Efficacy and safety of rituximab for systemic lupus erythematosus treatment: a meta-analysis

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Abstract:

Background: Given the inconsistency of previous studies and the newly emerging evidence, we decided to conduct a meta-analysis.

Methods: The meta-analysis included 2 randomized controlled trials and 13 observational studies 742 patients in total. Qualified studies were properly searched from databases . Data were analyzed by the RevMan 5.3 software. Results were demonstrated as WMD , SMD and RR with 95% CIs, I^2 and P value.

Results: we observed that a remarkable increase of complement C3 in the rituximab group than placebo group (WMDfixed=7.67mg/dL, 95%CIs=-0.16~15.50, I2=0%, P=0.05). A significant increase of complement C4 was observed in the rituximab group than placebo group (WMDfixed=3.14mg/dL, 95%CIs=1.06~5.22, I^2=0%, P=0.003). Notably decreased peripheral CD19+B cells in rituximab group than placebo group (WMDfixed=-117.93n/μl, 95%CIs=-172.94~-62.91, I^2=0%, P<0.0001) in RCTs. Patients with severe or refractory SLE got more satisfactory efficacy results after receiving rituximab in observational studies, such as British Isles Lupus Assessment Group index score, SLE Disease Activity Index score, complement C3/C4, anti-dsDNA antibodies, peripheral $CD19^+$B cells and so on. Safety profiles were no difference between rituximab and placebo groups.

Conclusion: although the efficacy of rituximab is highly controversial for SLE, our study shows that rituximab presents a satisfying efficacy and safety for SLE.

Keywords: Efficacy; safety; rituximab; systemic lupus erythematosus; meta-analysis.

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Introduction

Systemic lupus erythematosus (SLE) is an auto-immune disease that involves widely differing tissues and organs with diverse clinical symptoms. The incidence of SLE in women is estimated to be approximately 10 times higher than that in men[1]. However, the pathogenesis of SLE is still unclear; the production of autoantibodies and deposition of immune complexes in multiple organs leads to various abnormalities, including rash, arthritis, serositis, cytopenia, nephritis, and psychosis[2,3]. Conventional therapies for SLE include nonsteroidal anti-inflammatory drugs, corticosteroids, hydroxychloroquine (HCQ) and immunosuppressive agents. Among these therapies, corticosteroids and immuno-

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suppressive agents are primarily associatedwith mortality and morbidity[4]. More effective treatments should be developed for SLE. B cells are widely thought to play a crucial role in the pathogenesis of SLE. B cells act as antigen-presenting cells and present autoantigens to T cells; subsequently, T cells activate and produce cytokines. T cell cytokines stimulate and induce B cells to secrete autoantibodies. Autoantigen-specific B cells interact with T cells and produce autoantibodies that are present only in non-healthy individuals. The evidence suggests that depletion of B cells has a favorable effect on SLE[3]. Rituximab is a chimeric monoclonal antibody that targets the CD20 marker[5]. Findings of previous studies have suggested that rituximab has a beneficial effect and satisfactory tolerance profile for serious refractory SLE[6-8]. However, two randomized placebo-controlled double-blinded trials showed no clinically significant differences between rituximab and a placebo[9,10]. These previous studies are controversial. Borba found unsatisfactory variations between rituximab and a placebo in the efficacy results of a systematic review and meta-analysis, which included results for clinical reactions, British Isles Lupus Assessment Group (BILAG) C scores, time-adjusted area under the curve minus baseline(AUCMB) for the BILAG index, and modification of the SF-36 physical component summary(PCS)[11]. Given the inconsistency of previous studies and newly emerging evidence, we decided to conduct a meta-analysis. The purpose of our study is to determine other parameters to investigate the efficacy and safety of rituximab for SLE patients that may be used for reference by clinicians.

Methods

We conducted a meta-analysis to estimate the efficacy and safety of rituximab treatment for SLE and followed the Cochrane Handbook[12].

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) The SLE diagnosis satisfied the standards specified by the American College of Rheumatology13. (2) The trials included rituximab as an intervention treatment for SLE. (3) Placebo group as control group in RCTs. Baseline group when patients did not receive rituximab as control group in observational studies. (4) The study included efficacy and safety results, and the parameters of effi- cacy were the BILAG score, SLEDAI score, comple-ment C3/C4 levels, anti-dsDNA antibodies, peripheral $CD19^{+}$B cells, serum creatinine, 24-h urinary protein and Up/Ucr. The safety results included the incidence of SAEs, deaths, infections, gastrointestinal disorders, infusion-related SAEs and infusion-related AEs. (5) Both RCT and observational studies that met the above conditions can be included in this study. Trials without clinical outcomes and articles that were merely obtaina- ble as abstracts were excluded from the meta-analysis11. No language restrictions were implemented.

Search strategy and data extraction

The PubMed, Cochrane Library, EMBASE, Clinicaltrials and CNKI and Chinese database of WanFang databases were searched for relevant articles, most of which were published in English. The search was conducted using the following strategy, according to recognized methodologies[45]. Descriptors in the PubMed database included the Medical Subject Headings terms "Lupus Erythematosus, Systemic"and "Rituximab" combined with free terms. The process showed the results of electronic searches with Boolean operators such as "AND" and "OR". Two reviewers (SSW and JJZ) independently performed electronic searches on several databases. Initial screening was performed by title and abstract. Then, two reviewers read the full-text article during the final screening. In the case of discrepancies between the two reviewers, the results were discussed with a third reviewer. Reviewers assessed the included studies according to the Cochrane Collaborations tool; the evaluation bias risk is reported in the Cochrane Handbook[46]. Two reviewers independently extracted data, and other reviewers verified and ensured that data had been exactly recorded. When data could not be obtained from the full-text article, we contacted the authors by e-mail to obtain raw data.

Quality assessment

The quality of included RCTs was estimated by the Jadad scale, which ranges from 0 to 5. Low-quality RCTs frequently receive a score of 2 or less, and high-quality research receives a score of at least 3[47]. According to the Cochrane Collaboration approach, the risk of bias is reported as low, moderate, or high; reporting of bias leads to an uncertain potential risk of bias. The quality of the included observational studies was estimated by the Newcastle-Ottaa Scale (NOS)[48]. The NOS score for studies ranges from 5 to 9. Scores ≥ 6 are defined as high-quality research. Thirteen observational studies were defined as high-quality, and the average score was 7.5, as shown in Table 4.

Data analysis

The extracted data are expressed as the means$\pm$SD at

baseline and at the endpoint. The results were reported as weighted mean differences (WMDs), standard mean differences (SMDs) and relative risks (RRs) with 95% CIs, I^2 values and P values. The I^2 value indicated the heterogeneity among included studies; I^2 values of over 25%, 50%, and 75% are commonly defined as low, medium and high heterogeneity, respectively[49]. When $I^2 \geq 50\%$, heterogeneity is significant, the random effect model is applied. In this case, the inverse variance statistical method was utilized to calculate the WMD or SMD with 95%CI. The RR and 95% CI were calculated with the Mantel-Haenszel statistical method. A value of $I^2 \leq 25\%$ was regarded, as low heterogeneity, and the fixed-effects model was utilized. To ensure the homogeneity of the included studies, when $I^2 \geq 75\%$, a study with obvious heterogeneity would be removed to determine whether it was the source of heterogeneity. All tests were two-tailed, and a value of $P \leq 0.05$ was regarded as a significant difference. The statistical analysis was performed using RevMan version 5.3.

