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ORIGINAL RESEARCH

Clinical efficacy and safety of rituximab in lupus nephritis

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Background: Long-term treatment programs with low toxicity represent a therapeutic challenge in lupus nephritis (LN). Although a therapeutic benefit of rituximab (RTX) has been reported in LN patients who have failed conventional treatment, the results are controversial. We aimed to assess the clinical efficacy and safety of RTX as a new immunosuppressive medicine in the treatment of LN with a meta-analysis.

Methods: Based on predetermined criteria, PubMed, Embase, and Cochrane Library were used to identify the eligible studies. Cochrane Review Manager version 5.3 was applied to pool the data extracted from individual investigations and provide summary effect estimates.

Results: Twenty-four studies with 940 patients were analyzed. In case series trials with specific LN assessment, the complete remission (CR) rate at 12 months was 35.9% (95% CI: 24.2%–49.5%), and total remission (TR: CR plus partial remission) was 73.4% (95% CI: 66.0%–79.7%). In controlled trials, RTX was associated with a higher probability of TR (OR =2.02, 95% CI: 1.23–3.32, $P<0.01$). The CR in the RTX group was higher than that in the control group, although there was no significant difference between the two groups (OR =1.98, 95% CI: 0.90–4.39, $P>0.05$). Additionally, RTX treatment significantly decreased proteinuria (mean difference: −2.79, 95% CI: −3.95 to −1.62, $P<0.01$) as well as the renal activity index in patients with LN (mean difference: −3.46, 95% CI: −4.43 to −2.50, $P<0.01$). In controlled trials, the relative risks of the adverse events of infection and infusion reaction were not notably different between the two groups.

Conclusion: RTX is a promising therapy for the treatment of LN due to significant clinical efficacy and a favorable safety profile. In future studies, larger study populations and longer-term time points may identify additional important patient-centered outcomes.

Keywords: systemic lupus erythematosus, lupus nephritis, rituximab, efficacy, safety, meta-analysis

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multiorgan damage and the production of autoantibodies directed against multiple cellular components.[1–3] Lupus nephritis (LN) occurs in up to 60% of adults with SLE, and up to 30% of LN patients progress to end-stage renal disease (ESRD).[4,5] ESRD is the most severe manifestation of LN and often requires dialysis or transplantation. The "gold standard" treatment for LN includes mycophenolate mofetil (MMF) as well as corticosteroids and cyclophosphamide (CYC),[6] which results in significant morbidity from infections and ovarian failure.[7] As a relapsing/remitting autoimmune disease, long-term treatment programs with low levels of toxicity remain a major interventional objective.

Lupus B cells are characterized by various alterations in phenotype and clonal expansion, and hyperreactive B cells play a central role through the production of

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autoantibodies and adverse regulatory effects on mediators of inflammation and general immune functions.[8] Rituximab (RTX) is a chimeric antibody which binds specifically to the B-cell surface antigen CD20.[9] CD20 protein is expressed on immature and mature B lymphocytes, but it is not found in early B-cell precursors or plasma cells.[10] Targeting and transiently depleting B cells is an ideal therapeutic approach for LN. RTX was the first approved agent for the treatment of patients with relapsed or refractory lymphoma, and has subsequently been used for various autoimmune diseases, including LN.

Therapeutic benefit of RTX has been reported in LN patients where conventional treatment had failed,[11,12] although the randomized controlled trials have failed to identify any superiority to placebo.[13] The reasons for RTX failure may include too few patients, strong placebo effects, use of background therapies, heterogeneous outcome measures, heterogeneous patient population, and liberal steroid use. In this study, we aimed to evaluate the clinical efficacy and safety of RTX as a new immunosuppressive treatment for LN with a meta-analysis of the recent literature.

Materials and methods

Data sources and search terms

The search strategy was designed to identify the full length of studies reporting outcomes of RTX treatment in LN patients. Two independent reviewers performed the searches in the following databases: PubMed, Embase, and Cochrane Library. PubMed was searched using Medical subheading using the terms "Rituximab" and "Lupus Nephritis" published from January 1, 2000, to October 31, 2018. As per this method, the entry terms for RTX were: Rituximab; Rituxan; CD20 Antibody, Rituximab CD20 Antibody; IDEC C2B8 Antibody; Mabthera; IDEC C2B8; IDEC-C2B8; IDEC-C2B8 Antibody; GP2013. The entry terms for LN were: Lupus Nephritis; Nephritis Lupus; Lupus Glomerulonephritis; Glomerulonephritis Lupus; Glomerulonephritides Lupus; Lupus Nephritides; Nephritides Lupus; Lupus Glomerulonephritides. Similarly, other database searches were conducted using a combination of rituximab and lupus nephritis terms. No language restrictions were applied. Reference lists of the research articles and reviews were screened to manually identify additional articles.

Inclusion and exclusion criteria

Inclusion criteria

Inclusion criteria were: 1) retrospective study, prospective study, or controlled trials (randomized controlled study [RCT], case-control study) indicating the outcomes of RTX therapy in at least seven LN patients; 2) presence of data on therapeutic efficacy and safety; and 3) enrolled patients with a diagnosis of LN disease based on the American College of Rheumatology criteria.

