

ORIGINAL ARTICLE

Therapy of Rituximab in Idiopathic Membranous Nephropathy with Nephrotic Syndrome: A Systematic Review and Meta-analysis

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Key words: rituximab; idiopathic membranous nephropathy; nephrotic syndrome; meta analysis

Objective To investigate the efficacy and safety of rituximab (RTX) in the treatment of idiopathic membranous nephropathy (IMN) with nephrotic syndrome with a systematic review and meta-analysis.

Methods PubMed, Embase, Cochrane Library and Clinical Trials (December 2016) were searched to identify researches investigating the treatment of RTX in adult patients with biopsy-proven IMN. Complete remission (CR) or partial remission was regarded as effective therapy, and the cumulated remission rate was calculated.

Results Seven studies involved 120 patients (73% were men) were included in our systematic review and meta-analysis. All were prospective observation cohort studies or matched-cohort studies, mainly came from two medical centers, and one study was multi-centric (four nephrology units in northern Italy). The creatinine clearance was more than 20 ml/(min·1.73 m²) and persistent proteinuria higher than 3.5 g/d for at least 6 months. All patients received treatment previously [44 (36.7%) had immunosuppressive treatment]. In 12- and 24-month, 56% (95%CI, 0.47-0.65) and 68% (95%CI, 0.41-0.87) patients could reach remission, while 15% (95%CI, 0.09-0.23) and 20% (95%CI, 0.12-0.32) patients could reach CR. The reduction in proteinuria was gradual and obvious, paralleled with upward trend of serum albumin level and decreasing serum cholesterol level. Renal functions were stable. Relapses happened in 24 months were around 8%. RTX related adverse events were mild and were mostly infusion-related reactions.

Conclusions RTX treatment in IMN was efficient, well tolerated and safe. More than 60% patients can reach partial remission or CR in 24 months, and relapse is rare. Adverse events of RTX are mostly infusion-related reactions and generally mild.

Received for publication July 31, 2017. Published on online 2018-02-13.

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Supported by the Key Projects in the National Science and Technology Pillar Program during the Twelfth Five-year Plan Period (2011BAI10B03).

Cited this article as: Peimei Zou, Hang Li, Jianfang Cai, Zhenjie Chen, Chao Li, Xuewang Li. Therapy of Rituximab in Idiopathic Membranous Nephropathy with Nephrotic Syndrome: A Systematic Review and Meta-analysis. Chinese Medical Sciences Journal 2018; 33(1): 9-19.

IDIOPATHIC membranous nephropathy (IMN) is one of the most common cause of adult nephrotic syndrome (NS), accounting for about 75% of membranous nephropathy (MN) cases. About 20%-30% IMN patients (often with non-nephrotic proteinuria) entered spontaneous remission,¹ and 30%-40% of patients progress to end-stage renal disease (ESRD) within 5 to 15 years.² M-type phospholipase A2 receptor (PLA2R), which can be detected on glomerular podocytes and in subepithelial immune deposits, presented in 70%-80% IMN patients.³

Immunosuppressive treatment including corticosteroid, alkylating agents, calcineurin inhibitors (CNIs), mycophenolate mofetil (MMF) and azathioprine, is advised to high-risk patients (proteinuria > 8 g/d with or without renal insufficiency) and medium-risk patients (normal renal function, proteinuria > 4 to < 8 g/d) when nephrotic proteinuria persisted more than 6 months.⁴⁻⁵ However, these immunosuppressive agents bring along with adverse events such as infection, myelosuppression and nephrotoxicity. Novel drugs are needed to improve the situation.

Rituximab (RTX), a monoclonal antibody targeting CD20, applied in chronic lymphocytic leukaemia, non-Hodgkin lymphoma, vasculitis and rheumatoid arthritis, recently emerged to be an option for the treatment of NS.⁶ Animal experiments suggested that B cells were involved in the pathological process of MN. B cells mediate typical subepithelial immune deposits in glomeruli, accelerate injury of the glomerular filtering barrier and result in proteinuria. Although IMN autoantigens remain elusive and the role of B cells has not been fully understood in humans, agents that specifically interfere with B cells would ideally represent the first step toward selective therapy in humans.⁷ Lots of studies reported successful use of RTX in the treatment of both IMN and secondary MN, as first-line and second-line therapy. However, these studies were small sample prospective observation studies or case reports, further investigation is required. Thus, combining the current evidences of RTX therapy in IMN from eligible studies, we carried out this systematic review and meta-analysis, to systematically evaluate the efficacy and safety of RTX in IMN.