Results

Review profiles and included studies

We retrieved 4139 articles in the following electronic databases: PubMed 631, Cochrane Library 12, EMBASE 3465, Clinicaltrials 4, China National Knowledge Infrastructure (CNKI) 9 and Chinese database of Wan-Fang 18. After duplicates were removed (n=650), 3451 articles were deemed unsuitable according to their title or abstract because animal experiments were conducted or the studies were case reports, meeting abstracts or reviews. The remaining 38 articles were assessed independently after a full-text reading by two reviewers (SSW and JJZ). At the end of the screening, 2 RCTs and 13 observational studies were included based on the established inclusion criteria[9,10,12-24]. A flowchart of the literature search and screening procedure is shown in Fig. 1.

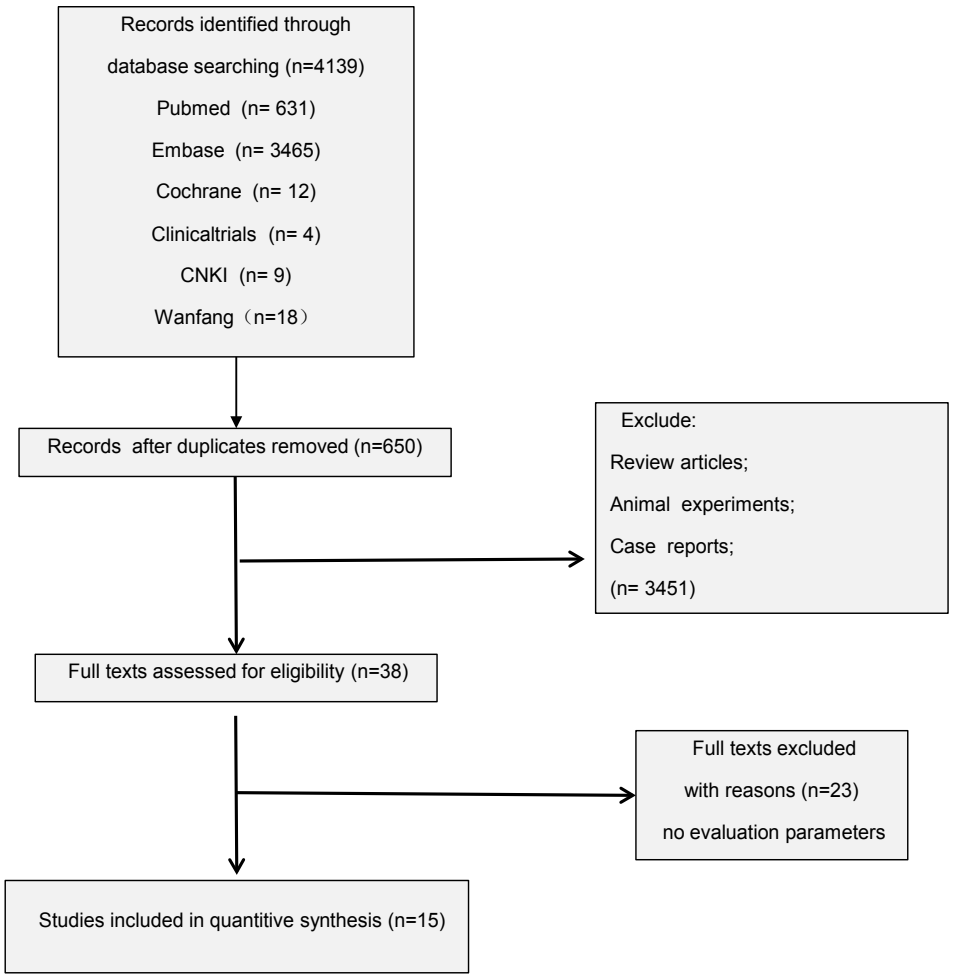

Fig.1 Flowchart of study selection

Inherent differences exist between RCTs and observational studies; therefore, they were analyzed separately. RCTs exhibited high quality and low risk of bias. Observational studies with greater numbers of patients were included, but the potential risk for selection bias and residual confounding were increased. The baseline features of the 2 included RCTs are summarized in Table 1. The baseline characteristics of the 13 observational studies are shown in Table 2.

Table 1 Baseline characters of patients in 2 RCTs

Study		Jadad Score	N*	Enrolled patients	Endpoint (week)	Age (year) mean±SD	Female sex(%)	SLEduration (year) mean±SD	Treatment	BILAG score mean±SD	Anti-dsDNA (IU/mL) mean±SD	C3 (mg/dL) mean±SD	C4 (mg/dL) mean±SD	$CD19^+B$ cells (n/μL) mean±SD
LUNAR	rituximab	3	72	Patients with class III or classIV lupus nephritis	52	31.8±9.6	87.5	32.4±48.0 (months)	Rituximab or placebo 1,000 mg administered intravenously on days 1, 15, 168 and 182	15.3±6.4	453.2±795.7	73.6±29.4	14.7±8.5	280.5±350.2
	placebo		72			29.4±9.3	93.1	28.8±51.6 (months)		15.3±6.2	350.6±634.0	74.1±27.9	13.8±9.4	243.2±313.5
EXPLORER	rituximab	3	169	Patients with moderately to severely active extrarenal SLE	52	40.2±11.4	89.9	8.5±7.2	Rituximabor placebo (2 infusions 1,000mg given 14 days apart)administered intravenously on days 1, 15, 168 and 182	14.0±5.1	282.3±799.0	99.0±32.3	15.6±8.1	210.4±286.1
	placebo		88			40.5±12.8	93.2	8.7±7.6		14.5±5.6	209.2±535.2	96.3±35.3	15.5±8.6	182.8±196.1

* The number of enrolled patients

Table 2 Safety of rituximab (1,000 mg) at week 52

Outcome	Rituximab	Placebo	RR(95%CIs)	I^2(%)	P
Severe adverse events	88	61	0.94[0.72,1.23]	0	0.67
Deaths	6	1	2.86[0.51,16.15]	0	0.23
Infections	30	29	0.73[0.46,1.16]	28	0.18
Gastrointestinal disorders	11	13	0.55[0.25,1.22]	0	0.14
Any infusion-related severe adverse events	17	17	0.55[0.29,1.03]	0	0.06
1st infusion infusion-related adverse events *	62	44	0.91[0.65,1.27]	0	0.58
2nd infusion infusion-related adverse events *	35	22	0.97[0.59,1.61]	0	0.91
3rd infusion infusion-related adverse events *	31	12	1.52[0.81,2.88]	0	0.19
4th infusion infusion-related adverse events *	31	6	2.95[1.26,6.90]	0	0.01

*IV infusions of rituximab or placebo infusion-related adverse events

Sensitivity analysis

Sensitivity analysis is often used to evaluate the reliability of results. Ignoring the data of individual studies did not change the overall outcomes, which showed that outcomes were quite stable. Sensitivity analysis of the pooled data from the 13 observational studies was assessed. A significant change was not found in the outcomes, revealing that results of our observational studies are reliable.

