







Outcomes of rituximab therapy in refractory lupus: A meta-analysis

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Abstract

Objective: Conventional treatment of systemic lupus erythematosus (SLE) and lupus nephritis (LN) is associated with damage accrual, hence increased morbidity rate. Off-label use of rituximab (RTX) has shown significant promise in this patient group; however, data are still controversial. We aimed to analyze the outcomes of RTX therapy in refractory lupus using a meta-analysis approach.

Methods: Electronic search of the medical literature was conducted using a combination of relevant keywords to retrieve studies on the safety and efficacy of RTX in SLE and LN patients. Results were screened against our inclusion and exclusion criteria and two reviewers independently extracted the data for analysis. Comprehensive meta-analysis software was used to pool the data from individual studies and provide summary effect estimates.

Results: Thirty-one studies that enrolled 1112 patients were finally eligible for the meta-analysis. The overall global, complete, and partial response rates to RTX therapy were 72%, 46%, and 32%, respectively. RTX significantly decreased Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and British Isles Lupus Activity Group (BILAG) scores ($p < 0.001$). Prednisone dose was significantly reduced after RTX treatment in both SLE and LN groups ($p < 0.001$), and proteinuria was lowered in SLE ($p < 0.001$) than in LN patients ($p = 0.07$). Infection and infusion-related reactions were the most common side effects.

Conclusion: RTX therapy in refractory SLE and LN patients proved clinical efficacy and favorable safety outcomes. Larger well-designed randomized clinical trials are warranted.

Keywords: Systemic lupus erythematosus; lupus nephritis; rituximab (RTX); B-cell depletion therapy



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Introduction

Systemic lupus erythematosus (SLE) is defined as a systemic autoimmune disorder of idiopathic occurrence. The primary pathogenesis is the overproduction of organ-specific antibodies targeting nuclear antigens, which massively develop immune complex depositions in multiple organs, leading to inflammation and tissue damage (1). One of the major complications and the most common mortality-leading cause, in more than 75% of SLE cases, is lupus nephritis (LN), which causes proteinuria and may progress to end-stage renal failure (2, 3).

Corticosteroids in conjunction with cyclophosphamide or mycophenolate mofetil are the current standard treatment for LN, as they have relatively shown a short-term improvement in disease prognosis (4, 5). Yet, LN resistance to the standard treatment develops rapidly, and the renal response rates at first year reach 50%-80% and then it fails to control the relapse (6, 7). In addition to the toxicity and the fatal infections rising from prolonged use of immunosuppressive agents, the demand for a less toxic, more effective, and fertility-sparing treatment is critical.

Recently, a new medication has been introduced targeting a new member of the immune system, the B cell, usually uncommon to be implicated in autoimmunity (8). However, B lymphocytes are believed to play a principal role in the pathogenesis of SLE, either directly by the production of organ-specific antibodies and cytokines or indirectly by antigen-presenting activity (9). A suggestive chimeric anti-CD20 monoclonal antibody, rituximab (RTX), has been found to suppress immune response with a better efficacy and less toxicity than the standard treatment (10-19). RTX has firstly been approved as a treatment of B-cell lymphomas and then afterward for rheumatoid arthritis and antineutrophil cytoplasmic antibody (ANCA)-asso-

ciated vasculitis (20, 21). Recently, clinical trials suggest RTX as a more effective treatment for LN. Nevertheless, its effectiveness is still controversial among studies (22-25), which either demonstrate a trending superiority or noninferiority compared to conventional treatment. In this systematic review and meta-analysis, we aimed to identify and review clinical trials and observational studies that investigated the effectiveness and safety of rituximab in patients with refractory lupus by analyzing the results from individual studies to create a class one clear evidence.

Methods

Data sources and search terms

Search strategy was designed to identify the full length of publications reporting outcomes of RTX treatment in refractory SLE, refractory LN, or refractory neuropsychiatric SLE (NPSLE) patients. PubMed was searched using Medical subheading (MeSH) using the terms "Rituximab" and "Lupus erythematosus, systemic." As per this method, RTX is defined as "a murine-derived monoclonal antibody and antineoplastic agent that binds specifically to the CD20 antigen and is used in the treatment of leukemia, lymphoma, and rheumatoid arthritis" with entry terms: CD20 Antibody, Rituximab; Antibody, Rituximab CD20; Rituximab CD20 Antibody; Mabthera; IDEC-C2B8 Antibody; IDEC C2B8 Antibody; IDECC2B8 Antibody; IDEC-C2B8; IDEC C2B8; IDECC2B8; GP2013; or Rituxan. Lupus erythematosus, systemic is defined as "a chronic, relapsing, inflammatory, and often febrile multisystemic disorder of connective tissue, characterized principally by involvement of the skin, joints, kidneys, and serosal membranes; with unknown etiology, but thought to represent a failure of the regulatory mechanisms of the autoimmune system; marked by a wide range of system dysfunctions, an elevated erythrocyte sedimentation rate, and the formation of LE cells in the blood or bone marrow." The entry terms for SLE were: Systemic Lupus Erythematosus; Lupus Erythematosus Disseminatus; Libman-Sacks Disease; Disease, Libman-Sacks; or Libman Sacks Disease. This MeSH term also included the keywords Lupus Nephritis and Lupus Vasculitis and Central Nervous System. Hence, there was no need for a separate search for LN and NPSLE. Similarly, EMBASE search was conducted using a combination of SLE and rituximab Emtree terms. Filters were applied to select only English language publications reported on human subjects. Reference lists of the reviews and research articles were manually screened to identify further articles.