Exclusion criteria

Exclusion criteria were: 1) abstracts, case reports, reviews, and editorials; 2) studies with insufficient details; and 3) duplicate reports from the same study.

Study selection

Two independent investigators were responsible for determining whether the reports were eligible for inclusion in the meta-analysis. To resolve any inconsistencies, the investigators compared lists after reviewing the identified papers. A third investigator resolved any discrepancies to finalize the list of included studies.

Data extraction and data synthesis

A custom Excel sheet was used to collect all the relevant data on the surname of first author, publication year, patient, intervention, and outcome characteristics. Two investigators extracted the data independently. The results were compared and discussed when there was disagreement. The P(opulation) I(ntervention) C(omparison) O(utcome) of the study were defined as follows: P: Patients with LN; I: treated with RTX, MMF, CYC, or placebo/not treatment (P/NT); C: RTX vs MMF, RTX vs CYC, RTX vs P/NT; O: CR: complete remission, TR: total remission (CR plus partial remission), proteinuria, renal activity index (AI), adverse events.

Statistical analysis

All statistical analyses were conducted and Cochrane Review Manager version 5.3 (Cochrane Library, UK) was applied. Two meta-analysis models were constructed. Model 1: CR and TR of the patients to RTX therapy. TR was defined as CR plus partial remission. Model 2: mean change with statistical significance of AI and proteinuria after RTX therapy. The non-comparative percentages of response were pooled by using the method of the inverse of the variance with logit-transformed proportions.[14] A fixed-effects model was used to calculate the pooled statistic, and the heterogeneity among the included investigations was detected using I^2. A random-effects model was constructed when the P-value from the heterogeneity test was <0.1. Statistical significance was defined as $P<0.05$.

Results

Search results

Among the 940 publications identified, 24 studies met the inclusion criteria, with 19[12,15–32] retrospective or prospective case series and five comparative studies.[13,33–36]

Characteristics of included studies

The included studies consisted of 24 studies that investigated RTX therapy in 940 LN patients, detailed in Table 1. The studies were conducted between 2005 and 2018, and dose of RTX varied. Some investigators used 375 mg/m^2 qid., whereas others used 375 mg/m^2 at day 1 and day 15. Doses of 1,000 mg bid. 2 weeks apart, 1,000 mg at day 1 and day 15 every 6 months, and 600 mg qd were also infused in other cohorts.

Meta-analysis results

Case series with specific LN assessment

Nineteen case series trials[12,15–32] in patients with LN met our inclusion criteria. All studies used renal values as criteria to assess clinical outcome and define CR and TR. Based on renal outcome, the pooled percentage using logit-transformed proportions of TR was 72.9% (95% CI: 67.3%–77.8%; Figure 1). The pooled percentage of CR at 12 months was 35.9% (95% CI: 24.2%–49.5%; Figure 1), and the pooled percentage of TR at 12 months was 73.4% (95% CI: 66.0%–79.7%; Figure 1).

Controlled trials

Five controlled trials[13,33–36] analyzed clinical remission as an outcome. RTX was associated with a higher probability of TR (OR =2.02, 95% CI: 1.23–3.32, $P<0.01$; Figure 2). The CR in the RTX group was higher than that in control group, although there was no significant difference between the two groups (OR =1.98, 95% CI: 0.90–4.39, $P>0.05$; Figure 2). The CR and TR at 12 months were calculated and the pooled ORs for CR and TR were 2.03 (95% CI: 0.54–7.64, $P>0.05$; Figure 2) and 2.09 (95% CI: 1.23–3.57, $P<0.01$; Figure 2), respectively. This result indicates that treatment with RTX was associated with a higher TR.

Change in proteinuria

Proteinuria was used to evaluate renal injury in five studies.[19,21,22,27,32] RTX treatment decreased proteinuria (mean difference =–2.79, 95% CI: –3.95 to –1.62, $P<0.01$; Figure 3).

Change in renal activity index

Renal AI is determined by morphologic alteration in renal biopsy, and the maximum score is 24 points. Four studies[17,21,28,29] used AI to evaluate pathological renal changes (Figure 4). These trials mostly included patients with active LN despite treatment, WHO or International Society of Nephrology/Renal Pathology Association class III (eight patients), IV (33 patients), III–V (one patient), IV–V (seven patients). Twelve patients had class V LN. In all patients, there was a significant reduction in AI following RTX treatment (mean difference =–3.46; 95% CI: –4.43 to –2.50, $P<0.01$).

Adverse events

In the case series trials,[12,15–32] 97 (24.7%) patients suffered adverse events. Sixty-two (15.8%) patients had a total of 69 infections: 14 respiratory infections, ten urinary tract infections, three osteoarticular infections, four sepsis, ten herpes zoster, and one pneumococcal meningitis. Fifteen (3.8%) patients developed an infusion reaction. Two posterior reversible leukoencephalopathies and eight cases of neutropenia were observed. Three patients died during the follow-up period (due to invasive histoplasmosis, complications of surgery, and disease progression). In the controlled trials,[13,33,35,36] the relative risks of the following adverse events were not significantly different between RTX and other immunosuppressive agents (CYC/MMF): infection, 0.81 (95% CI: 0.46–1.43, $P>0.05$) and infusion reaction, 2.18 (95% CI: 0.43–10.98, $P>0.05$).