Net changes of efficacy parameters in RCTs

A total of 241 patients received rituximab and 160 patients received a placebo in the two RCTs9,10, with 52 weeks as the end point. No heterogeneity was found between the 2 RCTs, and the fixed-effects model was applied. Relative to the placebo group, we observed a remarkable net increase of serum complement C3 in the rituximab group (WMDfixed=7.67 mg/dL, 95% CI=-0.16-15.50, I^2=0%, P=0.05), as shown in Fig. 2A.

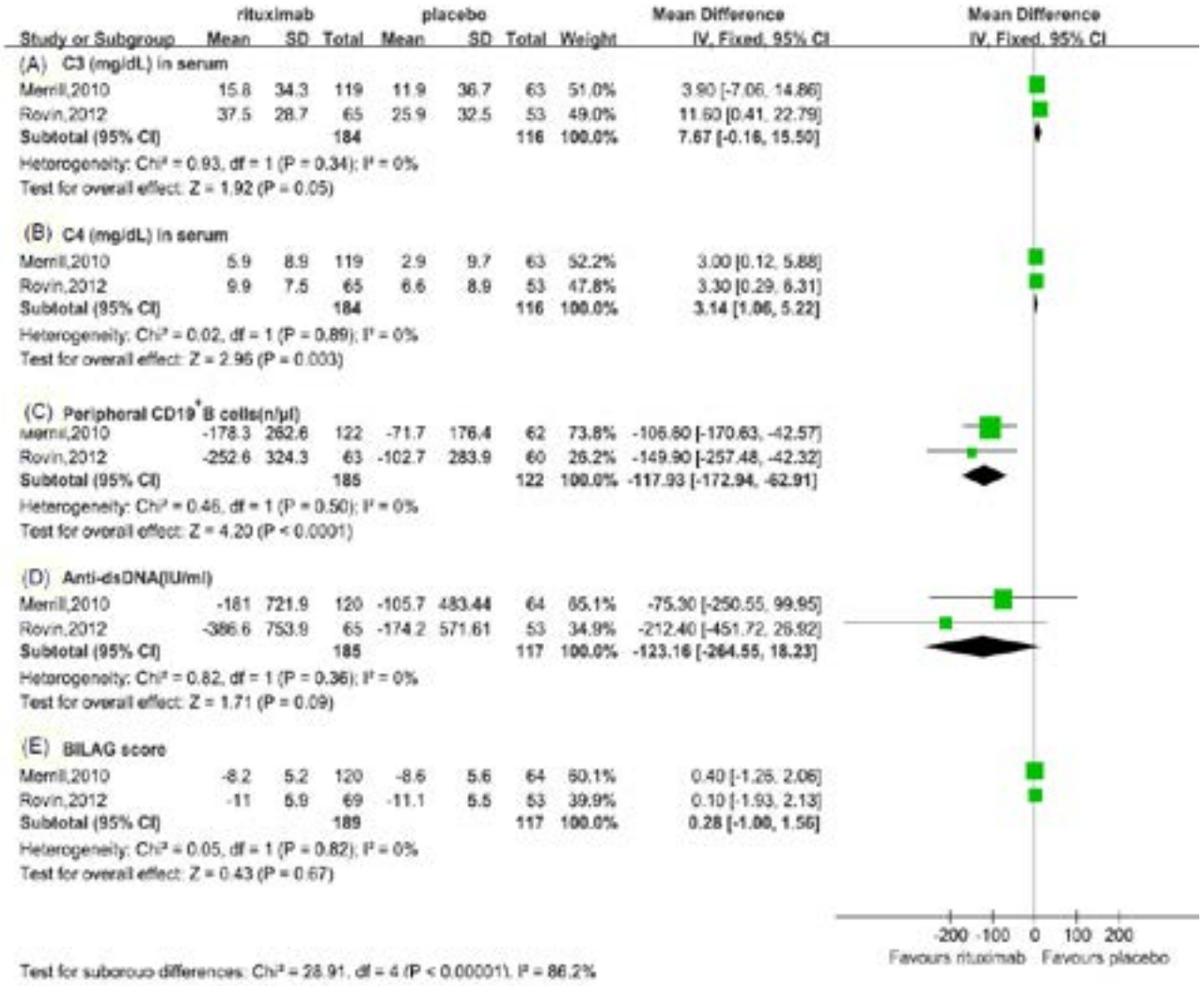

Fig.2 Efficacy parameters of rituximab (1,000 mg) in two RCTs.

Compared to the placebo group, a significant increase in serum complement C4 was observed in the rituximab group (WMDfixed=3.14 mg/dL, 95% CI=1.06-5.22, I^2=0%, P=0.003), as shown in Fig. 2B. A notable decrease in peripheral $CD19^+$ B cells was observed in the rituximab group (WMDfixed=-117.93 n/µL, 95% CI=-172.94--62.91, I^2=0%, P<0.0001), as illustrated in Fig. 2C. Changes in serum anti-dsDNA antibodies were not significantly different between the rituximab and placebo groups (WMDfixed=-123.16I U/mL, 95% CI=-264.55-18.23, I^2=0%, P=0.09), asdepicted in Fig. 2D. Changes in the BILAG score did not differ between the rituximab and placebo groups (WMDfixed=0.28, 95% CI=-1.00-1.56, I^2=0%, P=0.67), as shown in Fig. 2E. Clinical responses were assessed as the combination of complete and partial responses. The clinical responses were not significantly different between the rituximab and placebo groups (RRfixed=1.14, 95% CI=0.88-1.48, I^2=0%, P=0.31), as shown in Fig. 3.

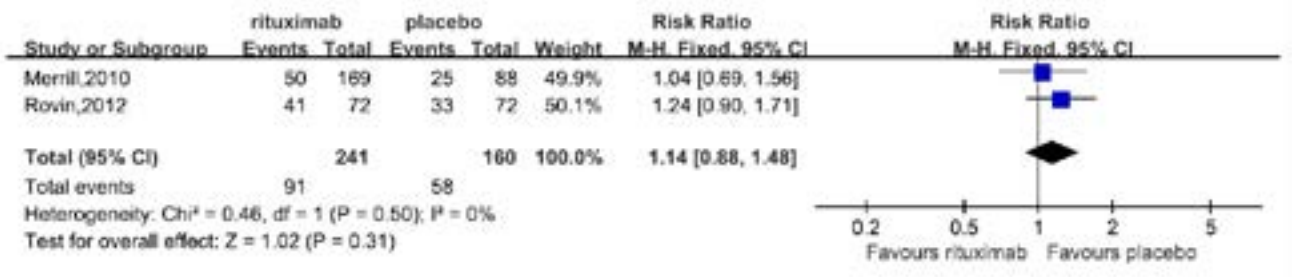

Fig.3 Clinical responses of rituximab (1,000 mg) in two RCTs

Safety of rituximab in RCTs

The safety outcomes of rituximab are summarized in Table 3. The occurrence and severity of adverse events(AEs) were classified according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (version 3.0). We considered the following AEs: SAEs, death, infections, gastrointestinal disorders, infusion-related SAEs and infusion-related AEs over 52 weeks. The above-mentioned safety parameters were dichotomous variables, and no heterogeneity was found between the two RCTs (I^2=0%). The statistical analysis revealed no significant differences between the rituximab and placebo group, except for the occurrence ratio of the 4th rituximab infusion, where infusion-related AEs were significantly increased in the rituximab group (RRfixed=2.95, 95% CI=1.26-6.90, I^2=0%, P=0.01), as illustrated in Fig. 4J.

