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...
autoantibodies and adverse regulatory effects on mediators of inflammation and general immune functions. Rituximab (RTX) is a chimeric antibody which binds specifically to the B-cell surface antigen CD20. CD20 protein is expressed on immature and mature B lymphocytes, but it is not found in early B-cell precursors or plasma cells. 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, although the randomized controlled trials failed to identify any superiority to placebo. 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; Glomerulonephritisides Lupus; Lupus Nephritides; Nephritides Lupus; Lupus Glomerulonephritisides. 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. 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 19,21,25–32 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/m² qid., whereas others used 375 mg/m² 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 trials12,15–32 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 trials13,33–36 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.19,21,22,27,38 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 studies17,21,28,29 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,13,33,35,38 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 al38 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   | Greece  | PCS          | 10  | 4×375 mg/m² | P                            | 0.5 mg/kg/d for 10 w, tapered by 4 mg every 2 w thereafter                  | 12  | CR: 50% TR: 80% | CR: normal serum creatinine and albumin, inactive urine sediment, urinary protein/24 h < 500 mg                                                                                                         |
| Vigna-Perez et al, 2005| Mexico  | PCS          | 22  | 2×0.5–1 g | NM                           |                                                                             | 3   | CR: 23% TR: 55% | PR: ≥50% improvement in renal parameters that had been abnormal at baseline, without deterioration in any of them                                                                                          |
| Gunnarsson et al, 2007 | Sweden  | PCS          | 7   | 4×375 mg/m² | CYC: 2×0.5 mg/m²; 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% | CR: normal serum creatinine, inactive urine sediment, urinary protein/24 h < 500 mg                                                                                                                     |
| Lindholm et al, 2008   | Sweden  | RCS          | 17  | 4×375 mg/m² | NM                           |                                                                             | 12  | CR: 12% TR: 65% | PR: >40% improvement in renal parameters that had been abnormal at baseline                                                                                                                             |
| Boletis et al, 2009    | Greece  | PCS          | 10  | 4×375 mg/m² | 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% |                                                                                                              |
| Melander et al, 2009   | UK      | RCS          | 20  | 4×375 mg/m² | 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                                                                                                                     |
| Pepper et al, 2009     | 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)                                                                                                          |
| Garcia-Carrasco et al, 2010 | Mexico | RCS          | 13  | 2×1 g     | MTP: 2×500 mg                | 16 mg/d at entrance (dose adjusted during trial)                            | 6   | CR: 38% TR: 76% | PR: ≥50% improvement in proteinuria, stabilization, or normalization of serum creatinine                                                                                                                |
| Ramos-Casals et al, 2010 | Spain  | RCS          | 49  | 4×375 mg/m² | NM                           |                                                                             | 26  | CR: 80%         | CR: normal serum creatinine and albumin, inactive urine sediment, urinary protein/24 h < 500 mg                                                                                                           |
| Study                        | Country | Control | Doses | CYC Dose | MTP Dose | Initial Dose | CR Rate | TR Rate | Adverse Effects |
|------------------------------|---------|---------|-------|----------|----------|--------------|----------|----------|----------------|
| Catapano et al, 2010         | UK      | RCS     | 11    | 4×375 mg/m² (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% |
| Jónsdóttir et al, 2013       | Sweden  | PCS     | 25    | 4×375 mg/m² | 2×0.5 g (2 pts), MMF (2 pts), P | CYC: 2×0.5 g, MMF | 6×500 mg | 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) |
| Davies et al, 2013           | UK      | PCS     | 18    | 2×1 g | CYC: 2×0.5 g, MTP: 2×500 mg | NM | | | 6 | CR: 61% TR: 72% |
| Condon et al, 2013           | UK      | PCS     | 50    | 2×1 g | MTP: 2×500 mg, MMF: 0.5–1.5 g/d | NM | | | 12 | CR: 52% TR: 86% |
| Tsanyan et al, 2014          | 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% |
| Contis et al, 2016           | France  | RCS     | 17    | 4×375 mg/m² (10 pts) 2×1 g (7 pts) | MTP: 100–750 mg | NM | | | 12 | CR: 24% TR: 53% |
| Kotagiri et al, 2016         | Australia | PCS    | 14    | 1×375 mg/m² | AZA (6 pts), MMF (7 pts), CYC (1 pts) | NM | | | 6 | CR: 14% TR: 79% |
| Chavarot et al, 2017         | France  | RCS     | 15    | 4×375 mg/m² (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) |