Inclusion criteria-retrospective/prospective case series or controlled trials reporting the outcomes of RTX therapy in at least 10 SLE/LN/NPSLE patients' refractory to traditional therapy. It was also mandatory that the studies reported the score used for measuring the clinical outcomes [SLEDAI (Systemic Lupus Erythematosus Disease Activity Index), BILAG (British Isles Lupus Activity Group), Renal Outcomes].

Exclusion criteria-abstracts, conference proceedings, posters, case reports, reviews, editorials, and non-English publications were excluded. Studies with mixed cohorts or providing insufficient details were not eligible.

Ethics approval was obtained for this study from the institutional review board at college of medicine, Umm Al-Qura University. Disagreements between authors were solved by discussion. Authors of this paper claim no conflict of interest.

Study selection

Duplicate articles were identified and removed. The titles and abstracts of the remaining articles were reviewed by two independent investigators, who were responsible for determining whether the articles were eligible to be included in the study. To address any inconsistencies, the investigators compared lists before they reviewed the full text of the studies identified as eligible. When the final list of articles was complete, a third investigator resolved final discrepancies.

Data extraction and meta-analysis

A standardized custom excel sheet was used to extract all the relevant and specific data on study, patient, intervention, and outcome characteristics. These data were extracted independently by two investigators and compared with resolve discrepancies.

The primary objective was to measure the number of patients showing global response, complete response, and partial response after RTX therapy. The secondary objective was to estimate the change in BILAG or SLEDAI score, proteinuria, and prednisone dose after therapy. Articles qualifying for more than one variable of interest were considered as different data points for each of the variable.

Two meta-analysis models were constructed

Model 1: Pooled estimation of global, complete, and partial response of the patients to RTX therapy.

Model 2: Mean change with statistical significance of SLEDAI/BILAG score, proteinuria, and prednisone dose after RTX therapy.

Publication bias was visualized through funnel plots and quantified with the Egger's test. A qualitative estimate of statistical heterogeneity between studies was assessed using Cochrane Q. For the chi-square test, $p < 0.05$ was considered statistically significant. In the presence of significance heterogeneity, I² statistic was used to quantify the level of heterogeneity. I² was interpreted on the basis of

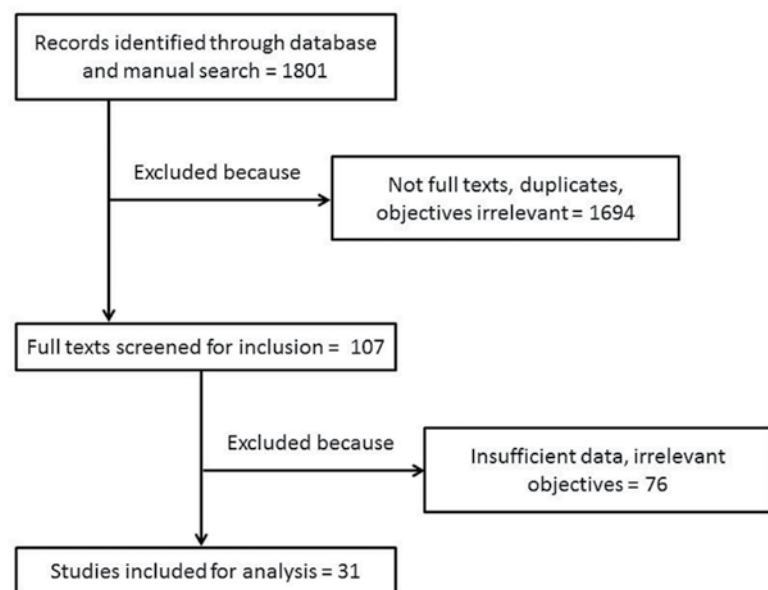


Figure 1. PRISMA flow diagram of study selection for meta-analysis

Higgins and Thompson criteria, where 25%, 50%, and 75% correspond, respectively, to low, medium, and high heterogeneity (26). Statistical heterogeneity, forest plot, publication bias, and sensitivity analysis were conducted with Comprehensive Meta-analysis (CMA software) version 3. To accommodate between study heterogeneity, the Dersimorian and Laird random-effects model was used for all of the meta-analysis models (27). Effect size was represented with mean difference (28), which directly reflects the actual difference between the interventions, in all included studies.

