Systematic Review and Meta-Analysis

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Efficacy and safety of rituximab in the treatment of membranous nephropathy

A systematic review and meta-analysis

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Abstract

Background and objectives: Rituximab (RTX) is considered to be a promising drug for curing membranous nephropathy. However, the efficacy and safety of RTX in treating membranous nephropathy remain uncertain. This meta-analysis aimed to investigate the efficacy and safety of RTX in patients with membranous nephropathy.

Methods: A literature search was performed using Pubmed, Embase, OVID, and Cochrane Library and randomized controlled trials (RCTs) case-controls and cohort studies published till 30 July 2019 were assessed. The studies assessing the efficacy and safety of RTX in patients with membranous nephropathy were included.

Results: Eight relevant trials involving 542 patients were included in the meta-analysis. It was found that RTX did not significantly improve serum albumin levels and e-GFR when compared with the control group (including cyclosporine and cyclophosphamide, chlorambucil, prednisone, non-immunosuppressive anti-proteinuria treatment), serum albumin levels (OR = 0.31, 95%CI–0.12–0.74, $P = .15$), e-GFR (OR = –1.49, 95%CI–17.14–14.17, $P = .85$). However, RTX did reduce the serum creatinine (OR = –0.01, 95%CI–0.36–0.34, $P = .95$) and urinary protein (OR = –2.39, 95%CI –7.30 –2.53, $P = .34$) levels. Also, in comparison to the control group, RTX did improve the total remission rate (OR = 1.63, 95%CI 0.48–5.54, $P = .43$), achieve a higher rate of complete remission (OR = 2.54, 95%CI 1.65–3.90, $P < .01$) and also reduced the amount of M-type phospholipase A2 receptor-Antibody depletion in patients (OR = 5.59, 95%CI 1.81–17.2, $P = .003$). RTX-related adverse events were mostly mild (most infusion-related reactions) in nature and serious adverse events were rare.

Conclusion: RTX proved to be efficient, well-tolerated and a safe drug in the treatment of membranous nephropathy. Most patients reach complete remission during the follow-up period, and relapse is rare. RTX may turn out to be promising in membranous nephropathy patients.

Abbreviations: ESRD = end-stage renal disease, PLA2R = M-type phospholipase A2 receptor, RTX = rituximab, SCr = serum creatinine.

Keywords: efficacy, membranous nephropathy, meta-analysis, rituximab, safety, therapy

1. Introduction

Membranous nephropathy (MN) is one of the leading causes of nephrotic syndrome in adults[1–4] (about 25% cases) and accounts for nearly 40% of glomerulopathy recurring after kidney transplant.[5,6] MN is characterized by an accumulation of immune deposits (mostly IgG and the complement protein C3) on the outer aspect of the glomerular basement membrane, causing a membrane-like thickening.[7] Previous studies have reported that 5% to 30% and 40% of patients progressed to end-stage renal disease (ESRD) within 5 to 15 years of chronic kidney disease.[8,9] In 2009, Beck and coworkers first reported that the major pathogenic antibody of idiopathy membranous nephropathy targets M-type phospholipase A2 receptor (PLA2R). Approximately 70% to 80% of the patients have circulating antibodies against PLA2R, a cell surface transmembrane receptor, expressed on the surface of podocytes. In patients with circulating anti-PLA2R antibodies, there is a definite connection between levels and treatment resistance, disease activity and outcomes.[10–12] Optimum treatment of MN is both controversial and challenging. Immunosuppressive symptomatic treatment is recommended as the first-line therapy for patients with MN nowadays, which includes cyclophosphamide or cyclosporine along with corticosteroids. However, these therapeutic regimens pose inherent problems since they are not effective in all patients, commonly exhibit partial rather than complete remissions, present worrisome adverse effects, and may relapse after the termination of the treatment. Rituximab (RTX) is a B-cell depleting anti-CD20 chimeric monoclonal antibody with a chimeric human/mouse immunoglobulin IgG1 monoclonal

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]

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antibody, binding specifically to the CD20 antigen present on the surface of normal and neoplastic B lymphocytes.[13,14]

RTX was first developed for the treatment of B-cell non-Hodgkin's lymphoma.[15] Now, it is used in the treatment of a variety of autoimmune diseases, such as granulomatosis with polyangiitis, rheumatoid arthritis,[16] microscopic polyangiitis[17] etc. Several studies have shown that RTX represents a new therapeutic hope for the treatment of MN in improving remission.[10,18] However, the efficacy and safety of RTX in this disease is still uncertain. The authors thereby performed a systematic review of all studies examining the efficacy and safety of RTX therapy in patients with MN.

2. Material and methods

The data analyzed were derived from previously published studies. Therefore, no ethical approval or patient consent was required.

2.1. Literature and review

Two independent reviewers performed the literature search in PubMed, Embase, OVID, and Cochrane Library databases to seek articles published until July 30, 2019. A total of 8 relevant studies that met all the eligibility criteria were obtained. RCTs, case-controls, and cohort studies evaluating the efficacy and safety of RTX in treating adult patients with MN were included. There was no restriction on the language of the articles. The keywords that were used to search the databases included "rituximab", "anti-CD20 monoclonal antibodies", "membranous nephropathy", "membranous glomerulonephritis" and "meta-analysis". Additional relevant studies were also identified on manual searching, although the search was limited to articles published in the English language.