Table 3 Baseline characteristics of 13 observational studies

No	Study	Enrolled patients characters	n	T_e	Female sex (%)	Rituximab dose	Other treatment	SLEDAI score mean±SD	BILAG score mean±SD	Anti-dsDNA (IU/mL) mean±SD	C3 (mg/dL) mean±SD	C4 (mg/dL) mean±SD	$CD19^+B$ cells (n/μL) mean±SD	serum creatinine (μmol/L) mean±SD	24-h urinary protein(g/24h) mean±SD	urinary protein-creatinine ratio(g/L)/(μmol/L) mean±SD
1	Leandro et al.(19)	Patients failed conventional immunosuppressive therapy	24	24	91.7	6 patients 2 infusions of 500mg, 18 patients 2 infusions of 1000mg given 2 weeks apart	Infusion CYC or prednisolone, continue prednisolone and HCQ	Not mentioned	13.6±5.8	270.3±251.7	65.0±5.0	Not mentioned	Not mentioned	Not mentioned	Not mentioned	417.6±103.0
2	Abitbol et al.(20)	Patients with severe SLE and lupus nephritis age < 16 years	18	24	88.9	The initial dose was188 mg/m^2,subsequent doses were 375 mg/m^2	Low-dose corticosteroids and HCQ, maintenance doses of MMF or AZA	Not mentioned	Not mentioned	1350.5±402.1 mg/dl	61.4±8.4	12.0±2.1	243.0±223.0	1.2±0.4 mg/dl	Not mentioned	4.0±3.5 (mg/mg)
3	Tamimoto et al.(21)	Refractory SLE failed to corticosteroids and immunosuppressive	8	48	87.5	100 $mg/m^2$for 3, 250 mg/m^2 for 2, 375 mg/m^2 for 3 on days 1, 8, 15 and 22	Prednisolone 12.5-50.0 mg, cyclosporine A 75-175 mg and corticosteroids	17.6±10.2	Not mentioned	Not mentioned	Not Mentioned	Not mentioned	75.5±64.5	Not mentioned	Not mentioned	Not mentioned
4	Li et al.(22)	Patients with Class III or intravenous (IV) lupus nephritis	19	24	89.5	Infusion of 1000mg	IV methylprednisolone 250mg, prednisolone reduce from 30 to 5 mg/day, IV infusions CYC 750mg for 10	9.2±3.4	Not mentioned	693.5±345.0	55.0±21.0	14.0±9.0	Not mentioned	118.2±71.2	4.0±2.2	Not mentioned
5	Pepper et al. (23)	Patients with class III/IV/V lupus nephritis	18	48	83.3	Two infusions 1g on days 1 and 15	IV methylprednisolone 500 mg , maintenance with MMF 1 g/day	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	96.8±45.5	Not mentioned	324.6±290.2
6	Ortega et al. (24)	Active SLE with severe manifestations	10	48	80.0	IV infusions of 1g	Dexamethasone 8mg on days 1and 15	12.0±5.9	Not mentioned	Not mentioned	Not mentioned	Not mentioned	175.4±50.8	Not mentioned	Not mentioned	Not Mentioned
No	Study	Enrolled patients characters	n	t_e	Female sex (%)	Rituximab dose	Other treatment	SLEDAI score mean±SD	BILAG score mean±SD	Anti-dsDNA (IU/ml) mean±SD	C3 (mg/dl) mean±SD	C4 (mg/dl) mean±SD	$CD19^+B$ cells (n/μl) mean±SD	serum creatinine (μmol/L) mean±SD	24-h urinary protein(g/24h) mean±SD	urinary protein-creatinine ratio(g/L)/(μmol/L) mean±SD
7	Catapano et al. (25)	Relapsing or refractory SLE	31	48	90.3	375 mg/m^2/week × 4 infusions for 16, 1000 mg × 2 infusions for 15 patients	IV intravenous CYC 500mg and IV methylprednisolone 500–1000	Not mentioned	Not mentioned	Not mentioned	52.0±7.0	8.0±1.0	Not mentioned	86.8±17.2	Not mentioned	Not mentioned
8	Vital et al. (26)	Active severe SLE	39	40	Not mentioned	1,000 mg on days 1 and 14	Infusions methylprednisolone 30-60mg on days1–14and background immunosuppressants		4.0±4.3	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
9	Bang et al. (27)	Refractory SLE for conventional therapy	39	24	92.1	2 infusions 500 mg for 23, 375 mg/m^2/week for 5, 2 infusions 1000 mg for 4	MMF for 19, CYC for 17, AZA for 13, cyclosporine for 9	10.8±7.1	Not mentioned	Not mentioned	70.9±27.9	15.6±12.6	Not mentioned	Not mentioned	Not mentioned	Not Mentioned
10	Zhang et al. (28)	Refractory and severelupus nephritis	42	24	73.8	4 infusions 375 mg/m^2	Methylprednisolone 500mg/day, prednisone 0.6 mg/kg daily for 4 weeks, CTX 800 mg at weeks 1 and 3	14.9±3.5	Not mentioned	Not mentioned	35.0±19.0	11.0±4.0	Not mentioned	115.1±32.4	4.8±1.9	Not mentioned
11	Qiu et al. (29)	Active severe SLE	27	64	81.5	100mg/week for 4 weeks	Methylprednisolone infusions 40 mg for 4 weeks	19.0±10.0	15.0±3.0	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
12	Liu et al. (30)	Active SLE	32	52	78.1	100mg/week for 4weeks	Methylprednisolone250-500 mg/day for 3 days	18.9±6.2	16.3±4.1	Not mentioned	Not mentioned	Not mentioned	570±130	Not mentioned	Not mentioned	Not mentioned
13	Jiang et al. (31)	Active SLE	34	52	79.4	100mg/week for 4weeks	Methylprednisolone250-500 mg/day for 3 days	18. 9±6.2	16.27±4.05	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned

SLE: Systemic lupus erythematosus; SLEDAI: Systemic lupus erythematosus disease activity index; BILAG: British Isles Lupus Assessment Group index; CYC: cyclophosphamide; HCQ: hydroxychloroquine; MMF: mycophenolate mofetil; AZA: azathioprine. n: number enrolled; t_e: follow-up end point (week).