Results

Search results

The databases and manual search retrieved 1801 journal articles. Title and abstract of all these articles were screened to eliminate 1694 studies that were duplicates, non-English, meeting abstracts or studied different objectives. In the next phase, 107 article full texts were obtained and screened. Seventy-six of these articles had to be further excluded, as these provided incomplete data or

had irrelevant objectives and were unsuitable for meta-analysis. Remaining 31 articles were included for meta-analysis (10-19, 29-49). Flowchart of the studies evaluated is represented in Figure 1.

Characteristics of included studies

The included studies consisted of 22 studies that investigated RTX therapy in 866 refractory SLE patients, 10 studies that enrolled 223 refractory LN patients, and one study with 10 NPSLE cases. Sixteen of the eligible studies were retrospective case series, 14 were prospective case series, and two studies were randomized controlled trials. The studies were conducted between 2005 and 2016, and the mean follow-up period was 10.6 months and ranged from 3 to 38 months. The dose of RTX varied among different studies; some investigators used 375 mg/m² q.i.d., whereas others used 500 mg b.i.d. or 1000 mg b.i.d., 2 weeks apart. Doses of 500 mg q.i.d., 375 mg/m² b.i.d or q.d., and 750 mg b.i.d. were also infused in other cohorts. Contis et al. used a dose of 375 mg/m² weekly for 4 weeks or 1 g at day zero and day 15 every 6 months.

Diverse array of adverse events was observed in the included patients. The most common adverse reactions were infection (urinary or respiratory), acute or delayed infusion reactions, sepsis-like syndrome, thrombocytopenia, and serum sickness-like reaction. One patient died from varicella pneumonia, another died from septicemia, and one case caught MRSA. Baseline characteristics of the included studies are summarized in Table 1, and a summary of these findings is shown in Table 2.

Meta-analysis results

Global response

Global response to RTX was reported by three studies that enrolled 57 LN patients and four studies with 206 SLE patients. There was low heterogeneity among these studies (I²=44%, p=0.1). The pooled proportion of global response among LN and SLE patients was 70% (95% CI, 55%-81%) and 73% (95% CI, 67%-78%), respectively, and the overall pooled percent was 72% (95% CI, 67%-78%) (Figure 2).