Discussion

The renal injury associated with SLE gradually progresses from early mild lesions to glomerular sclerosis and is a major cause of morbidity and mortality in the affected individuals.[37] Therefore, it is critical to initiate induction therapy with the best possible clinical efficacy at a very early stage of LN. The primary goals of LN management are renal remission with minimal toxic effects.[38]

In LN, B cells, attracted by the accumulative of immune complexes, migrate from the circulation into the renal tubule.[39] These B cells then undergo clonal expansion in response to local antigens, which perpetuates a cycle of interstitial inflammation and damage.[40] B-cell depletion therapies reduce immune complexes in both serum and kidney, and RTX has been of interest for use in LN as a chimeric anti-CD20 monoclonal antibody. Li et al[20] found that RTX monotherapy appeared to be effective in the induction therapy of patients with LN, and the addition of CYC had no additional beneficial effect.

Our findings indicate therapeutic efficacy of RTX in LN patients. RTX resulted in a higher TR than the control group.

Table 1 Summary of available information for each study included in the analysis

Study	Country	Study design	N	RTX dose	Affecting immune drugs added	P dose (mean)	F/U	Clinical outcome	Definition
Sfikakis et al, 2005[15]	Greece	PCS	10	4×375 mg/m^2	P	0.5 mg/kg/d for 10 w, tapered by 4 mg every 2 w thereafter	12	CR: 50% TR: 80%	[a]CR: normal serum creatinine and albumin, inactive urine sediment, urinary protein/24 h <500 mg PR: ≥50% improvement in renal parameters that had been abnormal at baseline, without deterioration in any of them
Vigna-Perez et al, 2005[16]	Mexico	PCS	22	2×0.5–1 g	NM	NM	3	CR: 23% TR: 55%	CR: normal serum creatinine, inactive urine sediment, urinary protein/24 h <500 mg PR: >40% improvement in renal parameters that had been abnormal at baseline
Gunnarsson et al, 2007[17]	Sweden	PCS	7	4×375 mg/m^2	CYC: 2×0.5 mg/m^2, MTP: 4×100–250 mg, P	1 mg/kg/d at first week, 0.75 mg/kg/d at second week, 0.5 mg/kg/d at third week then tapered	6	CR: 43% TR: 86%	[a]
Lindholm et al, 2008[18]	Sweden	RCS	17	4×375 mg/m^2	NM	NM	12	CR: 12% TR: 65%	[a]
Boletis et al, 2009[19]	Greece	PCS	10	4×375 mg/m^2	MMF: 2 g/d, P	0.5 mg/kg/d for 4 w, tapered by 5 mg, either every 2 or 4 w thereafter	38	CR: 70% TR: 80%	[a]
Melander et al, 2009[21]	UK	RCS	20	4×375 mg/m^2	None (but CYC 3 pts)	0.7 mg/kg/d at entrance	22	CR: 35% TR: 60%	CR: urinary protein/24 h <500 mg, no hematuria, normal GFR or >50% improvement in GFR PR: >50% decrease in 24 hours proteinuria, GFR stabilization
Pepper et al, 2009[22]	UK	PCS	18	2×1 g	MMF: 1 g/d, MTP: 2×500 mg, P	10 mg/d at entrance	12	CR: 33% TR: 67%	CR: normal serum creatinine and albumin, minimal proteinuria (protein: creatinine ratio <50) PR: ≥50% improvement in proteinuria, stabilization, or normalization of serum creatinine
Garcia-Carrasco et al, 2010[24]	Mexico	RCS	13	2×1 g	MTP: 2×500 mg	16 mg/d at entrance (dose adjusted during trial)	6	CR: 38% TR: 76%	[a]
Ramos-Casals et al, 2010[25]	Spain	RCS	49	4×375 mg/m^2 or 2×1 g	NM	NM	26	CR: 80%	CR: normal serum creatinine and albumin, inactive urine sediment, urinary protein/24 h <500 mg