MATERIALS AND METHODS

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement protocol.⁸

Eligibility and exclusion criteria

Prospective cohort studies that reported the use of RTX in biopsy-proven IMN adult patients with NS were included for review. Publications on secondary MN, other pathological types of glomerular diseases, and recurrence of disease after renal transplantation were excluded. Studies with follow-up period less than 12 months were excluded. Pediatric patients were excluded. We also excluded retrospective studies and two ongoing multicenter randomized controlled trials (RCTs).⁹⁻¹⁰

Literature search

A systematic literature search of the PubMed (2002 to December 2016), Embase (2002 to December 2016), Cochrane Library (2007 to December 2016) and Clinical Trials (2007 to December 2016) was conducted, using the key words "Rituximab", "anti-CD20 monoclonal antibodies", "membranous nephropathy", "membranous glomerulonephritis", "primary", "idiopathic", "nephrotic syndrome", and "adults". We also manually identified additional relevant studies. The search was limited to articles published in English language.

Study selection and data extraction

The eligible references obtained by literature search were assessed by two independent reviewers (Zou PM and Chen ZJ) according to a predetermined protocol. Data extracted by two independent reviewers (Zou PM and Chen ZJ) included: study characteristics (design, country, publication year), follow-up period, baseline data of patients (age, gender, course of disease, histopathologic features, baseline proteinuria, baseline renal function, previous treatment), RTX administration regime, and treatment response (remission situation and the definition, renal function, relapse, adverse events). Differences over inclusion of studies and interpretation of data were resolved by consensus discussion.

Quality assessment

The Newcastle-Ottawa Scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp), which graded studies according to the quality of selection, comparability and outcome of cohort, was performed to make quality assessments of the eligible references. Discrepancies were addressed by consensus discussion.

Statistical and bias analysis

Complete remission (CR) or partial remission (PR) was

regarded as effective therapy, and the cumulate rate (CR + PR) was calculated. We evaluated the 12-month and the 24-month pooled remission rates. Pooled relapse rate in 24-month was also assessed. Cochrane Q test and the inconsistency index (I^2) statistic were applied to analyze the heterogeneity of the included studies. We used a random effects model for the data analysis when a significant heterogeneity was observed ($P < 0.1$ or $I^2 > 50\%$), otherwise we used a fixed effect model. Sensitivity analysis was used by sequential omission of individual studies. Funnel plots were used to estimate the publication bias of the meta-analysis. All analyses were performed using R software and the meta/metaphor package (www.r-project.org). P value less than 0.05 was considered statistically significant.

RESULTS

Literature search

Totally, 639 articles were identified *via* database search. And 255 duplicate studies were removed by Endnote Software. After exclusion based on title and abstract, 37 full-text articles were reviewed. Five studies were

excluded for the following reasons: three studies used the same series of patients^{7, 11-12} and two studies did not reach our inclusion criteria.¹³⁻¹⁴ Finally, 7 studies were included.¹⁵⁻²¹ A flowchart of article screening for the meta-analysis has been illustrated in Fig. 1.

Study characteristics

Basic characteristics of 7 included studies are summarized in Table 1. All patients were renal biopsy-proven IMN with creatinine clearance $> 20 \text{ ml}/(\text{min} \cdot 1.73 \text{ m}^2)$, and persistent proteinuria $> 3.5 \text{ g/d}$ for at least 6 months with previous treatment [44 (36.7%) had immunosuppressive treatment]. Quality assessment by the Newcastle-Ottawa Scale is shown in Table 2. Among the 7 included studies, Ruggenti *et al*²¹ organized their research in two steps—first came the retrospective analysis of 14 IMN patients treated with RTX in their Nephrology Unit (the outcome of 8 of these patients was reported previously²⁰) and finally concluded that tubulointerstitial (TI) scores < 1.7 predicted better response to RTX. Then they did a prospective study including 9 IMN patients of TI scores < 1.7 . We only assessed the prospective part. Cravedi *et al*¹⁵ carried out