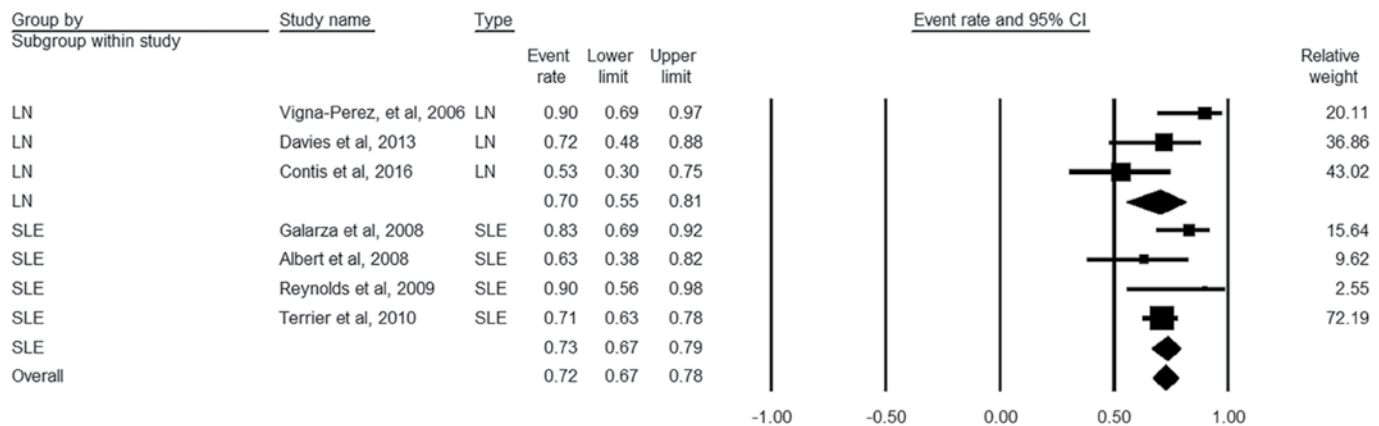


Figure 1. PRISMA flow diagram of study selection for meta-analysis

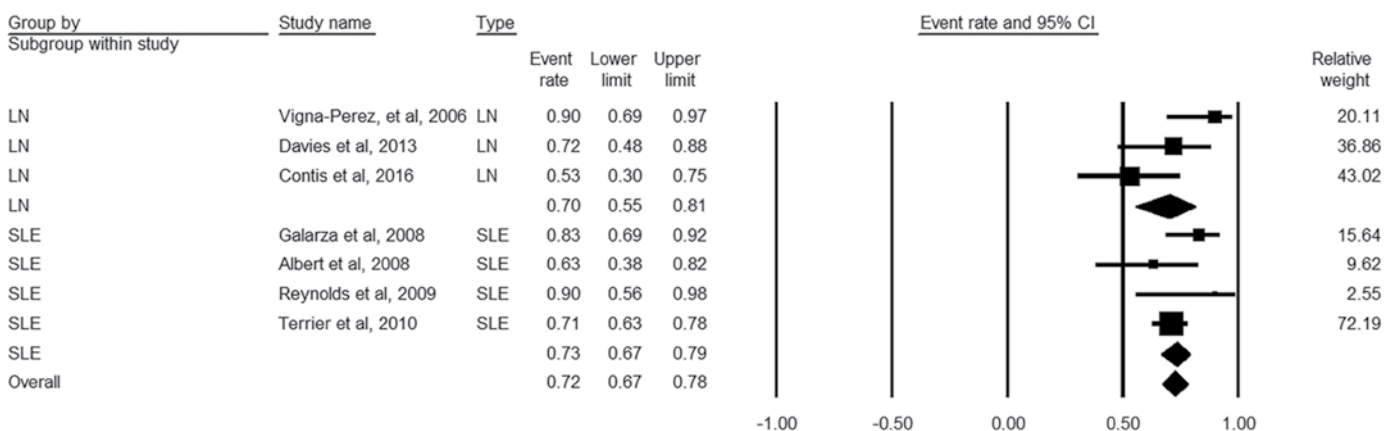


Figure 2. Forest plot of global response rate of LN and SLE patients to rituximab therapy

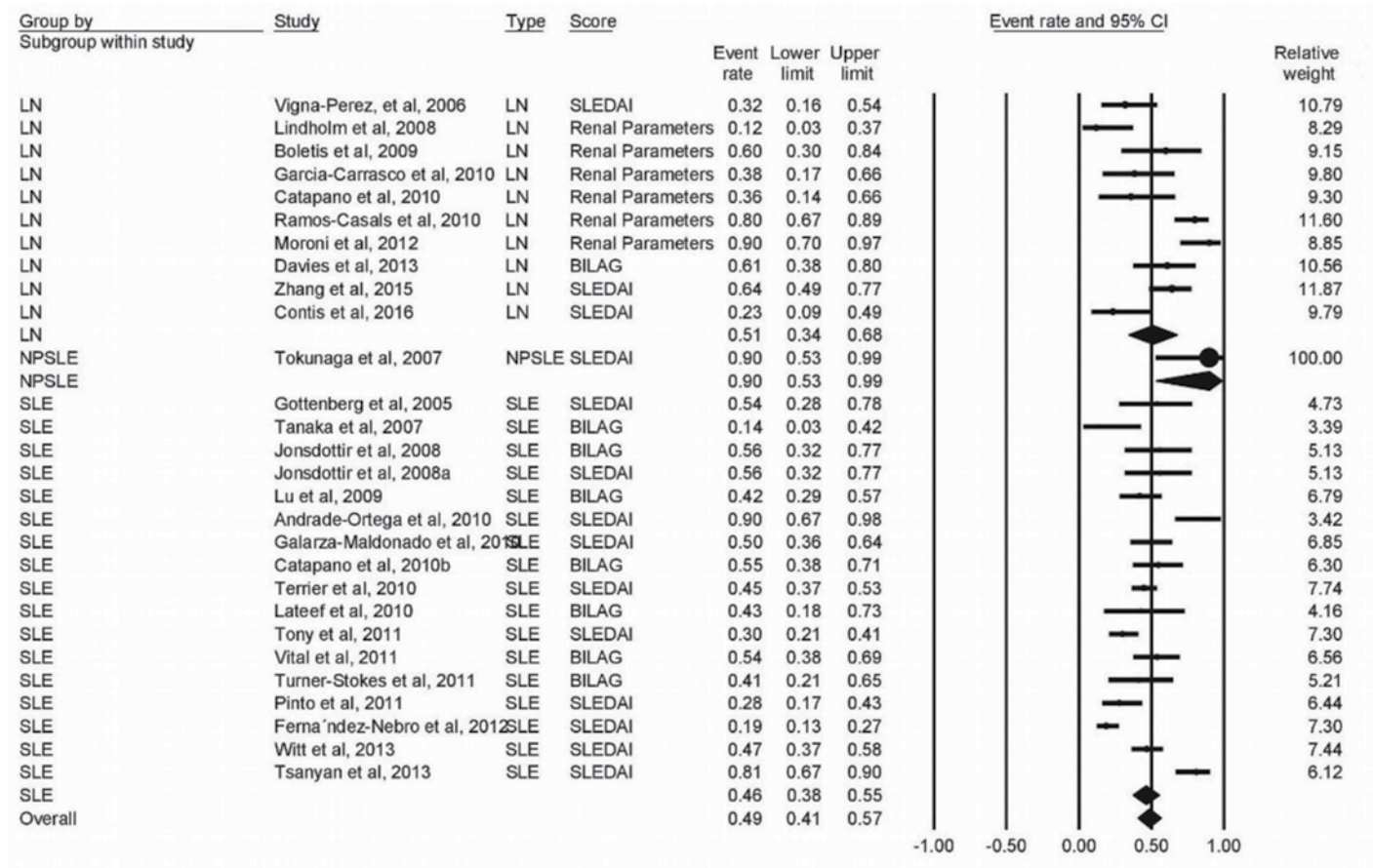


Figure 3. Forest plot of complete response rate of LN, NPSLE, and SLE patients to rituximab therapy