Catapano et al, 2010[23]	UK	RCS	11	4×375 mg/m^2 (4 pts) 2×1 g (7 pts)	CYC: 500 mg MTP: 500–1,000 mg	10 mg/d at entrance	4	CR: 36% TR: 91%	CR: stable or reduced serum creatinine, inactive urine sediment, urinary protein/24 h <500 mg PR: stable or reduced serum creatinine, <30 RBC/hpf, urinary protein/24 h 50% reduction
Jónsdóttir et al, 2013[28]	Sweden	PCS	25	4×375 mg/m^2	CYC: 2×0.5 g, MMF (2 pts), P	0.5 mg/kg/d during the treatment weeks then tapered rapidly thereafter	12	CR: 16% TR: 56% (6 m) CR: 20% TR: 80% (12 m)	CR: inactive urinary sediment, decrease in proteinuria to ≤0.2 g/d, normal, or stable renal function PR: inactive sediment proteinuria ≤0.5 g/day, normal or stable renal function
Davies et al, 2013[27]	UK	PCS	18	2×1 g	CYC: 2×0.5 g, MTP: 2×500 mg	NM	6	CR: 61% TR: 72%	[a]
Condon et al, 2013[26]	UK	PCS	50	2×1 g	MTP: 2×500 mg, MMF: 0.5–1.5 g/d	NM	12	CR: 52% TR: 86%	CR: UPC ratio <50 mg/mmol, serum creatinine level ≤115% of baseline PR: UPC ratio <300 mg/mmol with >50% reduction from baseline, serum creatinine level ≤115% of baseline
Tsanyan et al, 2014[29]	Russia	PCS	45	1×0.5 g (2 pts) 2×0.5 g (16 pts) 3×0.5 g (1 pts) 4×0.5 g (13 pts) 1×1 g (3 pts) 2×1 g (11 pts)	MTP: 6×250–1,000 mg	NM	6	CR: 81% TR: 86%	According to the SLICC RA/RE CR: baseline activity score >0 and follow-up score =0 PR: baseline activity score > follow-up score and follow-up score ≠0
Contis et al, 2016[30]	France	RCS	17	4×375 mg/m^2 (10 pts) 2×1 g (7 pts)	MTP: 100–750 mg	NM	12	CR: 24% TR: 53%	CR: normal serum creatinine, inactive urinary sediment, urinary protein/24 h <500 mg PR: >50% improvement in renal parameters
Kotagiri et al, 2016[31]	Australia	PCS	14	1×375 mg/m^2	AZA (6 pts), MMF (7 pts), CYC (1 pts)	NM	6	CR: 14% TR: 79%	CR: normalization of creatinine, albumin, proteinuria, and urinary RBCs PR: >50% improvement in at least 1 parameter, without deterioration in others
Chavarot et al, 2017[12]	France	RCS	15	4×375 mg/m^2 (6 pts) 2×1 g (9 pts)	P	Background steroids ≤20 mg/d	6	CR: 27% TR: 80% (6 m) CR: 47% TR: 60% (12 m)	CR: UPC ratio <0.5 g/g, normal, or near-normal GFR PR: ≥50% reduction in proteinuria to subnephrotic levels, normal or near-normal GFR

(*Continued*)

Table 1 (*Continued*)

Study	Country	Study design	N	RTX dose	Affecting immune drugs added	P dose (mean)	F/U	Clinical outcome	Definition
Hogan et al, 2018[32]	France	RCS	12	2×1 g	MTP: 500 mg, MMF: 1,200 mg/m^2/d	0.3, 0.10, 0.0 mg/kg/d at 3, 6, and 12 m	6	CR: 75% TR: 100% (6 m) CR: 75% TR: 100% (12 m)	CR: UPC ratio <5 mg/mg, normal serum creatinine PR: UPC ratio <30 mg/mg, serum creatinine level ≤115% of baseline
Li et al, 2009[20]	China	PCS	19	Group 1: 2×1 g (9 pts)	MTP: 250 mg, P	30 mg/d for 4 d, 0.5 mg/kg/d for 4 w, then a reduction of 5 mg every 2 w to 5 mg/d for the rest of the study	12	CR: 21% TR: 79%	According to the SLICC RA/RE CR: baseline activity score >0 and follow-up score =0 PR: baseline activity score > follow-up score and follow-up score ≠0
				Group 2: 2×1 g (10 pts)	MTP: 250 mg, P, CYC: 1×750 mg	f			
Moroni et al, 2014[33]	Italy	CS	54	Group 1: 2×1 g (17 pts)	MTP: 3×500–1,000 mg, P	0.5–1.75 mg/kg/d for 1 m, then tapered	12	CR: 71% TR: 100%	CR: serum creatinine <1.2 mg/dL or return to the baseline value, urinary protein/24 h <500 mg, <5 RBC/hpf PR: serum creatinine <1.2 mg/dL or return to the baseline value, urinary protein/24 h 0.5–2 g
				None (37 pts)	MTP: 3×500–1,000 mg, P, MMF (17 pts), CYC (20 pts)		12	CR: 59% TR: 92%	
Basu et al, 2017[35]	India	CS	44	Group 1: 2×375 mg/m^2 (17 pts)	MTP: 3×15 mg/kg/d, P	2 mg/kg/d for 1 m, then tapered	3	CR: 71% TR: 94%	CR: urinary protein/24 h ≤0.5 g, inactive urinary sediment, improvement in kidney function determined by GFR PR: ≥50% decrease in baseline proteinuria or proteinuria <1 g/24 h, ≤25% decrease in baseline GFR
				None (27 pts)	MTP: 3×15 mg/kg/d, P, MMF (12 pts), CYC (15 pts)		3	CR: 32% TR: 70%	
Goswami et al, 2018[36]	India	CS	222	Group 1: 1.9±0.25 g (22 pts)	MMF (4 pts), CYC (12 pts)	NM	6	CR: 73% TR: 91%	CR: serum creatinine <1.3 mg/dL, normal urinalysis, urinary protein/24 h <500 mg PR: serum creatinine <1.3 mg/dL, normal urinalysis, ≥50% decrease in baseline proteinuria
				None (200 pts)	MMF: 1.5–3 g/d (61 pts), LDCYC: 6×500 mg (26 pts), HDCYC: 6×750–1,200 mg (113 pts)	NM	6	CR: 66% TR: 83%	

