Efficacy and safety of rituximab in the treatment of membranous nephropathy
A systematic review and meta-analysis

WanJun Lu, MD, Shu-Hao Gong, MD, Juan Li, MD, Hong-Wen Luo, MD, Ying Wang, MD*

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: 0.96–0.94, 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: 0.48–6.54, 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.

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 2.5% 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...
antibody, binding specifically to the CD20 antigen present on the
technology 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.\(^{[10,18]}\)

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.

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 inhib-
itors 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 remis-
sion, 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-
analyses 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. Hetero-
genesis of the trial results was assessed by performing a chi-
square test of heterogeneity and the I² measure of inconsistency.
All statistical tests had a significant value of \(P < .05\) 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.
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; I² 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; I² 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; I² 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 (I² = 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
| 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   | 12 mo        | 10.3 ± 8.9                                      | 1 × 375 mg/m² (n=11) and 2 × 375 mg/m² (n=1) 4 × 375 mg/m², intravenously. | Severe reaction of nausea, vomiting, sweating and mild adverse reactions (nausea, chills, sweating, and face rush) |
|                  |       |                       |                        |             | 55 ± 15    |              |                                                 | 9.1 ± 3.8                                        |                                                          |
|                  |       |                       |                        |             |            |              |                                                 |                                                  |                                                          |
|                  |       |                       |                        |             | 55 ± 15    |              |                                                 |                                                  |                                                          |
|                  |       |                       |                        |             |            |              |                                                 |                                                  |                                                          |
| Cravedi[23]      | 2011  | Matched-cohort study  | 11/11                  | 20/2        | 48.6 ± 13.9| 24 mo        | 10.9 (6.6–18.6)                                 | 4 × 375 mg/m² (n=10) and B cell-driven protocol (n=12), intravenously. | Infectious complications                                                                 |
|                  |       |                       |                        |             | 50.1 ± 12.3|              |                                                 |                                                  |                                                          |
|                  |       |                       |                        |             |            |              |                                                 |                                                  |                                                          |
|                  |       |                       |                        |             | 50.1 ± 12.3|              |                                                 |                                                  |                                                          |
|                  |       |                       |                        |             |            |              |                                                 |                                                  |                                                          |
| Dahan[24]        | 2016  | RCTs                  | 37/38                  | 52/23       | 50.0 (42.0–63.0) | 6 mo      | 7680.0 (4584.3–10,399.0) | 2 × 375 mg/m² (n=37), intravenously. | Cardiac and vascular disorders, cancer, pain and fever |
|                  |       |                       |                        |             | 58.5 (43.0–64.0) |           | 7195.1 (5363.1–8965.1) |                                                  | Fatal, major cardiovascular events, infections |
| Vanderbrand[25]  | 2016  | Retrospective cohort study | 100/103               | 150/53      | 51.5 (15.9) | 40 mo       | 8400 (4400–8894) | 4 × 375 mg/m² or B cell-driven approach (a single dose then an additional dose if there were greater than 5 circulating B cells per cubic millimeter on the morning after the first dose) (n=100), intravenously. |                                                          |
|                  |       |                       |                        |             | 55.3 (12.7) |              | 8840 (5651–11,660) |                                                  |                                                          |
|                  |       |                       |                        |             |            |              |                                                 |                                                  |                                                          |
|                  |       |                       |                        |             | 55.3 (12.7) |              |                                                 |                                                  |                                                          |
|                  |       |                       |                        |             |            |              |                                                 |                                                  |                                                          |
| Rosenzwaj[7]     | 2017  | RCTs                  | 16/9                   | 20/5        | 57 (26–74) | 6 mo        | 6250 (3170–15900) | No reported                                      | No reported                                                                                     |
|                  |       |                       |                        |             |            |              | 7590 (3440–11000) |                                                  |                                                          |
|                  |       |                       |                        |             |            |              |                                                 |                                                  |                                                          |
| Cortazar[21]     | 2017  | Retrospective study   | 7/8                    | 8/7         | 52 (39–62) | 12 mo       | 6900 (5200–10200) | 2 × 1 g and 6 × 1 g [Initial therapy, n = 7, Relapsing or refractory disease, n = 8], intravenously. | Interval infections, hospitalizations, or other complications                                      |
|                  |       |                       |                        |             | 64 (57–67) |              | 10100 (8000–11700) |                                                  |                                                          |
|                  |       |                       |                        |             |            |              |                                                 |                                                  |                                                          |
|                  |       |                       |                        |             | 64 (57–67) |              |                                                 |                                                  |                                                          |
|                  |       |                       |                        |             |            |              |                                                 |                                                  |                                                          |
| Wang[26]         | 2017  | Prospective study     | 15/21                  | 30/6        | 51.4 ± 15.7| 12 mo       | 11.8 ± 6.5                                      | 4 × 375 mg/m² (n=15) and B cell-driven protocol - n=21, 1 infusion (n=3), 2 infusions (n=11), 3 infusion (n =7), intravenously. | Soft tissue infection                                                                                     |
|                  |       |                       |                        |             | 44.3 ± 18.6|              |                                                 |                                                  |                                                          |
|                  |       |                       |                        |             |            |              |                                                 |                                                  |                                                          |
|                  |       |                       |                        |             | 44.3 ± 18.6|              |                                                 |                                                  |                                                          |
|                  |       |                       |                        |             |            |              |                                                 |                                                  |                                                          |
| Fenencz[28]      | 2019  | RCTs                  | 65/65                  | 100/30      | 51.9 ± 12.6| 24 mo       | 8.9 (6.8–12.3)                                 | 2 × 1 g (n=65) and a second course at 6 mo (n=3), intravenously. | Gastrointestinal pain nausea and vomiting and so on                                                                 |
|                  |       |                       |                        |             | 52.2 ± 12.4|              |                                                 |                                                  |                                                          |
|                  |       |                       |                        |             |            |              |                                                 |                                                  |                                                          |
|                  |       |                       |                        |             | 52.2 ± 12.4|              |                                                 |                                                  |                                                          |
|                  |       |                       |                        |             |            |              |                                                 |                                                  |                                                          |