(Continued)
| Study                        | Country | Study design | N  | RTX dose | Affecting immune drugs added | P dose (mean) | F/U | Clinical outcome | Definition                                                                 |
|-----------------------------|---------|--------------|----|----------|------------------------------|---------------|-----|-----------------|----------------------------------------------------------------------------|
| Hogan et al, 2018<sup>32</sup> | France  | RCS          | 12 | 2×1 g    | MTP: 500 mg, MMF: 1,200 mg/m²/d | 0.3, 0.10, 0.0 mg/kg/d at 3, 6, and 12 m | 6   | CR: 75% TR: 100% (6 m)  | CR: UP ratio <5 mg/mg, normal serum creatinine  |
|                             |         |              |    |          |                              |               |     | CR: 75% TR: 100% (12 m) | PR: UP ratio <30 mg/mg, serum creatinine level ≤115% of baseline  |
| Li et al, 2009<sup>30</sup>  | 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 RARE  |
|                             |         |              |    |          |                              |               |     | CR: baseline activity score >0 and follow-up score =0 | CR: baseline activity score > follow-up score and follow-up score ≤0  |
| Moroni et al, 2014<sup>43</sup> | Italy   | CS           | 54 | Group 1: 2×1 g (17 pts) | MTP: >750 mg | 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  |
|                             |         |              |    |          |                              |               |     | CR: 59% TR: 92% | PR: serum creatinine <1.2 mg/dL or return to the baseline value, urinary protein/24 h 0.5–2 g  |
| Basu et al, 2017<sup>35</sup> | India   | CS           | 44 | Group 1: 2<375 mg/m² (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  |
|                             |         |              |    |          |                              |               |     | CR: 32% TR: 70% | PR: ≥50% decrease in baseline proteinuria or proteinuria <1 g/24 h, ≥25% decrease in baseline GFR  |
| Goswami et al, 2018<sup>36</sup> | India   | CS           | 222 | Group 1: 1.9±0.25 g (22 pts) | MTP: 3×15 mg/kg/d, P | NM | 6  | CR: 73% TR: 91% | CR: serum creatinine <1.3 mg/dL, normal urinalysis, urinary protein/24 h <500 mg  |
|                             |         |              |    |          |                              |               |     | CR: 66% TR: 83% | PR: serum creatinine <1.3 mg/dL, normal urinalysis, ≥50% decrease in baseline proteinuria  |
### Table: Summary of Clinical Trials on Rituximab (RTX)

| Study            | Country | Design | N  | Group | MMF | MTP | CR: 26% TR: 57% |
|------------------|---------|--------|----|-------|-----|-----|-----------------|
| Rovin et al, 2012 | 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 | CR: 26% TR: 57% |
| Zhang et al, 2015 | China   | RCT   | 84 | Group 1: 4 × 375 mg/m² (42 pts) | MMF: 1.5–3 mg/d, MTP: 2 × 1,000 mg, then 4 × 100 mg, P, 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 | CR: 26% TR: 57% |
| Zhang et al, 2015 | China   | RCT   | 84 | Placebo (72 pts) | MMF: 1.5–3 mg/d, MTP: 2 × 1,000 mg, then 4 × 100 mg, P, MTP: 3 × 500 mg, P, CYC: 2 × 800 mg | CR: 26% TR: 57% |
| Zhang et al, 2015 | China   | RCT   | 84 | None (42 pts) | MTP: 3 × 500 mg, P, CYC: 12 × 800 mg | CR: 26% TR: 57% |