2.2. Criteria for inclusion and exclusion

The inclusion criteria were as follows:

(1) randomized controlled trials, cohort studies, or case-control studies.
(2) i: studies focused on patients with proven MN based on biopsy reports; ii: patients over 18 years of age; iii: proteinuria of more than 5 g per 24 hours on average in two 24-hour urine samples for more than 3 months despite treatment with an Angiotensin-Converting Enzyme inhibitors or angiotensin receptor antagonist; iv: patients who completed at least 6 months follow up; v: meta-analyses including MN patients with untreated, relapsed, and refractory MN with complete remission, incomplete remission, or partial remission after administration of induced immunosuppressive agents.
(3) The studies that were published as full-length articles in English, available data that could be extracted from the article or obtained by calculation.

Any ongoing studies, non-randomized studies (including review articles, case reports, comments, meeting abstracts, editorials, etc), and studies with 10 or fewer study participants were excluded. Also, if the study population included children or pregnant patients, it was excluded. Those studies in which the data were not sufficient to fulfill the requirements of the meta-analysis were also excluded.

2.3. Data extraction and quality assessment

Data extraction was carried out using a standardized form and from each study, the following data were collected: the first author's name, publication year, study design, number of patients, sex, age, the follow up, the treatment methods and interventions (mainly RTX, dose, and usage). In addition, the serious side effects from each of the included papers were also retrieved. The quality of each study was assessed according to Cochrane Collaboration's "Risk of bias",[19] which included 6 main categories:

(1) random sequence generation;
(2) allocation concealment;
(3) blinding of participants and personnel, blinding of outcome assessment;
(4) incomplete outcome data;
(5) selective reporting;
(6) other bias.

Studies that had a high, low or unclear risk of bias for any of these 6 components were classified as high or low quality.

2.4. Statistical analysis

The extracted information was analyzed using RevMan software (version 5.3, The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). For relapse-free survival, the analysis was carried out using the odds ratio (OR), risk difference (RD) and its 95% confidence interval (CI). The meta-analysis was performed using fixed-effect or random-effect methods. Heterogeneity of the trial results was assessed by performing a chi-square test of heterogeneity and the I^2 measure of inconsistency. All statistical tests had a significant value of P ($P < .05$) during the evaluation.

3. Results

3.1. Description of included trials

The literature search identified 1398 articles, of which 983 were from PubMed, 299 from Embase, 19 from Cochrane Library, and 97 from OVID. Using Endnote software, 96 repetitive studies were removed. After the titles and abstracts of these researchers were filtered for potentially relevant articles, 1111 publications were excluded following the selection criteria. Of these, 191 were acquired in full-text form and 8 studies were found appropriate for inclusion in this meta-analysis (Fig. 1). The studies that were covered provided information on a total of 542 patients. The baseline characteristics of the included studies are summarized in Table 1.[7,20–26]

3.2. Quality assessment

The quality of included studies was assessed according to the Cochrane Handbook (Fig. 2), where most of the items were found to be at "low risk" based on the Cochrane Handbook, indicating that these studies are of good quality.

3.3. Efficacy of RTX in adults with MN

3.3.1. Relapse-free survival. One study reported that the median relapse-free survival rate was similar in the 2 groups ($P = 1.00$). A random-effect model was used and the results are outlined in Figure 3.