Rovin et al, 2012[13]	America	RCT	144	Group 1: 4×1 g (72 pts)	MMF: 1.5–3 mg/d, MTP: 2×1,000 mg, then 4×100 mg, P,	0.75 mg/kg/d for 16 d and tapered to ≤10 mg/d by 16 w	12	CR: 26% TR: 57%	CR: normal serum creatinine level or ≤115% of baseline, inactive urinary sediment, UPC ratio <0.5 PR: serum creatinine level ≤115% of baseline, ≤50% RBC/hpf, no red blood cells casts, >50% decrease in UPC ratio
				Placebo (72 pts)	MMF: 1.5–3 mg/d, MTP: 2×1,000 mg, then 4×100 mg, P		12	CR: 31% TR: 46%	
Zhang et al, 2015[34]	China	RCT	84	Group 1: 4×375 mg/m^2 (42 pts)	MTP: 3×500 mg, P, CYC: 2×800 mg	0.6 mg/kg/d for 4 w, then reduced at 5 mg every week till reached 10 mg/d	12	CR: 64% TR: 83%	CR: urinary protein/24 h <0.5 g, serum albumin ≥35 g/L, disappearance of LN symptoms PR: urinary protein/24 h <1.5 g, serum albumin ≥30 g/L
				None (42 pts)	MTP: 3×500 mg, P, CYC: 12×800 mg		12	CR: 21% TR: 57%	

Note: [a]The definition of CR and PR as per Sfikakis et al, 2005.[15]

Abbreviations: AZA, azathioprine; CR, complete remission; CS, controlled studies; CYC, cyclophosphamide; d, day; F/U, follow-up in months; GFR, glomerular filtration rate; h, hour; HDCYC, high-dose cyclophosphamide; hpf, high-power field; IS, immunosuppressive agents; LDCYC, low-dose cyclophosphamide; m, month; MMF, mycophenolate mophetil; MTP, methylprednisolone (intravenous infusion); N, number of patients with available data for analysis; NM, not mentioned; P, prednisolone; PCS, prospective case series; PR, partial remission; pts, patients; RBC, red blood cells; RCS, retrospective case series; RCT, randomized controlled trial; RTX, rituximab; SLICC RA/RE, systemic lupus international collaborating clinics renal activity/response exercise; TR, total remission; CR+PR, ; UPC, urine protein-to-creatinine; w, week.

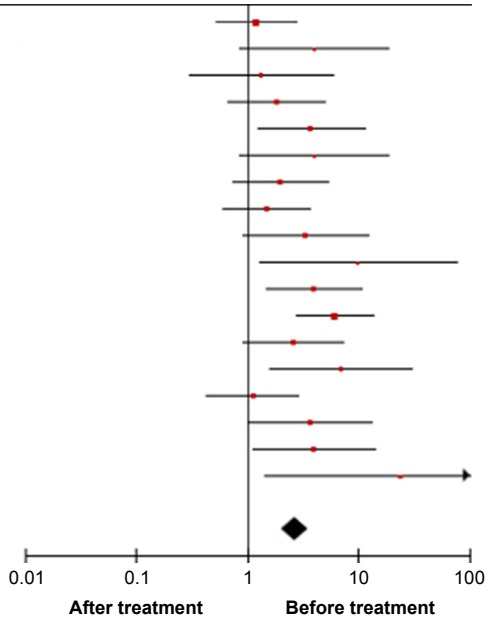
It significantly decreased renal AI as well as proteinuria, suggesting that RTX therapy may prevent the development of organ damage, at least over the short term. The findings of this meta-analysis were consistent with a previous study evaluating the comparative effects of CYC, azathioprine, MMF, methotrexate, and cyclosporin in 164 patients with biopsy-proven LN.[41] In that meta-analysis, RTX was ranked as the most effective therapy for LN patients, especially for refractory patients when compared to standard treatment or patients who experience a new flare-up after intensive immunosuppressive treatment. Similarly, a recent meta-analysis demonstrated that RTX induced remission of LN in patients who do not enter remission with standard therapies.[42] Our present study had several strengths, including the larger size of the sample and the new follow-up subgroup analyses, which allowed for a more accurate assessment of LN.