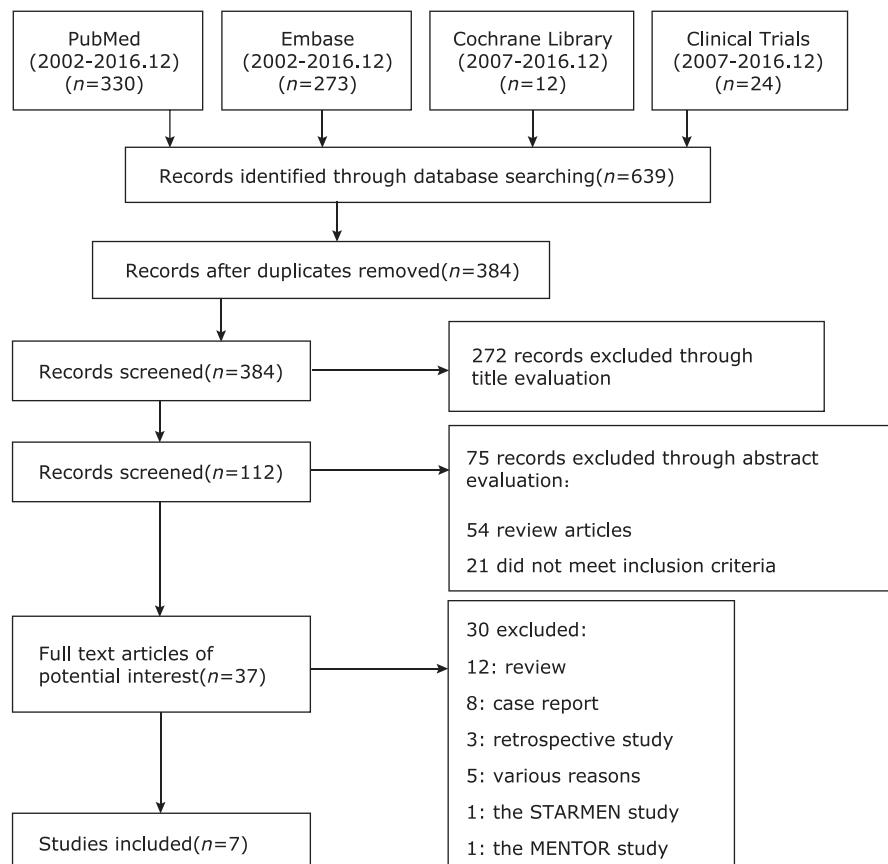


Figure 1. Flowchart of studies included in the meta-analysis.

Table 1. Baseline characteristics of the included studies[§]

Study	Country	Study design	Patient (n)	Sex (M/F, n)	Age (yrs)	Disease duration (mon)	Treatment before RTX	RTX administration	Follow-up time (mon)	Proteinuria prior to RTX (g/d)	Renal function prior to RTX	Quality score
Ruggenenti et al ²⁰	Italy	Prospective cohort study	8	3/5	52.8±19.6	29.7±13.5	Full-dose ACEi	4*375 mg/m ²	12	8.6±4.2	1.5±0.9	8
Ruggenenti et al ²¹	Italy	Retrospective and prospective cohort study	14 9 (TI) score<1.7)	8/6 4/5	60.2±18.2 51.2±13.2	31.5±18 Not mentioned	Full-dose ACEi Full-dose ACEi	4*375 mg/m ² 4*375 mg/m ²	12 12	9.2±3.9 8.9±5.3	1.7±0.7 1.0±0.3	9
Cravedi et al ¹⁵	Italy	Matched-cohort study	12 (B cell-driven protocol) 24 (four-dose protocol)	8/4 16/8	57±13 55±15	Not mentioned Not mentioned	Full-dose ACEi Full-dose ACEi	1*375 mg/m ² (n=11) and 2*375 mg/m ² (n=1) 4*375 mg/m ²	12 12	10.3±8.9 9.1±3.8	1.4±0.5 1.5±0.7	8
Fervenza et al ¹⁸	Canada	Prospective cohort study	15	13/2	47±8	13.1±13.6	Prednisone, CTX, CsA, MMF (n=7); ACEi/ARB (n=8)	2*1 g (n=5), 2*1 g and a second course at 6-month (n=10)	12	13.0±5.7	1.4±0.5	9
Fervenza et al ¹⁷	Canada	Prospective cohort study	20	17/3	48±13	29.7±39.7	Prednisone, CsA, CTX, MMF, tacrolimus (n=11); ACEi/ARB (n=9)	4*375 mg/m ² and a second course at 6-month	24	11.9±4.9	1.5±0.5	9
Cravedi et al ¹⁶	Italy	Matched-cohort study	11 (second-line therapy) 11 (first-line therapy)	10/1 10/1	48.6±13.9 50.1±12.3	51 (25.6-55.2) 9 (6.0-17.0)	Prednisone, CTX, CsA, immunoglobulin G Full-dose ACEi/ARB	4*375 mg/m ² (n=10) and B cell-driven protocol (n=12)	24 24	10.9 (6.6-18.6) 10.3 (5.8-13.8)	1.3±0.5 1.1±0.4	9
Moroni et al ¹⁹	Italy	Multi-centric prospective study	34	23/11	47.5 (22-77)	16.3 (0.2-176.4)	Methylprednisolone, MMF, CsA, and other immunosuppressive agents (n=15); not mentioned (n=19)	1*375 mg/m ² (n=18), 2*375 mg/m ² (n=16)	24	11.9±8.2	1.3±0.6	9