**Table 1**: Characteristics of the studies included in the meta-analysis.

**RCT** = randomized controlled trial, **UPCR** = Urine Protein to Creatinine Ratio.
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 m$^2$)

Dhan and Wang reported that there was no difference between the 2 groups in terms of estimated glomerular filtration

![Figure 2. Risk of bias: The summary of authors’ judgments about the risk of bias for each item included study.](image)

![Figure 3. Forest plot of relapse-free survival between the 2 groups.](image)
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; I² = 0%; P < .01) (Fig. 10).

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.

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

| Study or Subgroup | Experimental | Total | Weight | Odds Ratio | M-H, Fixed, 95% CI |
|-------------------|--------------|-------|--------|------------|-------------------|
| **A**              |              |       |        |            |                   |
| Total (95% CI)     | 149          | 154   | 100.0% | 3.14       | [1.88, 5.25]      |
| Total events       | 85           | 53    |        |            |                   |
| Heterogeneity: Ch² | 6.39         | df = 4 | P = 0.17 | 37%       |                   |
| Test for overall effect: Z = 4.37 (P < 0.0001) | | | | | |
| **B**              |              |       |        |            |                   |
| Total (95% CI)     | 23           | 35    | 100.0% | 0.06       | [-1.42, 1.54]     |
| Heterogeneity: Ch² | 0.11         | df = 1 | P = 0.74 | 0%        |                   |
| Test for overall effect: Z = 0.08 (P = 0.94) | | | | | |
| **C**              |              |       |        |            |                   |
| Total (95% CI)     | 30           | 42    | 100.0% | -0.06      | [-2.28, 1.17]     |
| Heterogeneity: Ch² | 0.19         | df = 2 | P = 0.91 | 0%        |                   |
| Test for overall effect: Z = 0.49 (P = 0.62) | | | | | |
| **D**              |              |       |        |            |                   |
| Total (95% CI)     | 63           | 70    | 100.0% | -0.01      | [-2.17, 0.14]     |
| Heterogeneity: Ch² | 2.97         | df = 2 | P = 0.23 | 33%       |                   |
| Test for overall effect: Z = 0.18 (P = 0.89) | | | | | |