### Abbreviations:
- CR: complete remission
- PR: partial remission
- MMF: mycophenolate mofetil
- MTP: methylprednisolone (intravenous infusion)
- P: prednisolone
- UPc: urine protein-to-creatinine
- GFR: glomerular filtration rate
- hpf: high-power field
- CS: controlled studies
- CYC: cyclophosphamide
- Day: day
- F/U: follow-up
- HC: high-calcium
- LDCYC: low-dose cyclophosphamide
- m: month
- MMF: mycophenolate mofetil
- 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
- PTX: rituximab
- SLICC RA/RE: systemic lupus international collaborating clinics renal activity/response exercise
- TR: total remission
- CR: complete response
- PR: partial response
- TNF: tumor necrosis factor
- LN: lupus nephritis
- AI: albumin index
- ANA: antinuclear antibody
- Bc: B-cells
- h: hour
- hpf: high-power field
- IS: immunosuppressive agents
- GFR: glomerular filtration rate
- h, hour
- LC: light chain
- h, hour
- mmol/L
- mg/dL
- mg/m²
- mg/kg
- mg/d
- mg/wk
- mg/m²/d
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### Figure 1

Results of the meta-analysis of remission in LN patients treated with rituximab in case series trials.

**Abbreviation:** LN, lupus nephritis.

#### Total remission

| Study or subgroup | Log (odds ratio) | SE | Weight (%) | Odds ratio IV, fixed, 95% CI | Odds ratio IV, fixed, 95% CI |
|------------------|------------------|----|------------|-----------------------------|-----------------------------|
| Vigna-Perez, 2005 | 0.182            | 0.428 | 10.1       | 1.20 (0.52, 2.78)           |                             |
| Stilakakis, 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)          |                             |
| Poppin, 2009      | 0.693            | 0.5   | 7.4        | 2.00 (0.75, 5.53)           |                             |
| Melandar, 2009    | 0.405            | 0.456 | 8.9        | 1.50 (0.61, 3.86)           |                             |
| 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)           |                             |
| Tsany, 2014       | 1.946            | 0.756 | 3.2        | 7.00 (1.59, 30.81)          |                             |
| Contsi, 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)          |                             |
| Chavaro, 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):**

- Logit transformed: 2.69 (2.06, 3.51)
- Heterogeneity: $\chi^2=21.94$, df=17 ($P=0.19$); $I^2=23$
- Test for overall effect: $Z=7.30$ ($P<0.00001$)

#### Complete remission at 12 months

| Study or subgroup | Log (odds ratio) | SE | Weight (%) | Odds ratio IV, random, 95% CI | Odds ratio IV, random, 95% CI |
|------------------|------------------|----|------------|-----------------------------|-----------------------------|
| Stilakakis, 2005  | 0                | 0.632 | 9.8        | 1.00 (0.29, 3.45)           |                             |
| Lindholm, 2008    | 0.015            | 0.753 | 8.2        | 0.13 (0.03, 0.58)           |                             |
| Pepper, 2009      | 0.452            | 0.5   | 11.9       | 0.50 (0.19, 1.33)           |                             |
| Li, 2009          | 0.132            | 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  | 0.07             | 0.5   | 11.9       | 0.25 (0.09, 0.67)           |                             |
| Contsi, 2016      | 0.00             | 0.572 | 10.7       | 0.31 (0.10, 0.94)           |                             |
| Chavaro, 2017     | 0.00             | 0.518 | 11.6       | 0.87 (0.32, 2.41)           |                             |
| Hogan, 2018       | 0.18             | 0.667 | 9.3        | 3.00 (0.81, 11.09)          |                             |

**Total (95% CI):**

- Logit transformed: 0.56 (0.32, 0.98)
- Heterogeneity: $I^2=71.45$; $\chi^2=21.86$, df=8 ($P=0.005$); $I^2=63$
- Test for overall effect: $Z=2.02$ ($P=0.04$)