§: Plus-minus values are means±SD.

RTX: rituximab; TI: tubulointerstitial; ACEi: angiotensin-converting enzyme inhibitors; CTX: cyclophosphamide; CsA: cyclosporin A; ARB: angiotensin receptor blockers;

MMF: mycophenolate mofetil.

Table 2. Quality assessment of the included studies by the Newcastle-Ottawa Scale (score)

Items	Ruggenenti <i>et al</i> ²⁰	Ruggenenti <i>et al</i> ²¹	Cravedi <i>et al</i> ¹⁵	Fervenza <i>et al</i> ¹⁸	Fervenza <i>et al</i> ¹⁷	Cravedi <i>et al</i> ¹⁶	Moroni <i>et al</i> ¹⁹
Selection							
Representativeness of the exposed cohort	1	1	1	1	1	1	1
Selection of the non-exposed cohort	1	1	1	1	1	1	1
Ascertainment of exposure	1	1	1	1	1	1	1
Demonstration that outcome of interest was not present at Start of study	1	1	1	1	1	1	1
Comparability	1	2	1	2	2	2	2
Outcome							
Assessment of outcome	1	1	1	1	1	1	1
Was follow-up long enough for outcomes to occur?	1	1	1	1	1	1	1
Adequacy of follow-up of cohort	1	1	1	1	1	1	1
Total score	8	9	8	9	9	9	9

a matched cohort study that compared the B cell-driven and the four-dose protocol of RTX, data of the 24 IMN patients of the four-dose protocol group came from their previous studies. To avoid inclusion of repeated data, we only evaluated the experimental group-12 patients accepted the B cell-driven protocol. All included studies defined CR as proteinuria ≤ 0.3 g/24 h or ≤ 0.5 g/24 h, and PR as proteinuria ≤ 3.5 g/24 h or ≤ 3.0 g/24 h. One study did not mention the definitions of CR and PR,²¹ so we regarded the authors used the generally accepted definitions (CR as proteinuria ≤ 0.3 g/24 h with normal serum creatinine, PR as proteinuria < 3.5 g/24 h and a $\geq 50\%$ reduction from peak values with improvement of serum albumin²²).

Efficiency of RTX therapy in severe IMN patients

The pooled CR rate and cumulate remission (CR + PR) rate at 12-month were 15% (95%CI, 0.09-0.23) and 56% (95%CI, 0.47-0.65) (Fig. 2). Only 3 studies^{16-17, 19} had a follow-up period of 24 months, the pooled CR rate and cumulate remission rate at 24-month were 20% (95%CI, 0.12-0.32) and 68% (95%CI, 0.41-0.87). Heterogeneity was revealed at 24-month remission rate with I^2 of 73% (Fig. 3). Sensitivity analysis suggested that the 24-month pooled remission rate was stable and omitting a single study did not change the significance of the pooled survival rates (95%CI, 0.49-0.74) (Fig. 4).