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

References

[1] Couser WG. Primary Membranous Nephropathy. Clin J Am Soc Nephrol 2017;12:983–97.
[2] Catrzan D, Brenchley P. Membranous nephropathy: thinking through the therapeutic options. Nephrol Dialysis Transplant 2017;32:22–9.
[3] Tran TH, Hughes J, Greenfeld G, et al. Overview of current and alternative therapies for idiopathic membranous nephropathy. Pharmacotherapy 2015;35:396–411.
[4] Kronbichler A, Oh J, Meijers B, et al. Recent progress in deciphering the etiopathogenesis of primary membranous nephropathy. BioMed Res Int 2017;2017:1936372.
[5] El-rohigy ZM, Grande JP, Fraile MG, et al. Recurrent idiopathic membranous nephropathy: early diagnosis by protocol biopsies and treatment with anti-CD20 monoclonal antibodies. Am J Transplant 2009;9:2800–7.
[6] Ronco P, Debiec H. Pathophysiological advances in membranous nephropathy: time for a shift in patient’s care. Lancet 2015; 385:1983–92.
[7] Rosenzweig M, Languille E, Debiec H, et al. B- and T-cell subpopulations in patients with severe idiopathic membranous nephropathy may predict an early response to rituximab. Kidney Int 2017;92:237–37.
[8] Beck LH, Bonegio RG, Lambeau G, et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med 2009;361:11–21.
[9] Vandenbrand JA, Hofsra JM, Wetzes JF. Low-molecular-weight proteins as prognostic markers in idiopathic membranous nephropathy. Clin J Am Soc Nephrol 2011;6:2846–53.
[10] Beck LH, Fervenza FC, Beck DM, et al. Rituximab-induced depletion of anti-PLA2R autoantibodies predicts response in idiopathic membranous nephropathy. Clin J Am Soc Nephrol 2011;6:2846–53.
[11] Ruggenenti P, Debiec H, Ruggiero B, et al. Anti-phospholipase A2 receptor antibody titer predicts post-rituximab outcome of membranous nephropathy. J Am Soc Nephrol 2015;26:2345–58.
[12] Pozdrik A, Brochirsch I, David C, et al. Membranous nephropathy and anti-podocytes antibodies: implications for the diagnostic workup and disease management. BioMed Res Int 2018;2018:6281054.
[13] Rozman S, Grabnar I, Novakovic S, et al. Population pharmacokinetics of rituximab in patients with diffuse large B-cell lymphoma and association with clinical outcome. Br J Clin Pharmacol 2017;81:1782–90.
[14] Rudnicki M. Rituximab for treatment of membranoproliferative glomerulonephritis and C3 glomerulopathies. BioMed Res Int 2017; 2017:2180508.
[15] Fajr AA, Asmar A, Alasbagh MM, et al. Rituximab in immunologic glomerular diseases. mAbs 2012;4:198–207.
[16] Looney RJ. B cells as a therapeutic target in autoimmune diseases other than rheumatoid arthritis. Rheumatology (Oxford, England) 2005;44 (Suppl 2):13–7.
[17] Cheunggasporn W, Kopecsky SL, Specks U, et al. Non-Ischemic cardiomyopathy after rituximab treatment for membranous nephropa-thy, J Renal Inj Prev 2017;6:18–25.
[18] Rituximab for idiopathic membranous nephropathy. Lancet 9337;360: 923–4.
[19] Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

[20] Fervenza FC, Appel GB, Barbour SJ, et al. Rituximab or cyclosporine in the treatment of membranous nephropathy. N Engl J Med 2019;381:36–46.

[21] Cortazar FB, Leaf DE, Owens CT, et al. Combination therapy with rituximab, low-dose cyclophosphamide, and prednisone for idiopathic membranous nephropathy: a case series. BMC Nephrol 2017;18:44.