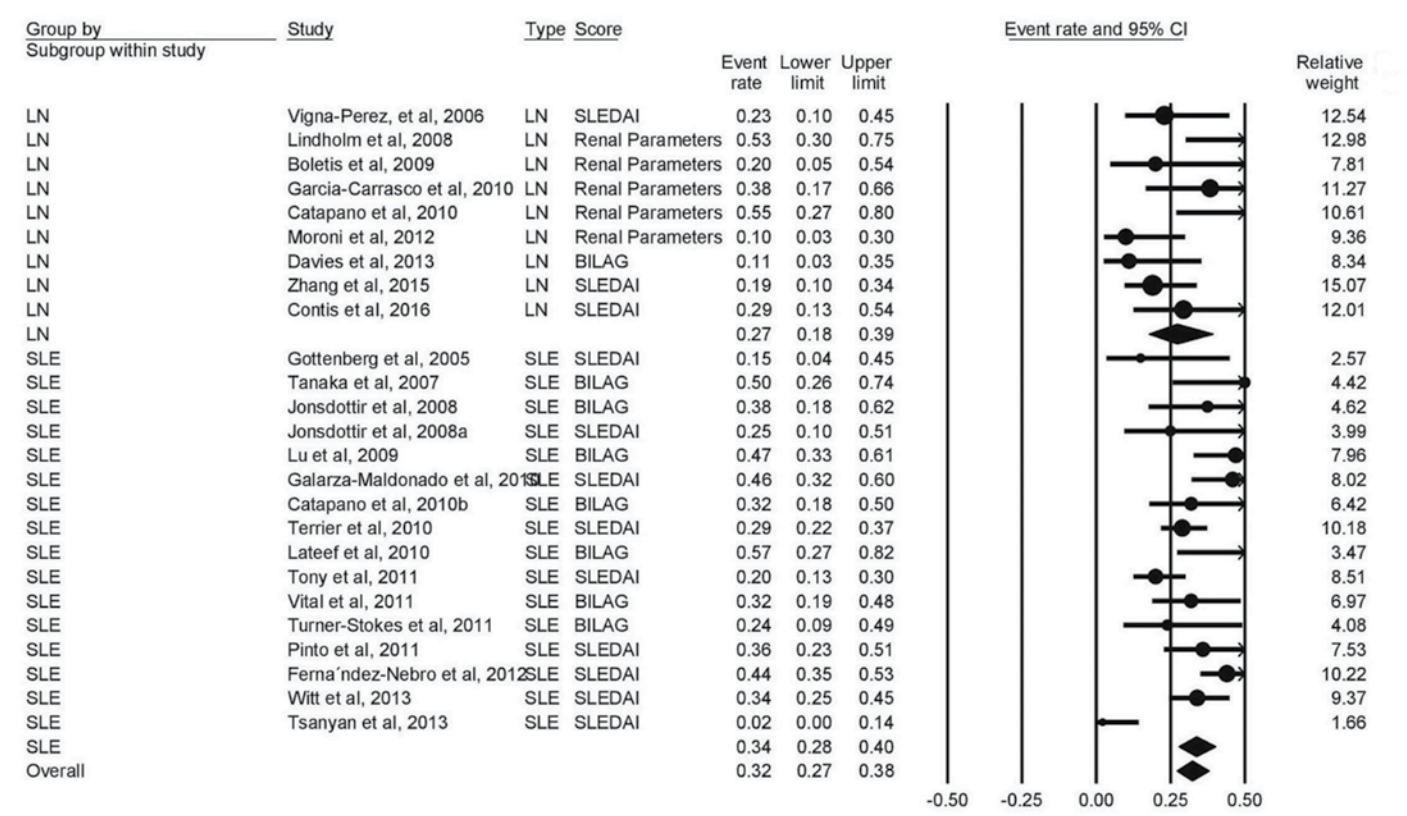


Figure 4. Forest plot of partial response rate of LN, NPSLE, and SLE patients to rituximab therapy