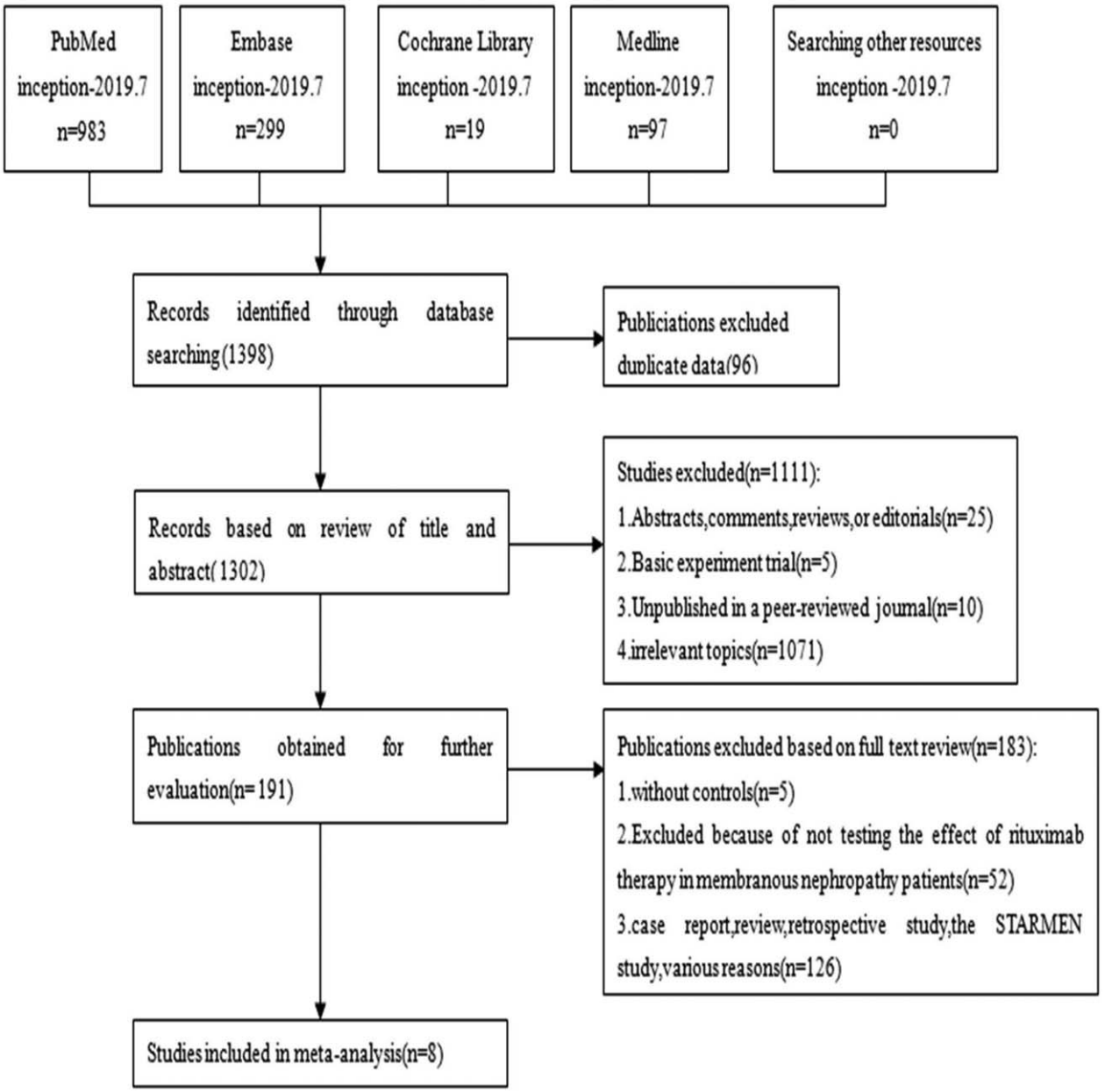

Figure 1. Flowchart of the selection process.

3.3.2. Total remission rate and complete remission rate. The total remission rate (TR) was reported in 7 studies. Pooled data from these 7 studies indicated that RTX treatment seemed to have higher TR (OR = 1.63, 95%CI 0.48 to 5.54; I^2 of 86% indicating heterogeneity, $P = .43$) (Fig. 4). Similarly, data from these 7 studies reported that the complete remission rate (CR) favored RTX group over the control group, with a statistically significant difference (H = 2.54; 95%CI = 1.65 to 3.90; I^2 of 31% indicating no heterogeneity; $P < .01$), as shown in Figure 5.

3.3.3. Biochemical indicators. Proteinuria (g/24 hour). Three studies reported 24-hour urinary protein at the end of treatment. When compared to RTX group and control group, RTX treatment had proteinuria levels of 2.39 g/day (MD = –2.39; 95%CI = –7.30 to 2.53; I^2 of 94% indicating heterogeneity; $P = .34$). The results are depicted in Figure 6.

3.3.4. Serum albumin (g/L). Five studies evaluated the serum albumin index after treatment. Pooled analysis of the data revealed that there was no significant difference between the 2 groups (MD = 0.31 g/dL, 95%CI = –0.12 to 0.74), with heterogeneity among these studies ($I^2 = 88\%$, $P = .15$) (Fig. 7).

3.3.5. Serum creatinine (mg/dL). Five studies assessed serum creatinine (SCr) in a total of 183 patients, 82 of whom were assigned to treatment groups and 101 to control groups. Because

Table 1

Characteristics of the studies included in the meta-analysis.

Study	Year	Study design	Population sample size	Sex (M/F,n)	Age (year)	The follow up	Proteinuria prior or UPCR to Treatment (g/24 h, mg/g)	Interventions (mainly rituximab, dose, and usage)	Events
Cravedi[22]	2007	Matched-cohort study	12/24	24/12	57±13 55±15	12 mo	10.3±8.9 9.1±3.8	1×375 mg/m^2 (n=11) and 2×375 mg/m^2 (n=1) 4×375 mg/m^2, intravenously.	Severe reaction of nausea, vomiting, sweating and mild adverse reactions (nausea, chills, sweating, and face rush)
Cravedi[23]	2011	Matched-cohort study	11/11	20/2	48.6±13.9 50.1±12.3	24 mo	10.9 (6.6–18.6) 10.3 (5.8–13.8)	4×375 mg/m^2 (n=10) and B cell-driven protocol (n=12), intravenously.	Infectious complications
Dahan[24]	2016	RCTs	37/38	52/23	53.0 (42.0–63.0) 58.5 (43.0–64.0)	6 mo	7680.0 (4584.3–10,399.0) 7195.1 (5363.1–8965.1)	2×375 mg/m^2 (n=37), intravenously.	Cardiac and vascular disorders, cancer, pain and fever
Vandenbrand[25]	2016	Retrospective cohort study	100/103	150/53	51.5 (15.9) 55.3 (12.7)	40 mo	6400 (4400–8894) 8840 (5651–11,660)	4×375 mg/m^2 or B cell–driven approach (a single dose then an additional dose if there were greater than 5 circulating B cells percubic millimeter on the morning after the first dose) (n=100), intravenously.	Fatal, major cardiovascular events, infections
Rosenzwaj[7]	2017	RCTs	16/9	20/5	57 (26–74)	6 mo	6250 (3170–15900) 7590 (3440–11000)	No reported	No reported
Cortazar[21]	2017	Retrospective study	7/8	8/7	52 (39–62) 64 (57–67)	12 mo	6900 (5200–10200) 10100 (8000–11700)	2×1 g and 6×1 g [Initial therapy, n=7, Relapsing or refractory disease, n=8), intravenously.	Interval infections, hospitalizations, or other complications
Wang[26]	2017	Prospective study	15/21	30/6	51.4±15.7 44.3±18.6	12 mo	11.8±6.5 12.6±5.6	4×375 mg/m^2 (n=15) and B cell-driven protocol - [n=21, 1 infusions (n=3), 2 infusions (n=11), 3 infusion (n=7)], intravenously.	Soft tissue infection
Fervenza[20]	2019	RCTs	65/65	100/30	51.9±12.6 52.2±12.4	24 mo	8.9 (6.8–12.3) 8.9 (6.7–12.9)	2×1 g (n=65) and a second course at 6 mo (n=3), intravenously.	Gastrointestinal pain nausea and vomiting and so on