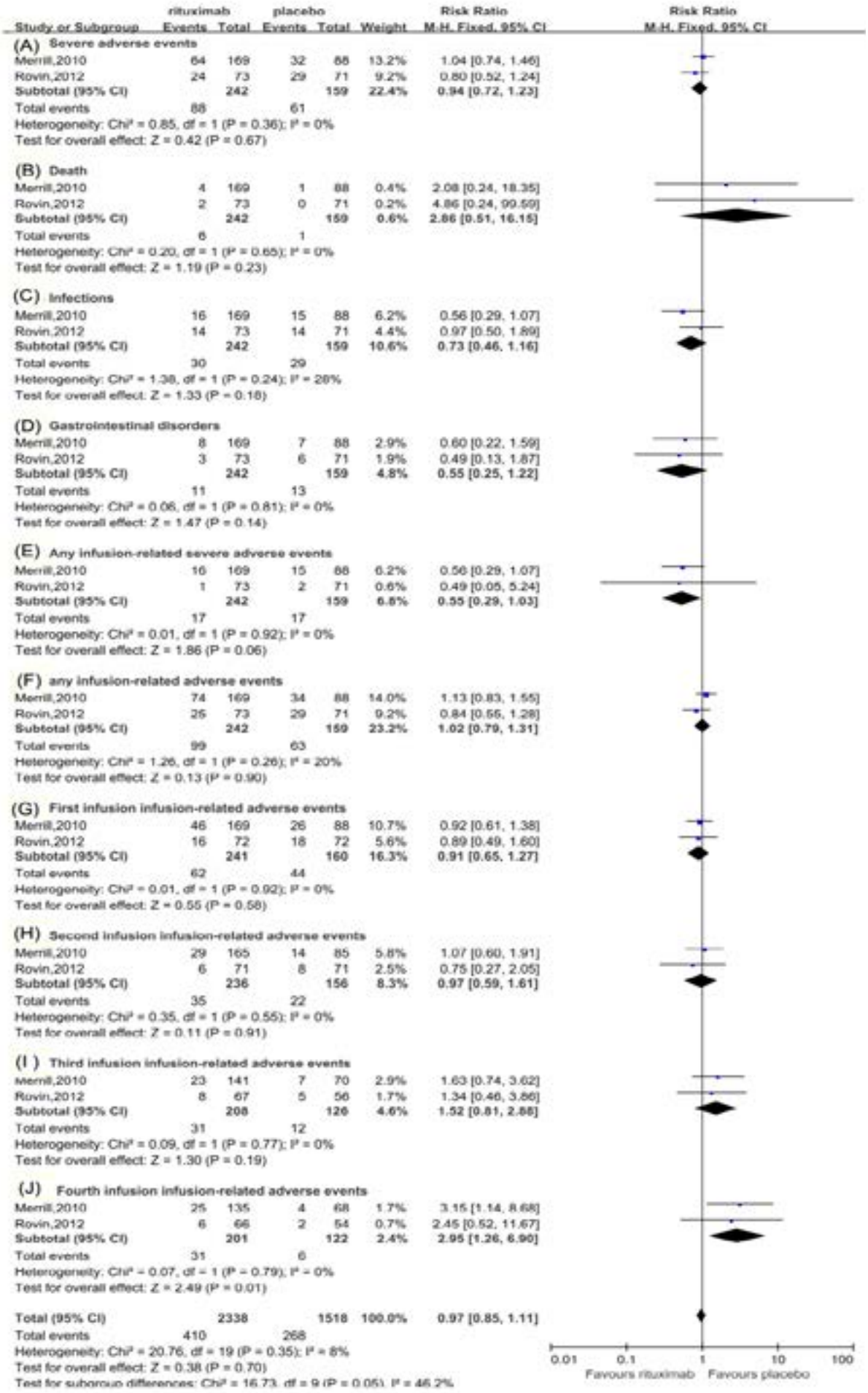

Fig.4 Safety of rituximab (1,000 mg) in two RCTs.

Table 4 Quality assessment of included studies based on the Newcastle-Ottawa Scale

Study	Quality evaluation ofobservational studies								
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Scores
Leandro et al. (19)	*	*	*	*	*	*	*	*	8
Abitbol et al. (20)	*	*	*	*	*	*	*	*	8
Tamimoto et al. (21)	*	*	*	*	*	*	*	*	8
Li et al. (22)	*	*	*	*	*	*	*	*	8
Pepper et al. (23)	*	*	*	*	*	*	*	*	8
Ortegaet al. (24)	*	*	*	*	*	*	*	*	8
Catapanoet al. (25)	*	*	*	*	*	*	*	*	8
Vital et al. (26)	*	*	*	*	*	*	*	*	8
Bang et al. (27)	*	*	*	*	*	*	*		7
Zhang et al. (28)	*	*	*	*	*	*	*		7
Qiu et al. (29)	*	*	*	*	*	*	*	*	8
Liu et al. (30)		*	*	*	*	*	*		6
Jiang et al. (31)		*	*	*	*	*	*		6

Evaluation of the efficacy of rituximab in observational studies

Observational studies data were grouped in this meta-analysis. Thirteen observational studies involving 341 patients (254 females) were included[12-24]. Summarized baseline characteristics of the included studies are shownin Table 3. Depending on whether patients received rituximab, patients were assigned to the baseline group and the "after rituximab" group. The baseline-group was considered the control group, and the "after rituximab" group was regarded as the intervention group.

In a total of 6 studies[14,17,21-24], 153 patients showed a net change in the SLE Disease Activity Index (SLEDAI) score. We adopted the random-effects model and observed that relative to baseline, rituximab useresulted in a significantly decreased in the "after rituximab" group (WMDrandom=-12.31, 95% CI=-14.09--10.52, I^2=57%, P<0.00001, Fig. 5A). Additionally, moderate heterogeneity was found among studies (I^2=57%).

Table 5 The two most important patient outcomes are listed in the summary of findings table

Rituximab Versus Placebo
Patient or population: patients with Systemic lupus erythematosus
Settings: in adult patients
Intervention: rituximab

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed Risk Control	Corresponding risk Death				
Death	6 per 1000	18 per 1000 (3 to 102)	RR 2.86 (0.51 to 16.15)	401 (2 studies)	⊕⊕⊕⊕ high	
Severe adverse events	384 per 1000	361 per 1000 (276 to 472)	RR 0.94 (0.72 to 1.23)	401 (2 studies)	⊕⊕⊕⊕ high	

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio.

In a total of 5 studies[12,19,22-24], 156 patients showed net changes in the BILAG score. The fixed-effects model was used, and compared to baseline, the BILAG score was obviously decreased in the "after rituximab" group (WMDfixed=-9.72, 95% CI=-10.42--9.01, I^2=0%, P<0.00001, Fig. 5C). Homogeneity was found among studies (I^2=0%).