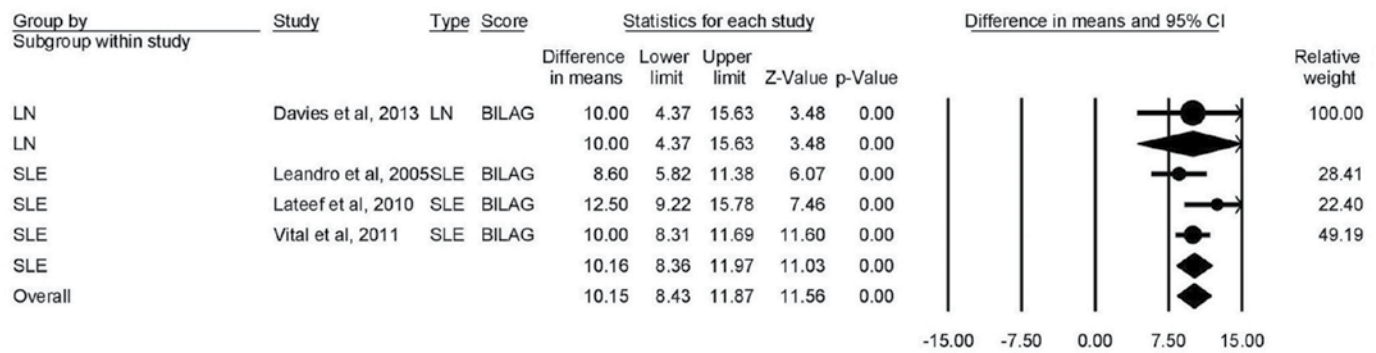


Figure 5. Forest plot of effect of rituximab therapy on BILAG score in LN and SLE patients

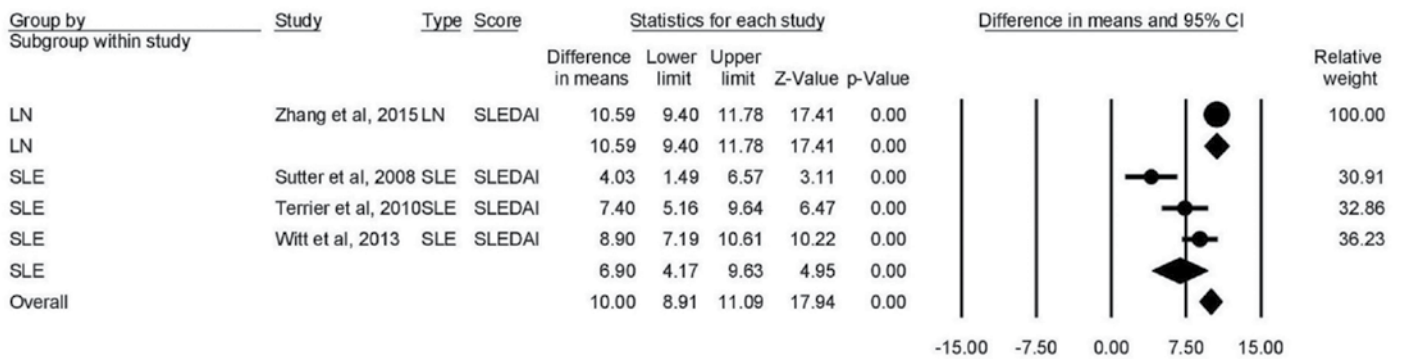


Figure 6. Forest plot of effect of rituximab therapy on SLEDAI score in LN and SLE patients

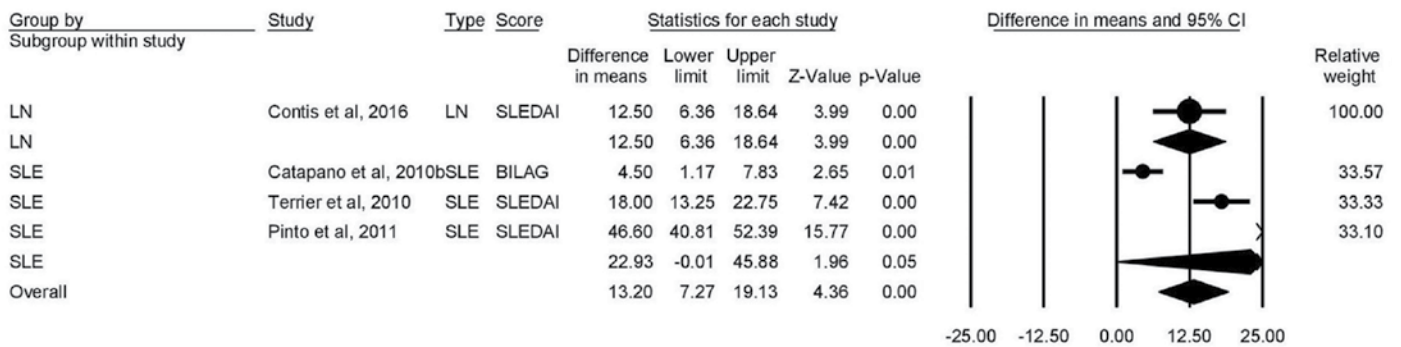


Figure 7. Forest plot of effect of rituximab therapy on prednisone dose in LN and SLE patients