RCT=randomized controlled trial, UPCR=Urine Protein-to-Creatinine Ratio.

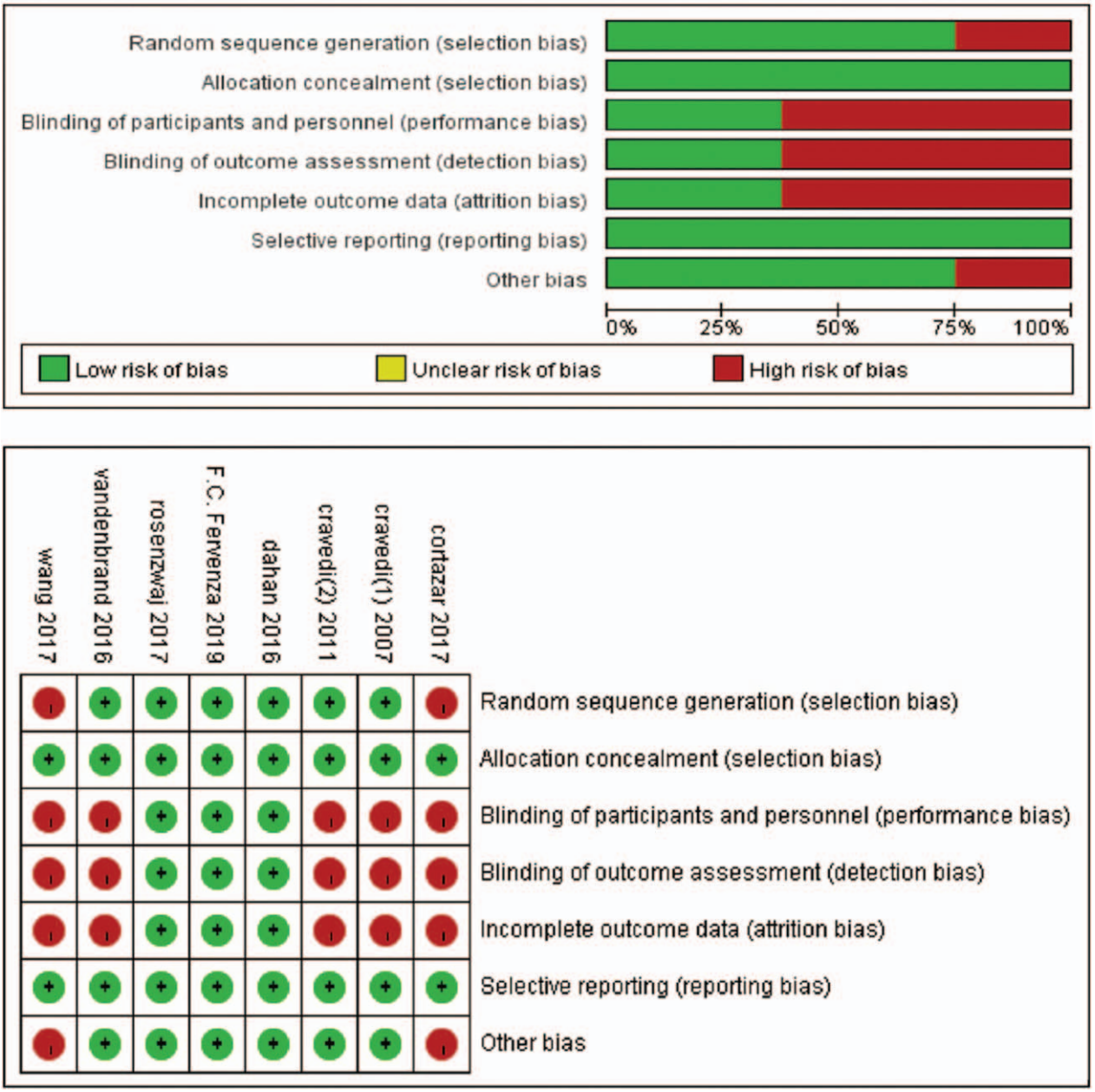

Figure 2. Risk of bias: The summary of authors' judgments about the risk of bias for each item included study.

there was significant heterogeneity, the random-effects model was utilized. The statistical analysis showed no significant difference (MD = –0.01; 95%CI = –0.36 to 0.34) with heterogeneity among these studies ($I^2 = 77\%$, $P = .95$) (Fig. 8).