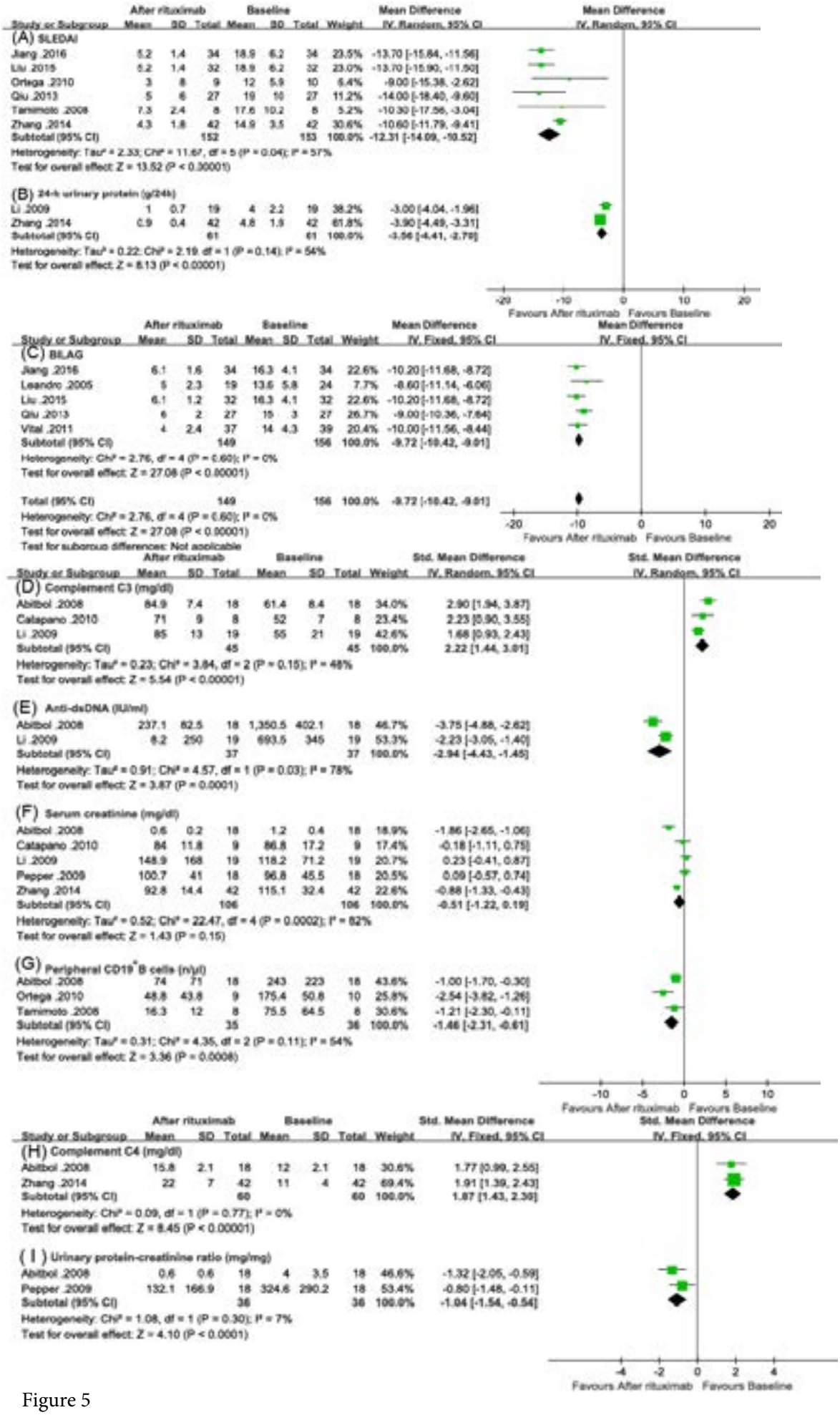
After rituximab
Baseline
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
(A) SLEDAI
Jiang ,2016 5.2 1.4 34 18.9 6.2 34 23.5% -13.70 [-15.84, -11.56]
Liu ,2015 5.2 1.4 32 18.9 6.2 32 23.0% -13.70 [-15.90, -11.50]
Ortega ,2010 3 8 9 12 5.9 10 5.4% -9.00 [-15.38, -2.62]
Qiu ,2013 5 6 27 19 10 27 11.2% -14.00 [-18.40, -9.60]
Tamimoto ,2008 7.3 2.4 8 17.6 10.2 8 5.2% -10.30 [-17.56, -3.04]
Zhang ,2014 4.3 1.8 42 14.9 3.5 42 30.6% -10.60 [-11.79, -9.41]
Subtotal (95% CI) 152 153 100.0% -12.31 [-14.09, -10.52]
Heterogeneity: Tau² = 2.33; Chi² = 11.67, df = 5 (P = 0.04); I² = 57%
Test for overall effect: Z = 13.52 (P < 0.00001)
(B) 24-h urinary protein (g/24h)
Li ,2009 1 0.7 19 4 2.2 19 38.2% -3.00 [-4.04, -1.96]
Zhang ,2014 0.9 0.4 42 4.8 1.9 42 61.8% -3.90 [-4.49, -3.31]
Subtotal (95% CI) 61 61 100.0% -3.56 [-4.41, -2.70]
Heterogeneity: Tau² = 0.22; Chi² = 2.19, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 8.13 (P < 0.00001)
-20 -10 0 10 20
Favours After rituximab Favours Baseline
After rituximab
Baseline
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
(C) BILAG
Jiang ,2016 6.1 1.6 34 16.3 4.1 34 22.6% -10.20 [-11.68, -8.72]
Leandro ,2005 5 2.3 19 13.6 5.8 24 7.7% -8.60 [-11.14, -6.06]
Liu ,2015 6.1 1.2 32 16.3 4.1 32 22.6% -10.20 [-11.68, -8.72]
Qiu ,2013 6 2 27 15 3 27 26.7% -9.00 [-10.36, -7.64]
Vital ,2011 4 2.4 37 14 4.3 39 20.4% -10.00 [-11.56, -8.44]
Subtotal (95% CI) 149 156 100.0% -9.72 [-10.42, -9.01]
Heterogeneity: Chi² = 2.76, df = 4 (P = 0.60); I² = 0%
Test for overall effect: Z = 27.08 (P < 0.00001)
Total (95% CI) 149 156 100.0% -9.72 [-10.42, -9.01]
Heterogeneity: Chi² = 2.76, df = 4 (P = 0.60); I² = 0%
Test for overall effect: Z = 27.08 (P < 0.00001)
Test for subgroup differences: Not applicable
-20 -10 0 10 20
Favours After rituximab Favours Baseline
After rituximab
Baseline
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
(D) Complement C3 (mg/dl)
Abitbol ,2008 84.9 7.4 18 61.4 8.4 18 34.0% 2.90 [1.94, 3.87]
Catapano ,2010 71 9 8 52 7 8 23.4% 2.23 [0.90, 3.55]
Li ,2009 85 13 19 55 21 19 42.6% 1.68 [0.93, 2.43]
Subtotal (95% CI) 45 45 100.0% 2.22 [1.44, 3.01]
Heterogeneity: Tau² = 0.23; Chi² = 3.84, df = 2 (P = 0.15); I² = 48%
Test for overall effect: Z = 5.54 (P < 0.00001)
(E) Anti-dsDNA (IU/ml)
Abitbol ,2008 237.1 82.5 18 1,350.5 402.1 18 46.7% -3.75 [-4.88, -2.62]
Li ,2009 8.2 250 19 693.5 345 19 53.3% -2.23 [-3.05, -1.40]
Subtotal (95% CI) 37 37 100.0% -2.94 [-4.43, -1.45]
Heterogeneity: Tau² = 0.91; Chi² = 4.57, df = 1 (P = 0.03); I² = 78%
Test for overall effect: Z = 3.87 (P = 0.0001)
(F) Serum creatinine (mg/dl)
Abitbol ,2008 0.6 0.2 18 1.2 0.4 18 18.9% -1.86 [-2.65, -1.06]
Catapano ,2010 84 11.8 9 86.8 17.2 9 17.4% -0.18 [-1.11, 0.75]
Li ,2009 148.9 168 19 118.2 71.2 19 20.7% 0.23 [-0.41, 0.87]
Pepper ,2009 100.7 41 18 96.8 45.5 18 20.5% 0.09 [-0.57, 0.74]
Zhang ,2014 92.8 14.4 42 115.1 32.4 42 22.6% -0.88 [-1.33, -0.43]
Subtotal (95% CI) 106 106 100.0% -0.51 [-1.22, 0.19]
Heterogeneity: Tau² = 0.52; Chi² = 22.47, df = 4 (P = 0.0002); I² = 82%
Test for overall effect: Z = 1.43 (P = 0.15)
(G) Peripheral CD19⁺B cells (n/µl)
Abitbol ,2008 74 71 18 243 223 18 43.6% -1.00 [-1.70, -0.30]
Ortega ,2010 48.8 43.8 9 175.4 50.8 10 25.8% -2.54 [-3.82, -1.26]
Tamimoto ,2008 16.3 12 8 75.5 64.5 8 30.6% -1.21 [-2.30, -0.11]
Subtotal (95% CI) 35 36 100.0% -1.46 [-2.31, -0.61]
Heterogeneity: Tau² = 0.31; Chi² = 4.35, df = 2 (P = 0.11); I² = 54%
Test for overall effect: Z = 3.36 (P = 0.0008)
-10 -5 0 5 10
Favours After rituximab Favours Baseline
After rituximab
Baseline
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI
IV, Fixed, 95% CI
(H) Complement C4 (mg/dl)
Abitbol ,2008 15.8 2.1 18 12 2.1 18 30.6% 1.77 [0.99, 2.55]
Zhang ,2014 22 7 42 11 4 42 69.4% 1.91 [1.39, 2.43]
Subtotal (95% CI) 60 60 100.0% 1.87 [1.43, 2.30]
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 8.45 (P < 0.00001)
(I) Urinary protein-creatinine ratio (mg/mg)
Abitbol ,2008 0.6 0.6 18 4 3.5 18 46.6% -1.32 [-2.05, -0.59]
Pepper ,2009 132.1 166.9 18 324.6 290.2 18 53.4% -0.80 [-1.48, -0.11]
Subtotal (95% CI) 36 36 100.0% -1.04 [-1.54, -0.54]
Heterogeneity: Chi² = 1.08, df = 1 (P = 0.30); I² = 7%
Test for overall effect: Z = 4.10 (P < 0.0001)
-4 -2 0 2 4
Favours After rituximab Favours Baseline