#### Total remission at 12 months

| Study or subgroup | Log (odds ratio) | SE | Weight (%) | Odds ratio IV, fixed, 95% CI | Odds ratio IV, fixed, 95% CI |
|------------------|------------------|----|------------|-----------------------------|-----------------------------|
| Stilakakis, 2005  | 1.186            | 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)          |                             |
| Contsi, 2016      | 0.118            | 0.486 | 13.7       | 1.13 (0.43, 2.92)           |                             |
| Chavaro, 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):**

- Logit transformed: 2.76 (1.94, 3.93)
- Heterogeneity: $I^2=12.97$, df=8 ($P=0.11$); $I^2=38$
- Test for overall effect: $Z=5.65$ ($P<0.000001$)

**Abbreviation:** LN, lupus nephritis.
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-
The authors report no conflicts of interest in this work.

Disclosure

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Emamikia S, Gentline C, Chatzidionysiou K, Arnaud L, van Vollenhoven R. Relationship between glucocorticoid dose and adverse events in systemic lupus erythematosus: data from a randomized clinical trial. Scand J Rheumatol. 2018;47(2):131–140.

2. Liu Y, Cui Y, Zhang X, et al. Effects of salvianolate on bone metabolism in glucocorticoid-treated lupus-prone b6.Mrl-fas (lpr) mice. Drug Des Devel Ther. 2016;10:2535–2546.

3. He Y-Y, Yan Y, Zhang H-F, et al. Methyl salicylate 2-O-β-D-lactoside alleviates the pathological progression of pristane-induced systemic lupus erythematosus-like disease in mice via suppression of inflammatory response and signal transduction. Drug Des Devel Ther. 2016;10:3183–3196.

4. Gadakchi L, Haji-allilo M, Nakhljavani M-R, et al. Efficacy and safety of mycophenolate mofetil versus intravenous pulse cyclophosphamide as induction therapy in proliferative lupus nephritis. Iran J Kidney Dis. 2018;12(5):288–292.

5. Jorge A, Wallace ZS, Zhang Y, et al. All-Cause and Cause-Specific Mortality Trends of End-Stage Renal Disease Due to Lupus Nephritis from 1995 to 2014. Hoboken, NJ: Arthritis & Rheumatology; 2018.

6. Hahn BH, Mcahoni MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res. 2012;64(6):797–808.

7. Park D-J, Choi S-E, Xu H, et al. Chronicity index, especially glomerular sclerosis, is the most powerful predictor of renal response following immunosuppressive treatment in patients with lupus nephritis. Int J Rheum Dis. 2018;21(2):458–467.

8. Huang W, Quach TD, Dascalu C, et al. Belimumab promotes negative selection of activated autoreactive B cells in systemic lupus erythematosus patients. JCI Insight. 2018;3(17):e122525.

9. Schioppo T, Ingegnoli F. Current perspective on rituximab in rheumatic diseases. Drug Des Devel Ther. 2017;11:2891–2904.

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.
10. Bordron A, Bagacean C, Mohr A, et al. Resistance to complement activation, cell membrane hypersialylation and relapses in chronic lymphocytic leukemia patients treated with rituximab and chemotherapy. Oncotarget. 2018;9(60):31590–31605.

11. Dööszi A, Tarr T, Nagy-Vinceze M, et al. Microthrombotic renal involvement in an SLE patient with concomitant catastrophic antiphospholipid syndrome: the beneficial effect of rituximab treatment. Lupus. 2018;27(9):1552–1558.

12. Chavarot N, Verhelst D, Pardon A, et al. Rituximab alone as induction therapy for membranous lupus nephritis: a multicenter retrospective study. Medicine. 2017;96(27):e7429.

13. Rovin BH, Furie R, Latins K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus nephritis assessment with rituximab study. Arthritis Rheum. 2012;64(4):1215–1226.

14. Dersimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–188.

15. Sílkakis PP, Boletis JN, Lionaki S, et al. Remission of proliferative lupus nephritis following B cell depletion therapy is preceded by down-regulation of the T cell costimulatory molecule CD40 ligand: an open-label trial. Arthritis Rheum. 2005;52(2):501–513.

16. Vigna-Perez M, Hernández-Castro B, Paredes-Saharopoulos O, et al. Clinical and immunological effects of rituximab in patients with lupus nephritis refractory to conventional therapy: a pilot study. Arthritis Res Ther. 2006;8(3):R83.

17. Gunnarsson I, Sundelin B, Jónsdóttir T, et al. Histopathologic and clinical outcome of rituximab treatment in patients with cyclophosphamide-resistant proliferative lupus nephritis. Arthritis Rheum. 2007;56(4):1263–1272.

18. Lindholm C, Börijesson-Asp K, Zendjanchi K, et al. Longterm clinical and immunological effects of anti-CD20 treatment in patients with refractory systemic lupus erythematosus. J Rheumatol. 2008;35(5):826–833.

19. Boletis JN, Marinaki S, Skalioti C, et al. Rituximab and mycophenolate mofetil for relapsing proliferative lupus nephritis: a long-term prospective study. Nephrol Dial Transplant. 2009;24(7):2157–2160.

20. Li EK, Tam LS, Zha TY, et al. Is combination rituximab with cyclophosphamide better than rituximab alone in the treatment of lupus nephritis? Rheumatology. 2009;48(8):892–898.

21. Melander C, Sallee M, Trollet P, et al. Rituximab in severe lupus nephritis: early B-cell depletion affects long-term renal outcome. Clin J Am Soc Nephrol. 2009;4(3):579–587.

22. Pepper R, Griffith M, Kirwan C, et al. Rituximab is an effective treatment for lupus nephritis and allows a reduction in maintenance steroids. Nephrol Dial Transplant. 2009;24(12):3717–3723.

23. Catapano F, Chaudhry AN, Jones RB, et al. Long-term efficacy and safety of rituximab in relapsing and restructuring systemic lupus erythematosus. Nephrol Dial Transplant. 2010;25(11):3586–3592.

24. García-Carrasco M, Mendoza-Pinto C, Sandoval-Cruz M, et al. Anti-CD20 therapy in patients with refractory systemic lupus erythematosus: a longitudinal analysis of 52 Hispanic patients. Lupus. 2010;19(2):213–219.

25. Ramos-Casals M, García-Hernández FJ, de Ramón E, et al. Off-label use of rituximab in 196 patients with severe, refractory systemic autoimmune diseases. Clin Exp Rheumatol. 2010;28(4):468–476.

26. Condon MB, Ashby D, Pepper RJ, et al. Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. Ann Rheum Dis. 2013;72(8):1280–1286.

27. Davies RJ, Sangle SR, Jordan NP, et al. Rituximab in the treatment of resistant lupus nephritis: therapy failure in rapidly progressive crescentic lupus nephritis. Lupus. 2013;22(6):574–582.

28. Jónsdóttir T, Zickert A, Sundelin B, et al. Long-term follow-up in lupus nephritis patients treated with rituximab – clinical and histopathological response. Rheumatology. 2013;52(5):847–855.

29. Tsanay ME, Soloviev SK, Radenska-Lopovok SG, et al. Clinical and morphological improvement of lupus nephritis treated with rituximab. Folia Med. 2014;56(4):245–252.

30. Contis A, Vanquathem H, Truchetet M-E, et al. Analysis of the effectiveness and safety of rituximab in patients with refractory lupus nephritis: a chart review. Clin Rheumatol. 2016;35(2):517–522.

31. Katagiri P, Martin A, Hughes P, Becker G, Nicholls K. Single-dose rituximab in refractory lupus nephritis. Intern Med J. 2016;46(8):899–901.