3.3.6. Estimated glomerular filtration rate (mL/minute/1.73 m²). Dnhan and Wang reported that there was no difference between the 2 groups in terms of estimated glomerular filtration

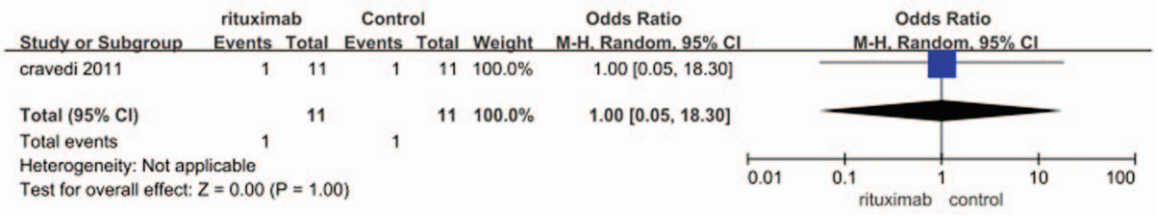

Figure 3. Forest plot of relapse-free survival between the 2 groups.

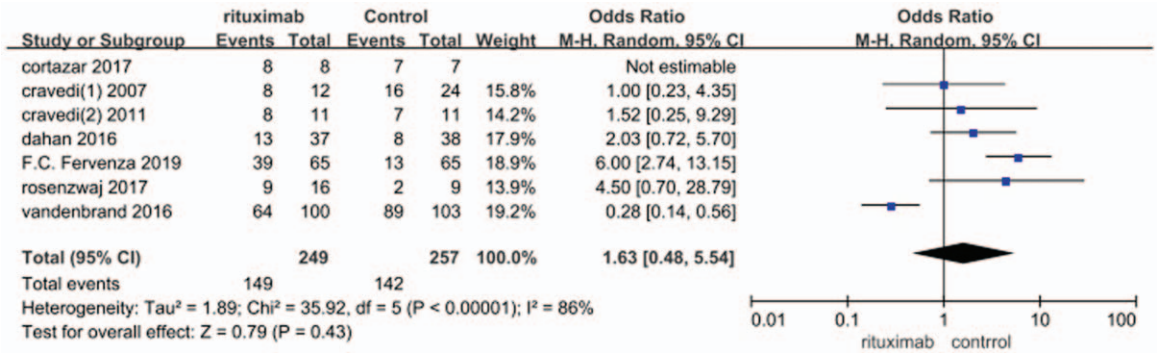

Figure 4. Assessment of total remission of rituximab vs control group.

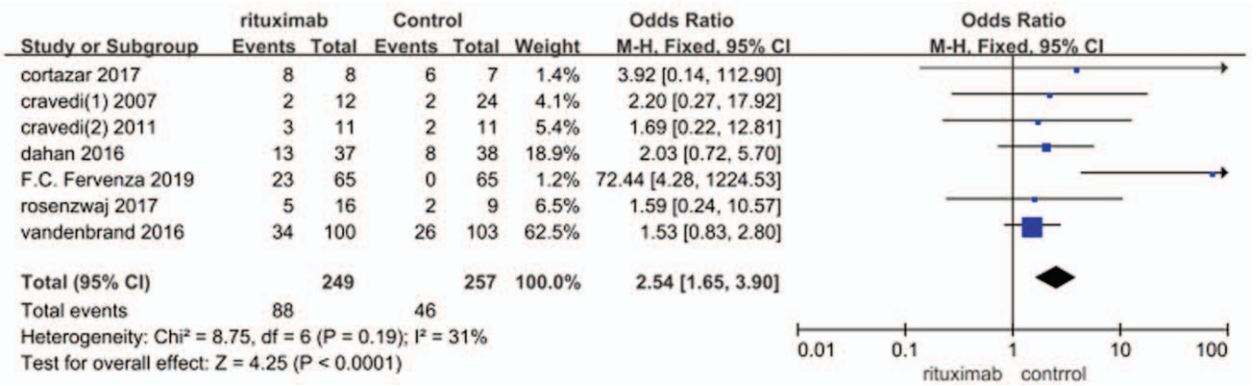

Figure 5. Assessment of complete remission of rituximab vs control group.

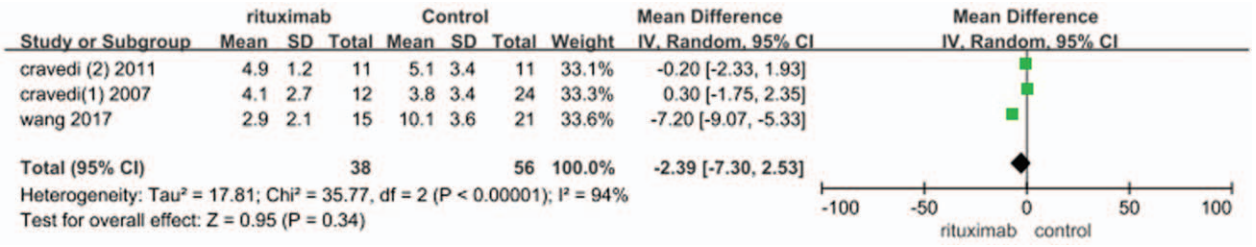

Figure 6. Forest plot of the effect of rituximab for proteinuria (g/24 hour) at the end treatment.

rate (e-GFR) at 6 months and 1-year follow-up time. It has been depicted in Figure 9.