Figure 5

In 3 studies, the serum complement C3 data 13, 15, 18 were reported for a total of 45 patients. We selected the random-effects model, and in contrast to baseline, a significant increase in complement C3 was observed in the "after rituximab" group (SMDrandom=2.22, 95% CI=1.44-3.01, I^2=48%, P<0.00001, Fig. 5D). These studies exhibited moderate heterogeneity (I^2=48%).

Serum complement C4 data were reported in 2 studies 13, 21 including a total of 60 patients. We adopted the fixed-effects model and discovered that compared to baseline, a significant increase was observed in the "after rituximab" group (SMDfixed=1.87, 95% CI=1.43-2.30, I^2=0%, P<0.00001, Fig. 5H). No heterogeneity was observed between the two studies (I^2=0%).

Serum anti-dsDNA antibodies data were reported in 2 studies including a total of 37 patients 13, 15. The random-effects model was adopted, and a remarkable decrease in anti-dsDNA antibodies was observed in the "after rituximab" group compared to baseline(SMDrandom=-2.94, 95%CI=-4.43--1.45, I^2=78%, P=0.0001, Fig.5E). High heterogeneity was observed between the two studies (I^2=78%). It was difficult to find the source of heterogeneity in the 2 studies.

Peripheral CD19+B-cell data were reported in 3 studies including a total of 36 patients13, 14, 17. The random-effects model was used, and a significant reduction in the "after rituximab" group was observed compared to baseline (SMDrandom=-1.46, 95%CI=-2.31--0.61, I^2=54%, P=0.0008, Fig.5G). These studies had moderate heterogeneity (I2=54%).

Serum creatinine data were reported in 5 studies including a total of 106 patients13, 15, 16, 18, 21. The random-effects model was adopted, and serum creatinine levels did not differ between the two groups (SMDrandom=-0.51, 95%CI=-1.22-0.19, I^2=82%, P=0.15, Fig.5F). High heterogeneity was observed among studies (I^2=82%).

The 24-h urinary protein excretion data were reported in 2 studies including a total of 61 patients15, 21. We adopted the random-effects model and observed that 24-h urinary protein excretion was significantly decreased in the "after rituximab" group compared to baseline (WMDrandom=-3.56, 95%CI=-4.41--2.70, I^2=54%, P<0.00001, Fig.5B). Medium heterogeneity was found between the two studies (I^2=54%).

Urinary protein-creatinine ratio data were reported in 2 studies including 36 patients[13,16]. The fixed-effects model was used, and a marked decrease in the urinary protein-creatinine ratio was observed in the"after rituximab" group compared to baseline (SMDrandom=-1.04, 95%CI=-1.54--0.54, I^2=7%, P<0.0001, Fig.5I). Low heterogeneity was found between the two studies (I^2=7%).

Discussion

In recent years, SLE patients have received many biotherapies, and these biological agents presented encouraging results. Rituximab is a biological agent that selectively targets $CD20^+$B cells. The earliest report of rituximab use in SLE patients was in 2001[25]. Favorable responses and satisfactory tolerance for rituximab use for refractory SLE patients were revealed in clinical trials. Particularly, these refractory patients had symptoms involving the renal, hematological and nervous systems[26,27]. A good therapy should control SLE activity and prevent more organs from being impaired by severe or fatal outcomes.

Borba previously reported the following efficacy outcomes for rituximab: clinical response, BILAG C score, time-adjusted AUCMB of the BILAG score and modification in the SF-36 PCS. Considering these results, significant variations were not found between the rituximab and placebo groups[11]. Duxbury viewed rituximab can effectively control the activity of SLE in observational studies. Two RCTs did not display the benefit of rituximab by observing the complete response and the partial response rate[28]. Nevertheless, in our meta-analysis, both RCTs and observational studies showed that rituximab had satisfactory efficacy and safety results.

The BILAG and SLEDAI scores were used to assess the disease activity. These assessments consider clinical symptoms, physical signs, laboratory results and physician judgments. A lower score indicates that SLE is controlled and indirectly reflects the curative effect. We observed that rituximab and a placebo exhibited no differences regarding changes in BILAG scores in RCTs. Observational studies indicated that both BILAG and SLEDAI scores were remarkably reduced in the "after rituximab" group compared to baseline. The results of both BILAG and SLEDAI scores are consistent with the observational studies of Lan LAN[29]. The observational study outcomes suggest that rituximab is effective.