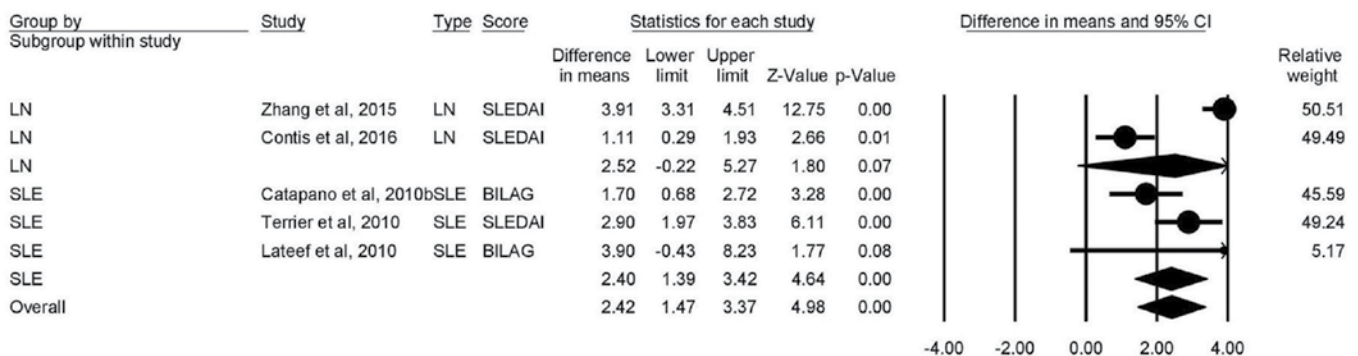


Figure 8. Forest plot of effect of rituximab therapy on proteinuria dose in LN and SLE patients

Complete response

Twenty-eight studies provided data on complete remission; of them, 17 studies (n=773 patients) were on SLE, 10 (n=223 patients) on LN, and one study enrolled 10 patients with NPSLE. The pooled proportion for complete response was 51% (95% CI, 34% to 68%) in LN patients, 90% (95% CI, 53% to 99%) in NPSLE patients, and 46% (95% CI, 38% to 55%) in SLE patients, with overall response rate of 49% (95% CI, 41% to 57%). There was significant heterogeneity among these studies ($I^2=80%$, $p<0.001$) (Figure 3).

Partial response

Partial response to RTX was reported by 25 studies (9 on LN and 16 on SLE) that enrolled 928 patients. Moderate heterogeneity was found among the studies ($I^2=57%$, $p<0.001$). The pooled proportion of patients with partial response to RTX was 27% (95% CI, 18%-39%) and 34% (95% CI, 28%-40%) for LN and SLE, with overall partial response rate of 32% (95% CI, 27%-38%) (Figure 4).

Change in BILAG score

Four studies provided data of BILAG score change from baseline. There was marked heterogeneity among these studies ($I^2=75%$, $p<0.001$). The BILAG score was significantly reduced in both LN (mean difference=-10; 95% CI [-4.37 to -15.63; $p<0.001$]) and SLE (mean difference=-10.16; 95% CI [-8.36 to -11.97; $p<0.001$]) patients after RTX therapy. The overall score was also significantly lowered (mean difference=-10.15; 95% CI [-8.43 to -11.87; $p<0.001$]) (Figure 5).

Change in SLEDAI score

The change in SLEDAI score was reported by four heterogeneous studies ($I^2=87%$, $p<0.001$). SLEDAI score significantly decreased in both LN (mean difference=-10.59; 95% CI [-9.40 to -11.78]; $p<0.001$) and SLE (mean difference=-6.90; 95% CI [-4.17 to -9.63]; $p<0.001$) patients after RTX therapy. The overall score was also significantly lowered (mean difference=-10; 95% CI [-8.91 to -11.09]; $p<0.001$) (Figure 6).

Change in prednisone dose

Five heterogeneous studies provided data on the change from baseline in prednisone dose. The pooled mean difference showed that prednisone dose (mg/d) was significantly decreased in both LN (mean difference=-12.50; 95% CI [-6.36 to -18.64]; $p<0.001$) and SLE (mean difference=-22.93; 95% CI [-0.01 to -45.88]; $p<0.001$) patients after RTX therapy. The overall score was also significantly lowered (mean difference=-13.20; 95% CI [-7.27 to -19.13]; $p<0.001$) (Figure 7).

Change in proteinuria

Four studies reported on the change of proteinuria. Proteinuria (g/d) was insignificantly decreased in LN patients (mean difference=-2.52; 95% CI [0.22 to -5.27]; $p=0.07$). The decline in proteinuria was significant in SLE patients (mean difference=-2.40; 95% CI [-1.39 to -3.42]; $p<0.001$). The overall score was significantly lowered (mean difference=-2.42; 95% CI [-1.47 to -3.37]; $p<0.001$) (Figure 8).

Discussion

Survival of SLE and LN patients has been markedly improved over the past 50 years mainly due to the use of glucocorticoids and other immunosuppressive agents as well as the introduction of renal dialysis and renal transplant (50). Nevertheless, the accumulation of damage caused by corticosteroid therapy increased morbidity rate among these patients (51). As a result, efforts have been directed to corticosteroid alternatives that can induce and maintain disease remission, attenuate cumulative damage, and improve overall outcomes. These goals have proven particularly challenging for SLE treatment (52).