[22] Cravedi P, Ruggenenti P, Sghirlanzoni MC, et al. Titrating rituximab to circulating B cells to optimize lymphocytolytic therapy in idiopathic membranous nephropathy. Clin J Am Soc Nephrol 2007;2:932–7.

[23] Cravedi P, Sghirlanzoni MC, Marasà M, et al. Efficacy and safety of rituximab second-line therapy for membranous nephropathy: a prospective, matched-cohort study. Am J Nephrol 2011;33:461–8.

[24] Dahan K, Debiec H, Plaisier E, et al. Rituximab for severe membranous nephropathy: a 6-month trial with extended follow-up. J Am Soc Nephrol 2017;28:348–58.

[25] Van den brand JA, Ruggenenti P, Chianca A, et al. Safety of rituximab compared with steroids and cyclophosphamide for idiopathic membranous nephropathy. J Am Soc Nephrol 2017;28:2729–37.

[26] Wang X, Cui Z, Zhang YM, et al. Rituximab for non-responsive idiopathic membranous nephropathy in a Chinese cohort. Nephrol Dial Transplant 2018;33:1558–63.

[27] Hofstra JM, Wetzel JS. Management of patients with membranous nephropathy. Nephrol Dial Transplant 2012;27:6–9.

[28] Waldman M, Austin HA. Controversies in the treatment of idiopathic membranous nephropathy. Nat Rev Nephrol 2009;5:469–79.

[29] Ponticelli C, Fasani P. Management of idiopathic membranous nephropathy. Exp Opin Pharmacother 2010;11:2163–75.

[30] Hofstra JM, Wetzel JS. Alkylating agents in membranous nephropathy: efficacy proven beyond doubt. Nephrol Dial Transplant 2010;25:1760–6.

[31] Zhao Z, Liao G, Li Y, et al. The efficacy and safety of rituximab in treating childhood refractory nephrotic syndrome: a meta-analysis. Sci Rep 2015;5:8219.

[32] Sprangers B, Lefkowitz GL, Cohen SD, et al. Beneficial effect of rituximab in the treatment of recurrent idiopathic membranous nephropathy after kidney transplantation. Clin J Am Soc Nephrol 2010;5:790–7.

[33] Van den brand JA, Van dijk PR, Hofstra JM, et al. Cancer risk after cyclophosphamide treatment in idiopathic membranous nephropathy. Clin J Am Soc Nephro 2014;9:1066–73.

[34] Faurschou M, Sorensen IJ, Mellemkjaer L. Malignancies in Wegener’s granulomatosis: incidence and relation to cyclophosphamide therapy in a cohort of 293 patients. J Rheumatol 2008;35:100–5.

[35] Zhang J, Bian L, Ma FZ, et al. Efficacy and safety of rituximab therapy for membranous nephropathy: a meta-analysis. Eur Rev Med Pharmacol Sci 2018;22:8021–9.

[36] Rituximab can reduce proteinuria in idiopathic membranous nephropathy. Nat Clin Pract Nephrol 2008;4:3017–3021.

[37] Fervenza F, Erickson S, Nachman P, et al. Rituximab (RTX) therapy in idiopathic membranous nephropathy (IMN): results at two years. NDT Plus 2010;3:277.

[38] Fiorentino M, Tondolo F, Bruno F, et al. Treatment with rituximab in idiopathic membranous nephropathy. Clin Kidney J 2016;9:788–93.

[39] Seitz-polinski B, Dahan K, Debiec H, et al. High-dose rituximab and early remission in PLA2R1-related membranous nephropathy. Clin J Am Soc Nephrol 2019;14:1173–82.

[40] Hartinger JM, Satrapova V, Hruskova Z, et al. Tolerance and safety of rapid 2-hour infusion of rituximab in patients with kidney-affecting autoimmune diseases and glomerulonephritides: a single-centre experience. Eur J Hosp Pharm 2019;26:210–3.