3.3.7. PLA2R-Antibody–depleted patients. Only 2 studies assessed patients with depleted PLA2R-Antibody. Twenty-one patients were assigned to treatment groups and five patients to control groups. The fixed-effects model was used for evaluation because there was no significant heterogeneity. No significant difference was observed among the groups (MD = 5.59; 95% CI = 1.81–17.21; $I^2 = 0\%$; $P < .01$) (Fig. 10).

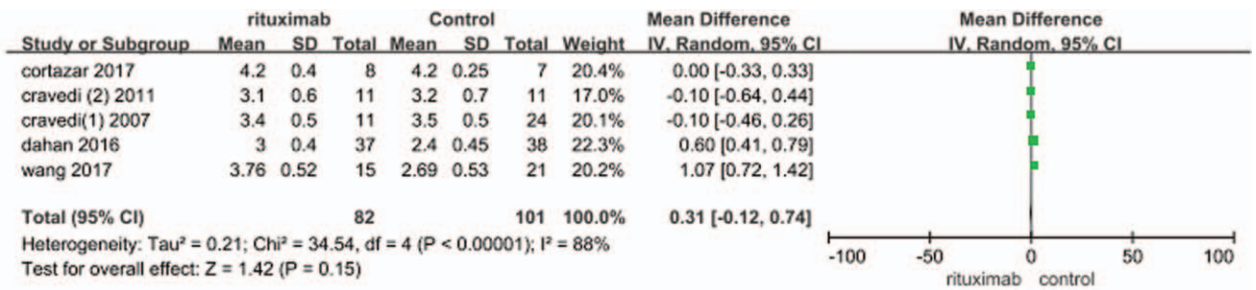

Figure 7. The effect of rituximab vs control group on serum albumin in patients with membranous nephropathy.

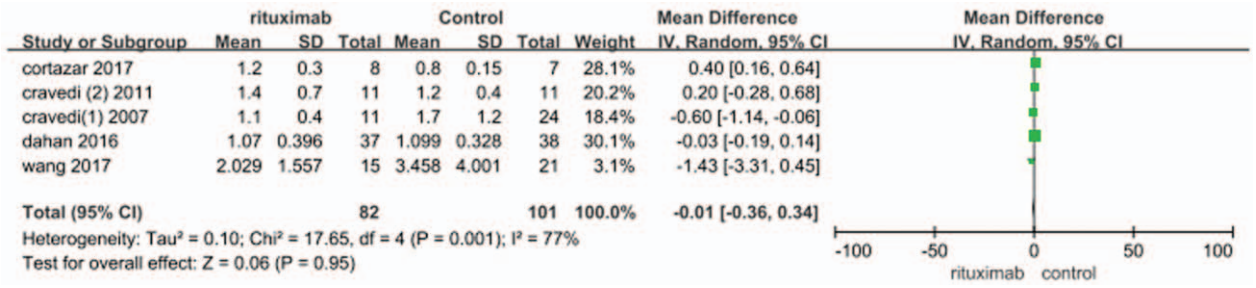

Figure 8. Forest plot of the random effects for the meta-analysis showing the difference between rituximab and control group on the serum creatinine on patients with membranous nephropathy.

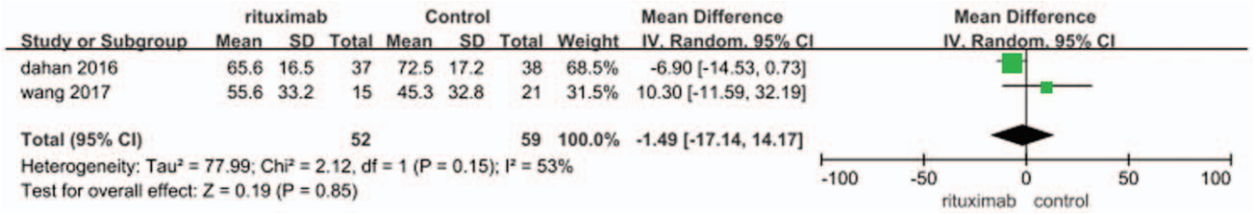

Figure 9. Forest plot of the random effects for the meta-analysis showing the differences between the rituximab and control group on e-GFR.

3.3.8. Safety and serious adverse events. RTX was well tolerated in most patients. Because of their minor severity, these mild events can rapidly and completely be resolved by reducing the drug infusion rate or providing minor supportive treatment. To ensure accuracy, we report only serious side events. The serious adverse events reported were grade 3 or higher which were life-threatening or required hospitalization. There was a slight tendency for patients in RTX maintenance arm to have less serious adverse events than patients in the control group (OR = 0.47, 95%CI 1.8–.19) with heterogeneity among these studies ($I^2 = 63\%$, $P = .11$) (Fig. 11).