Rituximab remains a common off-label prescription for the treatment of SLE despite the conflicting evidence from clinical studies (47, 53-56). Thereby, we aimed to generate a robust evidence on the clinical efficacy of RTX in SLE and LN patients, refractory to conventional treatment. Our findings suggest a potential therapeutic efficacy of RTX in both SLE and LN patients. RTX achieved up to 73% global response rate, 51% complete remission, and 34% partial remission in SLE and LN patients. Moreover, it significantly decreased BILAG and SLEDAI scores as well as proteinuria. Additionally, RTX showed a significant corticosteroid sparing effect through marked reduction of prednisone dose in both SLE and LN patients. These effects are consistent with evidence from recent clinical trials (57).

Rituximab displayed promising effects in cases of NPSLE through rapid improvement of cognitive dysfunction, psychosis, and seizures. NPSLE patients on RTX had long-lasting significant reduction of SLEDAI. However, these effects were shown in one study with 10 included patients, so further assessment of the role of RTX in NPSLE in larger studies is warranted.

In terms of adverse reactions, RTX was well tolerated by most of the patients enrolled in the included studies. The most common adverse reactions were infections, acute or delayed infusion reactions, and thrombocytopenia (29, 39, 40, 44, 46, 49). Sepsis-like

syndrome and serum sickness-like reaction occasionally occurred in three patients overall (14, 29, 36).

Although not yet authorized for the treatment of SLE and LN, RTX is widely used in these patient groups. Data from Ryden-Aulin et al. (58) study about the off-label use of RTX for SLE in Europe showed that RTX is used in 4% to 20% of SLE patients in Sweden, up to 11% in Spain, and 7% in the U.K. Moreover, adoption of RTX for management of SLE ranged from 1% to 4% in other European countries. The off-label use of RTX in SLE is enabled by its favorable safety profile and the documented benefit that led to its approval by the FDA and the European Medicines Agency for the treatment of rheumatoid arthritis and ANCA-associated vasculitis (20, 21). Clinicians have high expectations for RTX therapy owing to the favorable data from clinical practice and observational studies as well as some promising exploratory outcomes from LUNAR trial, such as potential advantage in African Americans (6, 8, 15, 59). Furthermore, off-label use of RTX is supported by the EULAR and ACR guidelines, which included it as one of the treatment options for patients with refractory LN (60).

B lymphocytes are documented to play a major role in the pathogenesis of SLE (61). Thus, B-cell depletion therapy has gained much interest for management of SLE and LN. RTX is a chimeric monoclonal antibody that binds to its target antigen, CD20, and induces B-cell depletion. CD20 is expressed exclusively on B lymphocytes but not on plasma cells; therefore, treatment with RTX would directly target only CD20+ B cells (62). Isenberg et al. (66) have led the early studies on B-cell depletion therapy with RTX for lupus treatment (50, 63). The first trial of RTX in SLE patients with active disease reported promising clinical efficacy and favorable safety profile (64). This was followed by wide adoption of RTX in clinical practice, and many case reports were published indicating its utility (41, 53). However, unexpectedly, RTX did not meet the primary endpoints in two large trials of non-renal (EXPLORER) and renal (LUNAR) SLE (59, 65). These trials had been later criticized for their poor design, particularly concomitant administration of high doses of corticosteroids, which may have concealed the clinical response attributable to RTX (54, 62, 66, 67).

The establishment of RTX B-cell depletion therapy in SLE by clinical trials has confronted several hurdles including the heterogeneity of the disease and the beneficial effects of background therapy that might mask the added

value of short-term RTX treatment (61). Small study size, lack of robust design, and short-term follow-up are further limitations of RTX clinical trials. These “missing pieces in the jigsaw” call for further large well-designed trials with longer follow-up periods given that the data from a long-term follow-up study by Moroni et al. showed promising complete remission after 2 years of follow-up in a significant number of patients (68).

Rituximab can also be used in several hematologic presentations of SLE-like autoimmune hemolytic anemia, immune-mediated thrombocytopenia, macrophage activation syndrome, antiphospholipid syndromes, and other conditions that can be refractory to conventional therapy (69-78). RTX has shown promising results with significant clinical improvement and normalized laboratory parameters. However, all these studies did not qualify inclusion in our analysis due to small sample size.

Our study possesses some limitations. First, there was some heterogeneity in the dose and regimen of RTX in the pooled studies. Second, data were pooled from studies that used different scores (BILAG, SLEDAI, and renal parameters) for the assessment of global complete and partial responses. Finally, some outcomes were provided by few studies (e.g., BILAG and SLEDAI scores in LN patients were reported by one study each).

To recapitulate, our findings demonstrate that RTX treatment achieved significant clinical efficacy and favorable safety profile in SLE and LN patients refractory to conventional treatment. Further large well-designed multicenter randomized controlled trials are warranted to the end of approval of RTX as a standard therapy for lupus.

Ethics Committee Approval: Ethics committee approval was received for this study from the institutional review board at Umm Al-Qura University School of Medicine.

Peer-review: Externally peer-reviewed.

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