Autoreactive pathogenic B cells may persist in an environment of high B-cell activating factor (BAFF), such as kidney tubulointerstitium, even with adequate peripheral B-cell depletion.[43] These cells cannot be easily measured (B-cell depletion was defined as absolute B-cell count $\leq 0.05\times10^9$/L, and repletion as B-cell count $>0.05\times10^9$/L post-depletion) and may lead to continued kidney injury. At 6 weeks post-RTX administration, complete depletion is regarded as a marker of good response to therapy.[44] A 4-year observational study reported that B cells in the kidney tubulointerstitium are resistant to depletion with RTX.[45] This process may require an extended period to reduce the expression of B cells in the kidney and observe a significant effect on CR. There is variability in peripheral blood B-cell depletion after RTX therapy, and treatment with anti-CD20 agents can be informed by B-cell monitoring to achieve greater efficacy and duration of effects, as well as a shorter time to complete depletion.

Combinations of symptoms and clinical manifestations of LN can vary widely among affected patients, and assessment and standardization of renal response to treatment remain a challenge.[46] The proper assessment of disease activity and damage accrual is dependent upon composite response indices. Repeated renal biopsies may be fundamental for evaluating the efficacy and prognosis of patients with nephritis.[47] Patients who do not achieve CR most often exhibit an insignificant reduction in proteinuria levels. Compared to 24-hour urine protein, spot protein/creatinine ratio is more effective at monitoring high levels due to the relatively short collection interval.[48] Therefore, it is necessary to dialectically interpret the laboratory data.

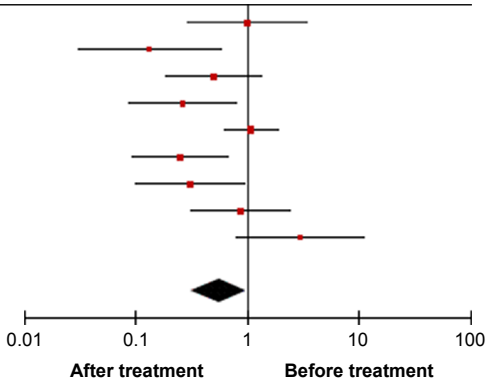
Total remission

Study or subgroup	Log (odds ratio)	SE	Weight (%)	Odds ratio IV, fixed, 95% CI
Vigna-Perez, 2005	0.182	0.428	10.1	1.20 (0.52, 2.78)
Sfikakis, 2005	1.386	0.791	2.9	4.00 (0.85, 18.85)
Gunnarsson, 2007	0.288	0.764	3.2	1.33 (0.30, 5.96)
Lindholm, 2008	0.606	0.508	7.1	1.83 (0.68, 4.96)
Li, 2009	1.322	0.563	5.8	3.75 (1.24, 11.31)
Boletis, 2009	1.386	0.791	2.9	4.00 (0.85, 18.85)
Pepper, 2009	0.693	0.5	7.4	2.00 (0.75, 5.33)
Melandar, 2009	0.405	0.456	8.9	1.50 (0.61, 3.66)
Garcia-Carrasco, 2010	1.204	0.658	4.3	3.33 (0.92, 12.11)
Catapano, 2010	2.303	1.049	1.7	10.00 (1.28, 78.18)
Jonsdottir, 2013	1.386	0.5	7.4	4.00 (1.50, 10.65)
Condon, 2013	1.815	0.408	11.1	6.14 (2.76, 13.66)
Davies, 2013	0.956	0.526	6.7	2.60 (0.93, 7.29)
Tsanyan, 2014	1.946	0.756	3.2	7.00 (1.59, 30.81)
Contis, 2016	0.118	0.486	7.8	1.13 (0.43, 2.92)
Kotagiri, 2016	1.299	0.651	4.3	3.67 (1.02, 13.13)
Chavarot, 2017	1.386	0.645	4.4	4.00 (1.13, 14.16)
Hogan, 2018	3.178	1.443	0.9	24.00 (1.42, 405.95)
Total (95% CI)			**100**	**2.69 (2.06, 3.51)**
Heterogeneity: χ^2=21.94, *df*=17 (*P*=0.19); I^2=23%				Logit transformed
Test for overall effect: *Z*=7.30 (*P*<0.00001)				**0.729 (0.673, 0.778)**



Complete remission at 12 months

Study or subgroup	Log (odds ratio)	SE	Weight (%)	Odds ratio IV, random, 95% CI
Sfikakis, 2005	0	0.632	9.8	1.00 (0.29, 3.45)
Lindholm, 2008	–2.015	0.753	8.2	0.13 (0.03, 0.58)
Pepper, 2009	–0.693	0.5	11.9	0.50 (0.19, 1.33)
Li, 2009	–1.322	0.563	10.9	0.27 (0.09, 0.80)
Condon, 2013	0.08	0.283	15.7	1.08 (0.62, 1.89)
Jonsdottir, 2013	–1.386	0.5	11.9	0.25 (0.09, 0.67)
Contis, 2016	–1.179	0.572	10.7	0.31 (0.10, 0.94)
Chavarot, 2017	–0.134	0.518	11.6	0.87 (0.32, 2.41)
Hogan, 2018	1.099	0.667	9.3	3.00 (0.81, 11.09)
Total (95% CI)			**100**	**0.56 (0.32, 0.98)**
Heterogeneity: τ^2=0.45; χ^2=21.86, *df*=8 (*P*=0.005); I^2=63%				Logit transformed
Test for overall effect: *Z*=2.02 (*P*=0.04)				**0.359 (0.242, 0.495)**