Renal function was stable and did not change significantly in most studies. But, Fervenza *et al*¹⁷ reported creatinine clearance increased from $72.4 \pm$

33 ml/(min $\cdot 1.73$ m²) at baseline to 88.4 ± 31.5 ml/(min/1.73 m²) at 24 months ($P = 0.02$) in their study published in 2010. Quite the opposite, in Moroni *et al*'s study,¹⁹ the mean serum creatinine of the 24 patients who were followed for at least 18 months after RTX therapy was significantly higher than that at 12 months (141.4 ± 70.7 versus 114.9 ± 44.2 μ mol/L; $P = 0.02$), however we cannot rule out the confounding factors brought by 6 non-responders. In Fervenza *et al*'s study,¹⁸ 2 patients who had the lowest creatinine clearance at entry [40 and 59 ml/(min $\cdot 1.73$ m²)] and proteinuria remained unchanged in the whole study, progressed to ESRD at 18-month and 19-month after RTX treatment.

Four studies^{16-17, 19, 21} reported relapse cases, mostly happened in the second year. Pooled data of the relapse rate in 24-month after RTX treatment was 8% (95%CI, 0.03-0.16) (Fig. 5).

Other parameters

The reduction in proteinuria was paralleled to a significant increase in serum albumin and decrease in total serum cholesterol.

After the first administration of RTX infusion, most included studies^{15-17, 19-21} recorded that circulating CD19+, CD20+ B cells depletion were achieved and remained below normal ranges by study end. Only one study found that the majority of patients had CD19+ B cells recovered to the normal range (mean 110 ± 97 cells/ml, range: 28-317) at 6-month.¹⁸ No significant changes in total white blood cell, hemoglobin, platelet,