3.3.9. Sensitivity analysis. A symmetrical funnel plot was constructed for estimation of remission rate, relapse-free survival, serious adverse events, proteinuria, eGFR, SCr, serum albumin, and PLA2R-Antibody depletion in patients. The plot marked

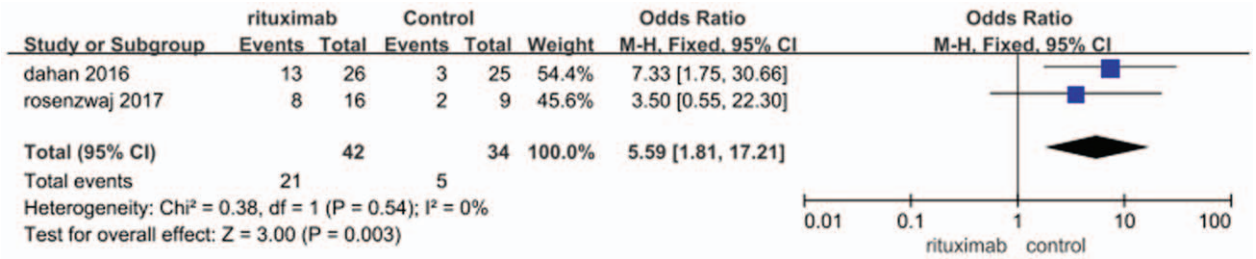

Figure 10. Forest plot of PLA2R-Ab–depleted patients between the 2 groups.

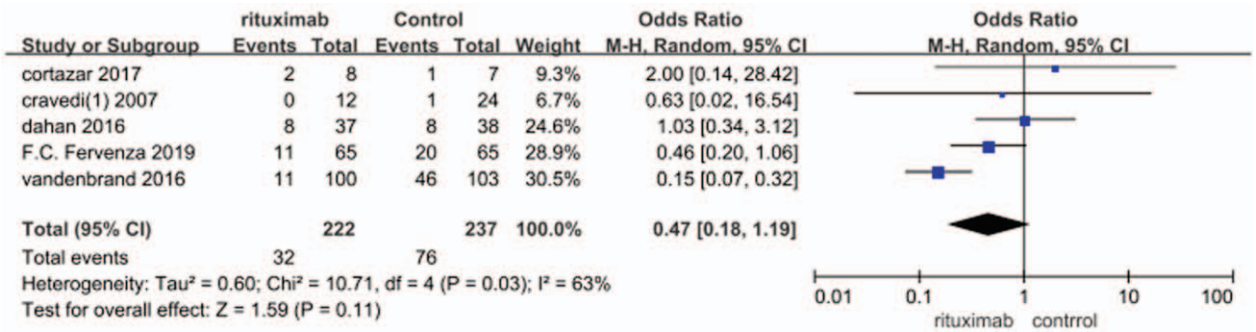

Figure 11. Forest plot of the random effects for the meta-analysis showing the difference between rituximab and control group on the rate of serious side events.