32. Hogan J, Godron A, Baudouin V, et al. Combination therapy of rituximab and mycophenolate mofetil in childhood lupus nephritis. Pediatr Nephrol. 2018;33(1):111–116.

33. Moroni G, Raffiotta F, Trezzi B, et al. Rituximab vs mycophenolate and vs cyclophosphamide pulses for induction therapy of active lupus nephritis: a clinical observational study. Rheumatology. 2014;53(9):1570–1577.

34. Zhang J, Zhao Z, Hu X. Effect of rituximab on serum levels of anti-C1q and antineutrophil cytoplasmic autoantibodies in refractory severe lupus nephritis. Cell Biochem Biophys. 2015;72(1):197–201.

35. Basu B, Roy B, Babu BG. Efficacy and safety of rituximab in comparison with common induction therapies in pediatric active lupus nephritis. Pediatr Nephrol. 2017;32(6):1013–1021.

36. Goswami RP, Sircar G, Sit H, Ghosh A, Ghosh P. Cyclophosphamide versus mycophenolate versus rituximab in lupus nephritis remission induction: a historical head-to-head comparative study. J Clin Rheumatol. 2019;25(1):28–35.

37. Zhou Y, Xiao L, Tang S. Annexin A2 and FTH1 are potential biomarkers for lupus nephritis. Exp Ther Med. 2018;16(5):3766–3776.

38. Sedbain A, Hada R, Agrawal RK, Bhattachari GR, Baral A. Low dose mycophenolate mofetil versus cyclophosphamide in the induction therapy of lupus nephritis in Nepalese population: a randomized control trial. BMC Nephrol. 2018;19(1):175.

39. Clark MR, Trotter K, Chang A. The pathogenesis and therapeutic implications of tubulointerstitial inflammation in human lupus nephritis. Semin Nephrol. 2015;35(5):455–464.

40. Gomez Mendez LM, Cascino MD, Garg J, et al. Peripheral blood B cell depletion after rituximab and complete response in lupus nephritis. Clin J Am Soc Nephrol. 2018;13(10):CNJ01070118–CNJ01071509.

41. Díaz-Lagares C, Croca S, Sangle S, et al. Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. Autoimmun Rev. 2012;11(5):357–364.

42. Alshaiki F, Obaid E, Almuallim A, et al. Outcomes of rituximab therapy in refractory lupus: a meta-analysis. Eur J Rheumatol. 2018;5(2):118–126.

43. Ahuja A, Teichmann LL, Wang H, et al. An acquired defect in IgG-dependent phagocytosis explains the impairment in antibody-mediated cellular depletion in lupus. J Immunol. 2011;187(7):3888–3894.

44. Md Yusof MY, Shaw D, El-Sherbiny YM, et al. Predicting and managing primary and secondary non-response to rituximab using B-cell biomarkers in systemic lupus erythematosus. Ann Rheum Dis. 2017;76(11):1829–1836.

45. Roccotello D, Sciascia S, Baldovino S, et al. A 4-year observation in lupus nephritis patients treated with an intensified B-lymphocyte depletion without immunosuppressive maintenance treatment—Clinical response compared to literature and immunological re-assessment. Autoimmun Rev. 2015;14(12):1123–1130.

46. Sjöwall C, Bentow C, Aure MA, Mahler M. Two-Parametric immunological score development for assessing renal involvement and disease activity in systemic lupus erythematosus. J Immunol Res. 2018;2018(2):1–9.

47. Fulgeri C, Carpio JD, Ardiles L. Kidney injury in systemic lupus erythematosus: lack of correlation between clinical and histological data. Nefrologia. 2018;38(4):386–393.

48. Shidham G, Ayoub I, Birmingham D, et al. Limited reliability of the spot urine Protein/Creatinine ratio in the longitudinal evaluation of patients with lupus nephritis. Kidney Int Rep. 2018;3(5):1057–1063.