Higher anti-dsDNA antibodies and lower complement C3/C4 levels demonstrate the disease activity. We found a remarkable net increase in complement C3/C4 in the rituximab group compared to the placebo group. Net changes of anti-dsDNA antibodies were similar between the rituximab and placebo groups, and the P value was close to 0.05(P=0.09); additional RCTs may make the results significant. In contrast to baseline, complement C3/C4 was significantly increased in

the "after rituximab" group, and a remarkable decrease in anti-dsDNA antibodies was observed in the "after rituximab" group in observational studies. Despite that a distinct improvement of anti-dsDNA and complement C3/C4 levels were not associated with Clinical outcomes, these changes correlated with the reduction of proteinuria in Lupus nephritis[9]. Fervenza observed that rituximab is superior to cyclosporine in maintaining complete or partial elimination of proteinura up to 24 months in membranous nephropathy[30]. The complement C3/C4 results were reliable and showed that rituximab was efficacious in RCTs and observational studies, which suggested that the immune system was improved. The pathogenesis of SLE is attributed to the incidence of immune complexes that prompt supplementary pathway activation and complement consumption. Low complement C3/C4 levels are considered in the immunologic criteria of the Systemic Lupus International Collaborating Clinics (SLICC) when diagnosing and monitoring SLE[31]. These results indicated that rituximab can control disease activity and improve the immune system, but further investigations are still needed.

B-lymphocyte dysregulation is the focus of SLE pathogenesis, and B cells act as antigen-presenting cells that present autoantigens to T cells; T cells activate and produce cytokines. T cells and B cells stimulate each other, and autoantigen-specific B cells produce autoantibodies[3]. This mechanism is complex; the role of B cells is not only restricted to producing antibodies[32]. Rituximab is a type of monoclonal antibody and targets CD20 on B cells5, which exhausts B cells through different methods[33]. $CD19^+$ lymphocytes are B cells, and peripheral $CD19^+$B cells were significantly decreased in the rituximab group compared to the placebo group. Patients who received rituximab over 52 weeks maintained good B-cell depletion. The peripheral $CD19^+$B cells of the "after rituximab" group were remarkably decreased in observational studies. Both RCTs and observational studies demonstrated that rituximab can deplete peripheral $CD19^+$B cells, and these results are reliable. Sfikakis reported that refractory lupus nephritis patients who received rituximab attained B-cell depletion and good clinical responses. The authors deduced that B-cell depletion was an effective therapy and that not only was an excessive production of autoantibodies avoided, but B cells were also hampered in presenting autoantigens to T cells, and the potential activation of T helper cells was quickly reduced[34]. The B-cell depletion was similar between Sfikakis's results and our analysis.

The 24-h urinary protein excretion extremely important for reflecting the activity and severity of renal impairment in chronic kidney disease. The spot urinary protein-creatinine ratio(Up/Ucr) may be more efficient, reliable and time-saving to diagnose proteinuria in patients who are not pregnant[35]. The results of 24-h urinary protein excretion and the Up/Ucr were significantly decreased in the "after rituximab" group compared to baseline in the observational studies. Our 24-h urinary protein result was the same as that of Lan LAN in observational studies[29]. Our analysis shows that rituximab may be effective in patients with refractory and severe lupus nephritis.

The possible reasons of failure of rituximab therapy in randomized placebo-controlled trials are explained below. Firstly, as a background therapy (e.g. high-dose corticosteroids and full-dose MMF), immunosuppressive therapy may have masked an obvious clinical benefit of rituximab{Ready V, 2013 #41}[36]. The composition of patients in the RCTs was different from that in the observational studies, as refractory patients were recruited in the observational studies but not enrolled in the RCTs. Moreover, factors of ethnic differences should be considered, with the African subgroup achieving a beneficial effect of rituximab in the RCTs. Secondly, we should pay more attention to background therapy. Ramos-Casals observed that the combination of rituximab and CYC may have synergistic effect and associated CYC with obvious benefits for complicated and refractory SLE[37]. Other views including Duxbury viewed that the number of patients in RCTs seemed too small (401 individuals) to reflect superiority of rituximab over placebo[28].

The safety results of RCTs included SAEs, deaths, infections, gastrointestinal disorders, any infusion-related SAEs and infusion-related AEs. Previously mentioned studies showed no significant variation between the rituximab and placebo groups, except for the occurrence rate of the 4^{th} rituximab infusion, where infusion-related AEs were notably increased but did not affect the safety of rituximab applications. Our safety results are consistent with those of Borba, who concluded that rituximab is relatively safe for SLE patients[11]. Another purpose of using rituximab is a reduction in steroids dose, which avoids the side effects of steroids[38]. There is a significant correlation between higher doses of rituximab and a decreased rate of infection. However, it cannot be excluded from the findings that infections led to the termination of rituximab treatment or lower doses[39]. Consequently, we recommend that rituximab

is safe, but more high-quality long-term information is required.

The reviewed safety outcomes of rituximab has been presented in a table using the GRADE profiler (Table 5)[9,10]. The two most important safety outcomes of patient with SLE are displayed in the table.

Patients with fewer immunosuppressive drugs previously low titers of complement C4 and severe disease may respond better. This indicates that the ideal candidates for rituximab may be patients without obvious refractory process[40-42]. Relapses are related to increased damage. Thus, we should pay close attention to an appropriate balance between the dose and toxic risk of immunosuppressive drugs. As a maintenance treatment, Rituximab may be considered for refractory patients, for whom first-line immunosuppressive drugs are invalid. Moreover, there will be a high risk if these patients simply wait for symptomatic treatments after relapse[42].

Conclusion

We observed that rituximab treatment may be promising, especially for severe and refractory SLE. However, further investigation and discussion are required.

Methods

We conducted a meta-analysis to estimate the efficacy and safety of rituximab treatment for SLE and followed the Cochrane Handbook[43].

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) The SLE diagnosis satisfied the standards specified by the American College of Rheumatology[44]. (2) The trials included rituximab as an intervention treatment for SLE. (3) Placebo group as control group in RCTs. Baseline group when patients did not receive rituximab as control group in observational studies. (4) The study included efficacy and safety results, and the parameters of efficacy were the BILAG score, SLEDAI score, complement C3/C4 levels, anti-dsDNA antibodies, peripheral CD19+B cells, serum creatinine, 24-h urinary protein and Up/Ucr. The safety results included the incidence of SAEs, deaths, infections, gastrointestinal disorders, infusion-related SAEs and infusion-related AEs. (5) Both RCT and observational studies that met the above conditions can be included in this study. Trials without clinical outcomes and articles that were merely obtainable as abstracts were excluded from the meta-analysis[11]. No language restrictions were implemented.

Authors' contributions

All authors made important contributions to this work. Shanshan Wu and Yanhai Wang conceived and designed this research. Shanshan Wu and Jiaojiao Zhang searched articles and extracted data. Bo Han, Wanli Gao, Ning Zhang and Cheng Zhang verified and analyzed the data. All figures and tables were prepared by Yanhai Wang. Baishan Wang, Feng Yan and Zhijing Li wrote the manuscript. All authors reviewed and approved the manuscript.

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Conflicts of interest

The authors declare that they have no potential conflicts of interest regarding the research, authorship, and publication of this article.

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