studies are required to evaluate the effect and safety of this regimen in LN patients in other ethnic groups.

Our findings suggest that the risk of adverse events is not clearly higher for C + doublet IT. In the patients treated with C + double conventional immunosuppressors in most of the included trials, the dosages of MMF (1.0 g/day) and cyclophosphamide (monthly dose of 0.4 g/m^2) were lower than the doses recommended in the KDIGO guideline [10] (monthly dose of 0.5–1 g/m^2 for cyclophosphamide used alone and maximum 3 g/day for MMF used alone). This indicates that, while these conventional immunosuppressive drugs were applied together at a lower than routine dose, there was no significant increase in the occurrence of AEs.

Six trials in this meta-analysis assessed the efficacy and safety of C + doublet IT including biologics such as RTX, abatacept, and ocrelizumab for LN. RTX and ocrelizumab are monoclonal antibodies that selectively target and deplete CD20+ B cells in the peripheral circulation [37]. Abatacept, a fusion protein containing CTLA-4 linked to the Fc portion of IgG1 [38], prevents antigen-presenting cells from binding to CD28 on T cells and then inhibits the activation of primary T cell–dependent immune responses [39]. RTX is recommended

Table 3 Subgroup analyses of renal responses between the two treatments

	No. of trials	No. of Pts	Complete response rate			Partial response rate			Overall response rate					
			RR (95% CI)	*P* value	I^2, %	RR (95% CI)	*P* value	I^2, %	No. of trials	No. of Pts	RR (95% CI)	*P* value	I^2, %	GRADE
Groups by whether the C + doublet IT regimen contained biologics														
No	4	749	1.66 (1.21 to 2.29)	< 0.01**	44	0.98 (0.78 to 1.24)	0.881	0	4	530	1.30 (1.13 to 1.50)	< 0.01**	25.0	⊕⊕⊕O Moderate[c]
Yes	6	902	1.22 (0.88 to 1.69)	0.244	52.7	1.02 (0.70 to 1.48)	0.922	51.4	6	902	1.14 (0.98 to 1.32)	0.084	28.3	⊕⊕⊕⊕ High
Groups by the type of immunosuppressive drug in C + doublet IT including biologics														
IVCY	4	329	1.54 (0.88 to 2.70)	0.131	56.5	0.87 (0.56 to 1.34)	0.533	30.9	4	329	1.16 (0.87 to 1.55)	0.301	59.6	⊕OOO Very low[a,b,c]
MMF	3	573	0.99 (0.76 to 1.30)	0.953	0	1.30 (0.78 to 2.14)	0.310	46.5	3	573	1.11 (0.93 to 1.33)	0.228	0	⊕⊕OO Low[b,c]
Groups by the treatment duration in C + doublet IT including biologics														
12 mo	5	768	1.26 (0.83 to 1.91)	0.278	61.6	1.03 (0.65 to 1.64)	0.889	60.1	5	768	1.17 (0.99 to 1.39)	0.069	32.0	⊕⊕⊕O Moderate[b]
6 mo	1	134	1.08 (0.66 to 1.77)	0.761	/	0.92 (0.53 to 1.61)	0.776	/	1	134	1.00 (0.76 to 1.33)	0.975	/	⊕OOO Very low[b,d]
Groups by the type of LN in C + doublet IT including biologics														
Refractory	1	84	3.00 (1.61 to 5.58)	< 0.01**	/	0.53 (0.25 to 1.12)	0.098	/	1	84	1.46 (1.09 to 1.96)	0.012*	/	⊕⊕OO Low[d]
Non-refractory	5	818	1.04 (0.83 to 1.30)	0.720	0	1.14 (0.80 to 1.62)	0.475	40.1	5	818	1.09 (0.95 to 1.25)	0.200	0	⊕⊕⊕O Moderate[b]

C, corticosteroids; *IT*, immunosuppressive therapy; *Pts*, patients; *RR*, risk ratio; *CI*, confidence interval; *IVCY*, intravenous cyclophosphamide; *MMF*, mycophenolate mofetil; *mo*, months