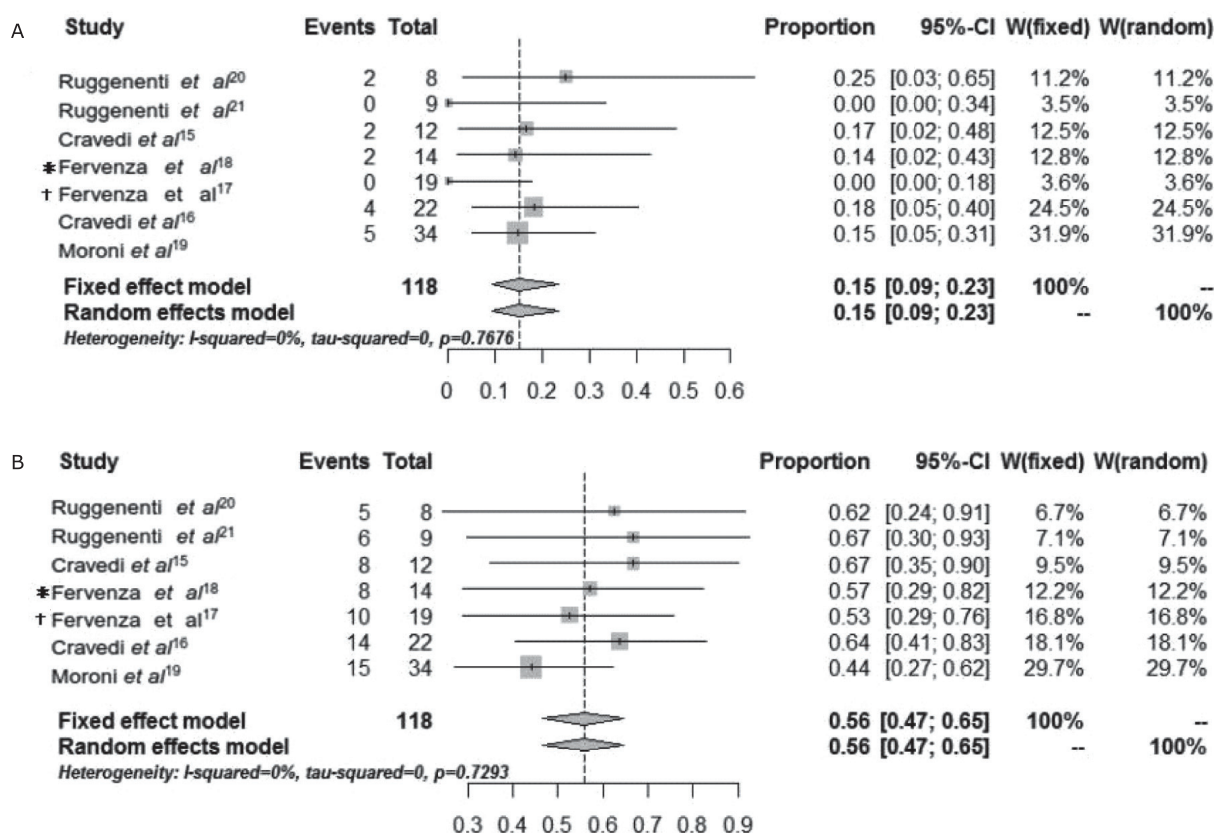


Figure 2. Pooled CR rate and remission (CR + PR) rate at 12 months. A. pooled 12-month CR rate; B. pooled 12-month CR+PR rate. CR: complete remission; PR: partial remission; W: weight. *In the 15 enrolled patients, 14 patients completed 12 months of follow-up; †In the 20 enrolled patients, 1 patient who was immunosuppression naive before entry was removed from the study at 6 months because of worsening proteinuria and rapidly declining kidney function.

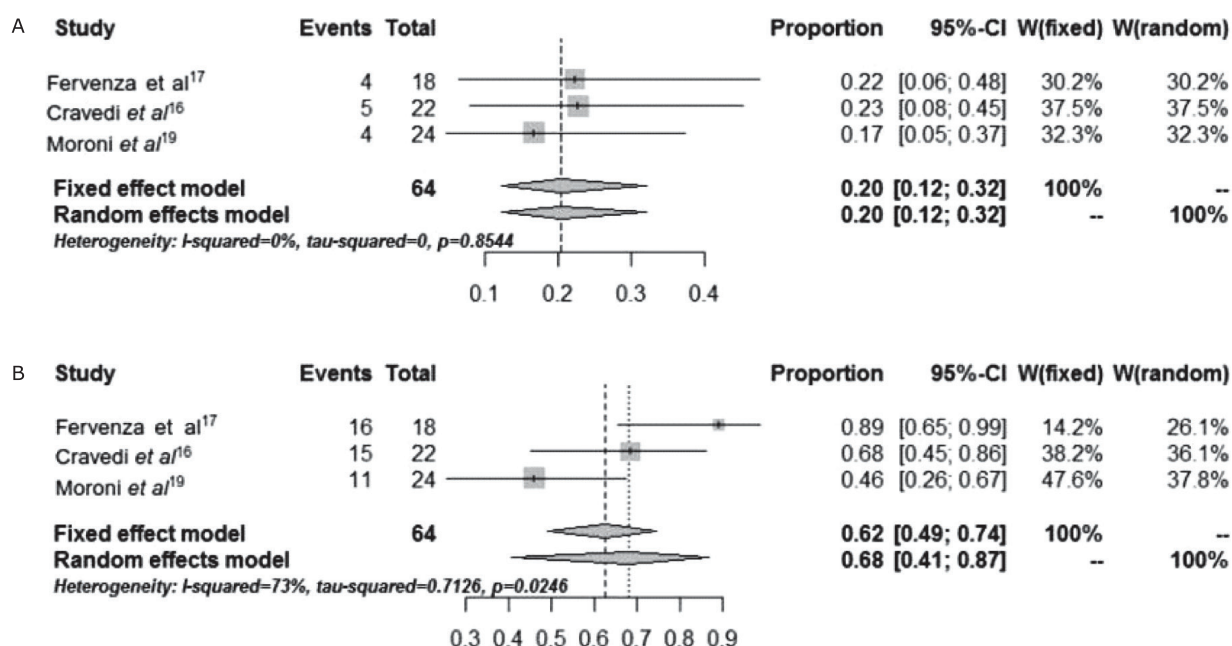


Figure 3. Pooled CR rate and remission (CR + PR) rate at 24 months. A. pooled 24-month CR rate; B. pooled 24-month CR+PR rate.