Total remission at 12 months

Study or subgroup	Log (odds ratio)	SE	Weight (%)	Odds ratio IV, fixed, 95% CI
Sfikakis, 2005	1.386	0.791	5.2	4.00 (0.85, 18.85)
Lindholm, 2008	0.606	0.508	12.5	1.83 (0.68, 4.96)
Pepper, 2009	0.693	0.5	12.9	2.00 (0.75, 5.33)
Li, 2009	1.322	0.563	10.2	3.75 (1.24, 11.31)
Jonsdottir, 2013	1.386	0.5	12.9	4.00 (1.50, 10.65)
Condon, 2013	1.815	0.408	19.4	6.14 (2.76, 13.66)
Contis, 2016	0.118	0.486	13.7	1.13 (0.43, 2.92)
Chavarot, 2017	0.405	0.527	11.6	1.50 (0.53, 4.21)
Hogan, 2018	3.178	1.443	1.6	24.00 (1.42, 405.95)
Total (95% CI)			**100**	**2.76 (1.94, 3.93)**
Heterogeneity: χ^2=12.97, *df*=8 (*P*=0.11); I^2=38%				Logit transformed
Test for overall effect: *Z*=5.65 (*P*<0.00001)				**0.734 (0.660, 0.797)**

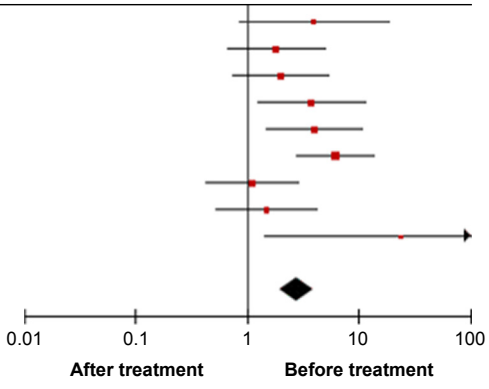


Figure 1 Results of the meta-analysis of remission in LN patients treated with rituximab in case series trials.
Abbreviation: LN, lupus nephritis.