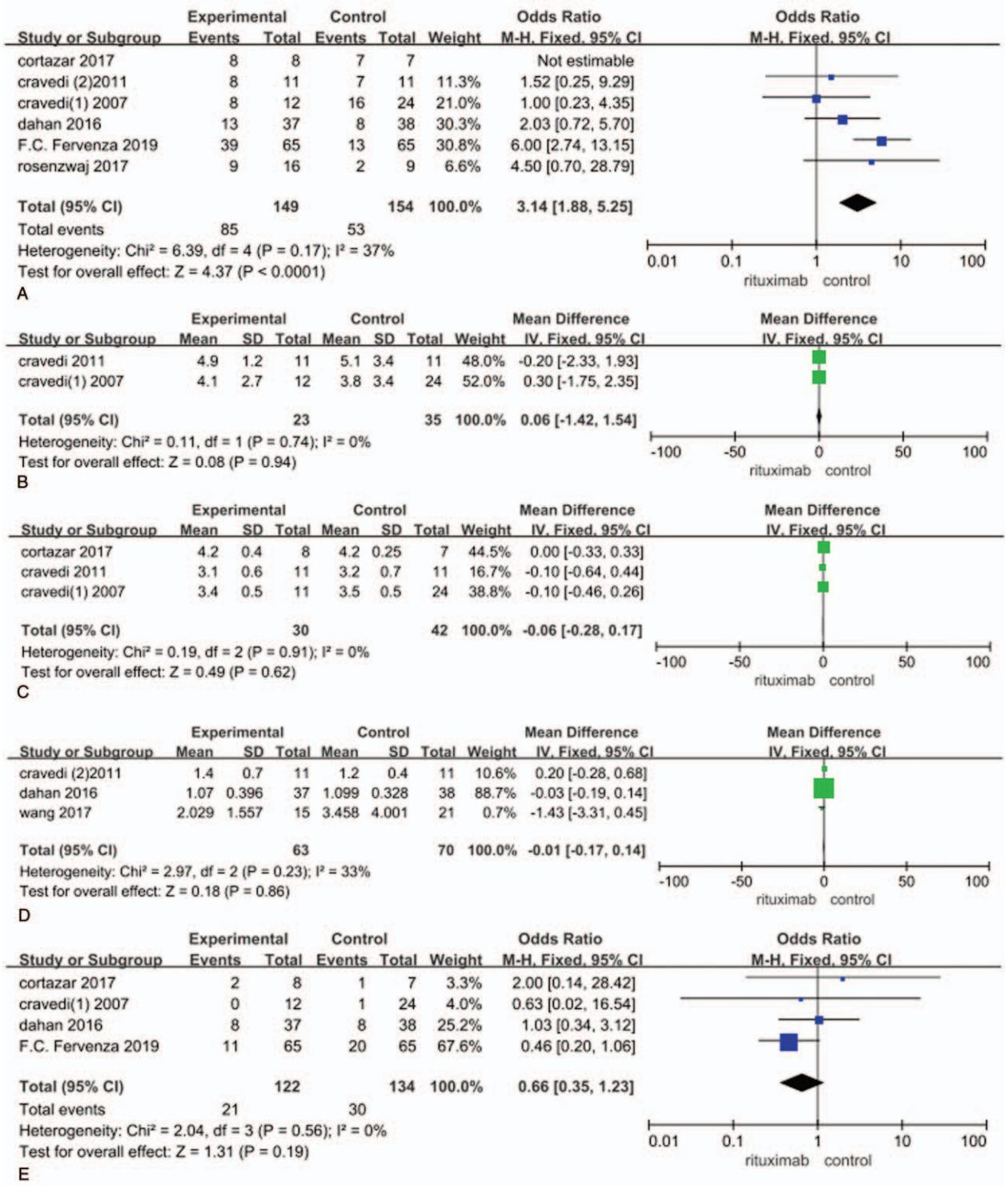

Figure 12. Forest plot of sensitivity analysis. A, Total remission; B, Proteinuria; C, Serum albumin; D, Serum creatinine; E, Serious adverse events.

moderate to severe heterogeneity between the trials in TR or CR, serious adverse events, serum albumin, proteinuria, and SCr. Sensitivity analyses were conducted to check whether or not, modification of the article quality of this meta-analysis affected the final results. Sensitivity analysis was performed using variables TR or CR, serious adverse events, proteinuria, serum albumin, and SCr in RevMan 5.3 software for their significant heterogeneity. The use of observation data for meta-analysis was often dismissed as being inferior in quality to data from RCTs. The funnel plots did not show obvious publishing bias, mainly for comparisons in TR or CR, serious adverse events, proteinuria, serum albumin and SCr (Fig. 12).

4. Discussion

MN is an organ-specific autoimmune disease and a major cause of mortality in patients with nephrotic syndrome worldwide.[10] Despite immunosuppression and corticosteroid being supposed to induce disease remission and reduce the risk of progression to ESRD or death,[27–30] as many as 20% patients with MN are refractory to treatment[31] and up to 40% patients develop ESRD during the course of treatment.[32] In addition, immunosuppressive agents are associated with significant toxicity, particularly infections, malignancy, and infertility.[33,34] Thus, novel therapeutic strategies are necessary for the superior clinical management of patients with MN. A number of controlled trials have found RTX to be safer or at least as efficacious as immunosuppressive agents in inducing renal remission. In the current meta-analysis, 8 studies (542 patients) were assessed and it was observed that RTX had higher efficacy and CR rates as compared to the control, which is in accordance with another meta-analysis.[35] Also, B-cell, titrated as effectively as standard RTX treatment, avoids repeated drug exposure and allows the limitation of adverse effects and cost of RTX therapy without affecting the efficacy of treatment. However, no difference in TR or PR was observed in the present study. The differences in the clinical index of the RTX group vs the control group are as follows: RTX has greater efficacy in lowering proteinuria levels. Similar patterns as decreased serum creatinine levels were observed with increased PLA2R-Antibody-depletion in patients. RTX turned to be more effective in decreasing proteinuria. Although the combined group showed significant effects in reducing proteinuria and increasing CR rate, the level of serum albumin was lower than that in the control group, with no statistical difference in e-GFR. In order to explore the heterogeneity of the meta-analysis, the authors dismissed some studies in the process of analyzing different outcomes and there are some conclusions that the quality of some of the included studies was low, while some sample sizes were small. Serious adverse events were observed more frequently in the control group.

Overall, RTX had better efficacy than the control, with low serious adverse effects. However, it showed the same relapse rate as that reported in one of the studies. There were no significant differences between RTX and the control in TR, e-GFR, proteinuria, serum creatinine level, relapse rate, serum albumin, and serious adverse events. Previous studies have suggested that treatment with RTX can significantly reduce proteinuria levels in patients with MN.[36–38] This meta-analysis also showed that RTX can significantly reduce the level of proteinuria. The levels of proteinuria in groups treated with RTX reduced significantly as compared to the controls. The heterogeneity of the RTX group was mostly derived from the study by Wang.[26] The results of this study suggest that RTX therapy may have a positive effect on CR. In addition, the treatment group showed a greater reduction in the risk of ESRD than the control group.[39] Sequential analyses showed that RTX could reduce the risk for ESRD without the need for a larger sample size. The use of RTX is often accompanied by side effects, mainly dose infusion reaction.[40] Only serious adverse events that patients defined as life-threatening or that required hospitalization, including interval infections, the severe reaction of nausea, vomiting and sweating have been reported in this research work. The sample sizes of some specific comparisons for assessment of serious adverse events were insignificant, making it difficult to detect differences.

Yet, this meta-analysis has some limitations including low quality of some of the included studies and small sample sizes. This potential limitation applied to different patients and follow-up duration, which was thought to give rise to a systematic bias adding to the disadvantage of the two treatment groups.

In conclusion, although RTX has the potential to replace other therapeutic regimens, its adverse reaction must be considered carefully.

Author contributions

Conceptualization: Ying Wang.
Data curation: Wanjun Lu, Shuhao Gong, Juan Li, Hongwen Luo.
Project administration: Wanjun Lu.
Writing – original draft: Wanjun Lu.
Writing – review & editing: Ying Wang.

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