*Significant *P* value < 0.05

**Significant *P* value < 0.01

[a] Downgraded (− 1) for inconsistency: substantial heterogeneity ($I^2 > 50\%$) was found among the trials

[b] Downgraded (− 1) for inconsistency: the 95% confidence intervals were wide; the study included no effect and failed to exclude important benefits or serious harmful effects

[c] Downgraded (− 1) for imprecision: potential for small sample bias

[d] Downgraded (− 2) for imprecision: only one study

for use in patients with LN refractory to conventional immunosuppressive drugs by the Guidelines of EULAR/ERA-EDTA [8], ACR [9], and KDIGO [10] published in 2012. Similarly, a meta-analysis published in 2013 also concluded that RTX effectively induced the remission of LN in patients who had failed to achieve remission with standard therapies [40].

Unexpectedly, our study demonstrated that adding biologics to C plus cyclophosphamide or MMF did not provide additional efficacy for active proliferative LN even though the treatment duration was prolonged to 1 year. This may be because of the following major factors. First, among the patients who received biologics (six trials with 902 participants), only 84 refractory LN patients were enrolled in the only trial [30] that showed that, compared with C plus cyclophosphamide, adding RTX to C plus cyclophosphamide produced better therapeutic efficacy and significantly improved the prognosis of refractory and severe LN. In the other trials, the renal response of LN patients to previous immunosuppressive treatment was unclear. Second, all of the patients enrolled in the trials were diagnosed with active proliferative LN according to the World Health Organization (WHO) 1982 classification [13] or the International Society of Nephrology/Renal Pathology Society 2003 classification [14], which were not based on the underlying disease pathophysiology. Some observations reminded us that different LN-associated histological lesions might involve different immune pathogeneses, including aberrant apoptosis, autoantibody production, immune complex deposition, and complement activation [41, 42], and these differences could influence patient sensitivity to different therapeutic strategies. Moreover, some types of lesions, including glomerular crescents, podocyte injury, tubulointerstitial lesions, and vascular injury, did not receive sufficient consideration in these classification systems [42]. Therefore, prospective trials are needed to identify the patients for whom C + doublet IT including biologics is efficacious.

As expected, SLE-DAI scores were significantly lower and the negative conversion ratio of anti-dsDNA was higher in the C + doublet IT group than in the C + single-agent IT group. Doublet immunosuppressive therapy was therefore effective in lessening SLE activity. Unfortunately, the trials included failed to show a lower requirement for corticosteroids in doublet immunosuppressive therapy.

This meta-analysis has several limitations that should be considered. First, the criteria for complete and partial renal responses used in the included trials were heterogeneous (Table S4). Wofsy et al. [43] compared several previously proposed criteria using the same data set as that used in a large trial of abatacept in LN. They found that the choice of definition for complete response affected whether an LN trial was interpreted as a success or a failure. Therefore, it is necessary to unify the definition of renal response to immunosuppressive treatments for LN in the future. Second, some trials in which children were enrolled did not perform a sub-analysis of the efficacy and safety in which patients were stratified according to age. Other limitations include heterogeneity in patient demographics, clinical manifestations and renal pathological lesions, and a lack of uniformity in the dose and type of immunosuppressors used among the included trials. Moreover, missing data related to adverse events may have caused us to underestimate or overestimate the RR for adverse effects.

Conclusion

The results of this meta-analysis provide further support for the notion that, compared with single-agent IT, a combination consisting of corticosteroids and doublet IT without biologics improved clinical outcomes in active proliferative LN. However, further studies are needed to identify the patients in whom C + doublet IT including biologics is most efficacious and to unify the definition of renal response to immunosuppressive treatments for LN.

Authors' contributions BL, YT, and APX designed the study. SF and PFL performed the literature searching and screening. BL, QYO, and YT extracted the data. YFY, ZJX, and YJC performed the statistical analysis. BL, QYO, and YT wrote the manuscript. All authors approved the final version of the manuscript.

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Compliance with ethical standards

Disclosures None.

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