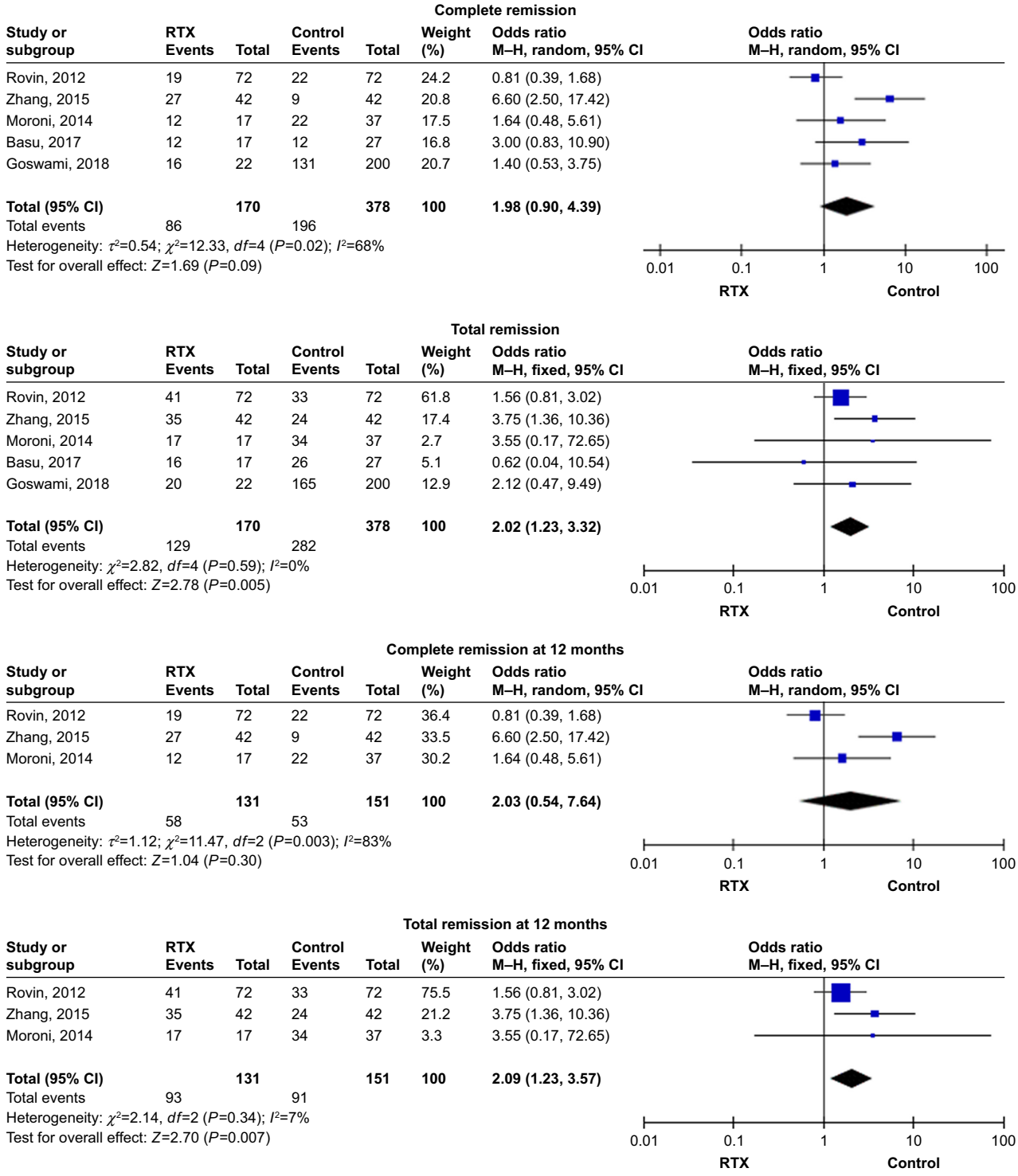


Figure 2 Results of the meta-analysis of remission in LN patients treated with rituximab in controlled trials.
Abbreviations: LN, lupus nephritis; RTX, rituximab.

Limitations

There were some limitations in this study. Only two RCTs and three case-control studies with various baseline regimens (MMF+ steroids or CYC+ steroids or steroids alone) were included in the meta-analysis, and these different regimens were not analyzed separately. Furthermore, the definition of complete and partial response used in each of the controlled trials was not same, and this could have introduced hetero-

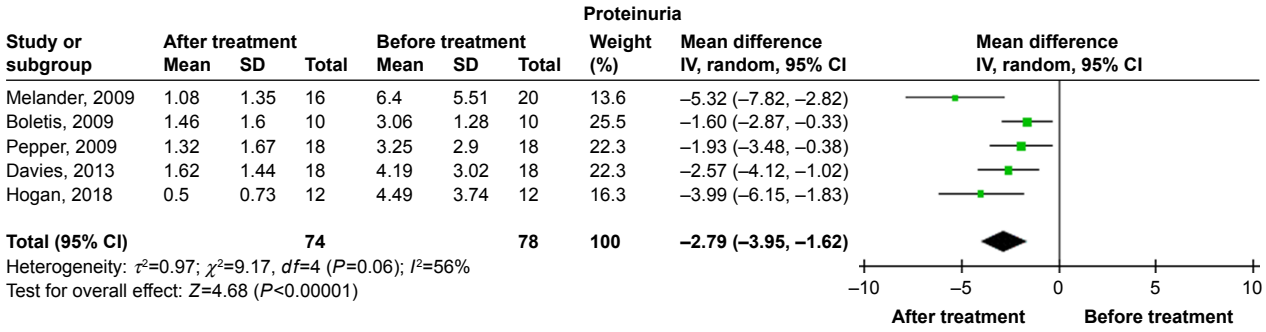


Figure 3 Results of meta-analysis of proteinuria in LN patients treated with rituximab.
Abbreviation: LN, lupus nephritis.

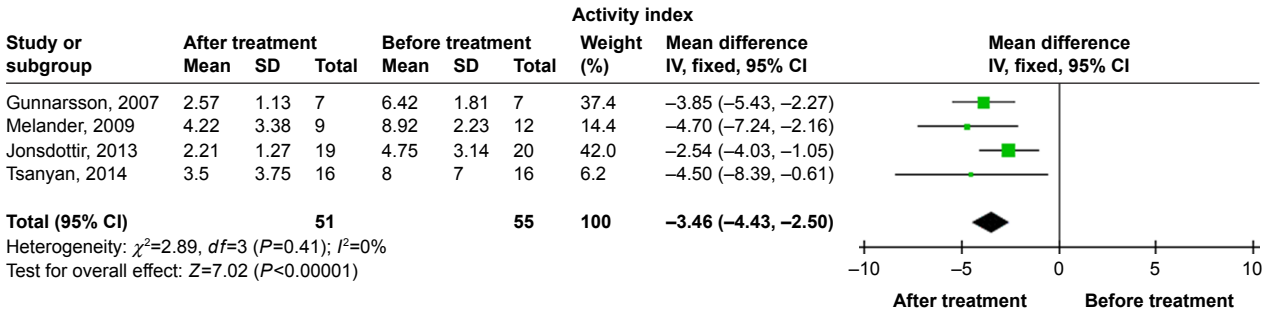


Figure 4 Results of meta-analysis of activity renal index in LN patients treated with rituximab.
Abbreviation: LN, lupus nephritis.

geneity among the included studies. While some trials lasted several years, most were 6–12 months long, and this has led to considerable uncertainty in the impact of treatment on the outcomes of these patients and has prevented patients and clinicians from evaluating the relative balance of treatment benefits and risk.

Conclusion

RTX is a promising therapeutic agent for LN treatment. However, in future studies, larger study populations and longer-term end points should be assessed to identify additional important patient-centered outcomes.

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Disclosure

The authors report no conflicts of interest in this work.

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