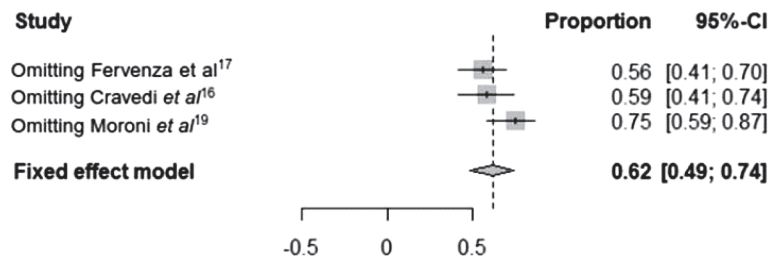


Figure 4. Sensitivity analysis of pooled 24-month CR+PR rate.

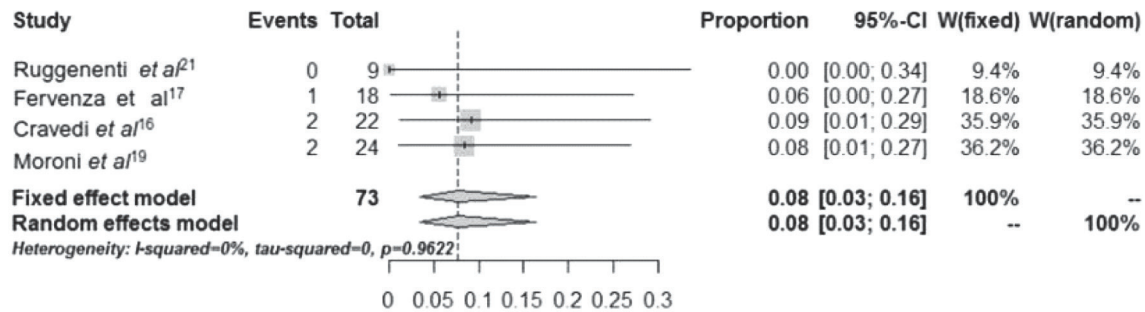


Figure 5. Pooled relapse rate at 24 months.

and lymphocyte counts and in lymphocyte subpopulations including CD3+, CD4+, CD8+, natural killer cells, and CD4+/CD8+ ratios.

Two studies reported that serum concentrations of IgG, IgA, and IgM did not change significantly throughout its whole study period;²⁰⁻²¹ but Fervenza *et al* in their two studies recorded significantly increase of baseline IgG level and decrease of IgM level, while serum IgA remained relatively stable at 12 months and later. Subsequent quantification of IgG subclasses proved total IgG increase was due to an increase in IgG1, IgG2, and IgG3 isotypes, whereas IgG4 levels remained unchanged.¹⁷⁻¹⁸

Safety

Adverse events observed in RTX treatment were mainly infusion-related reactions, including itchy throat, skin rash, chills, flu-like symptoms, *et al*. Symptoms were varied but generally not serious. Infections were uncommon, three studies¹⁷⁻¹⁹ reported infectious complications: 3 patients experienced community-acquired pneumonia and 2 patients experienced herpes zoster, relieved with oral-medications. Myocardial infarction, happened in 2 patients from two studies,^{17, 19} respectively occurred 3 months and 5 months after RTX infusion. Another patient was diagnosed with adenocarcinoma in the lung 3 months after the first infusion.¹⁸

Publication bias

As shown in Fig. 6, the shape of funnel plots did not reveal any obvious asymmetry. Begger's and Egger's

test confirmed that there was no publication bias ($P>0.05$).

DISCUSSION

Seven studies involving 120 patients (73% were men) were included in our systematic review and meta-analysis. RTX was used as first-line therapy or second-line therapy. Our results demonstrated that RTX was efficient in the treatment of IMN. The reduction in proteinuria was gradual and obvious, paralleled with serum albumin increasing and serum cholesterol decreasing. Renal functions were stable. Relapse was rare. Adverse events about RTX therapy were mostly infusion-related reactions and generally were not serious.

Spontaneous remission is a special characteristic of MN, occurred in about 30% patients, and generally happens in the first 2 years. Although spontaneous remission was more often seen in patients with lower baseline proteinuria levels, it also frequently occurred in patients with massive proteinuria: 26% among those with baseline proteinuria 8-12 g/24 h and 22% among those with proteinuria > 12 g/24 h.²³ Important independent predictors for spontaneous remission include: baseline serum creatinine and proteinuria, treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEi/ARBs), and a > 50% decline of proteinuria from baseline during the first year of follow-up.²³ Patients in all included

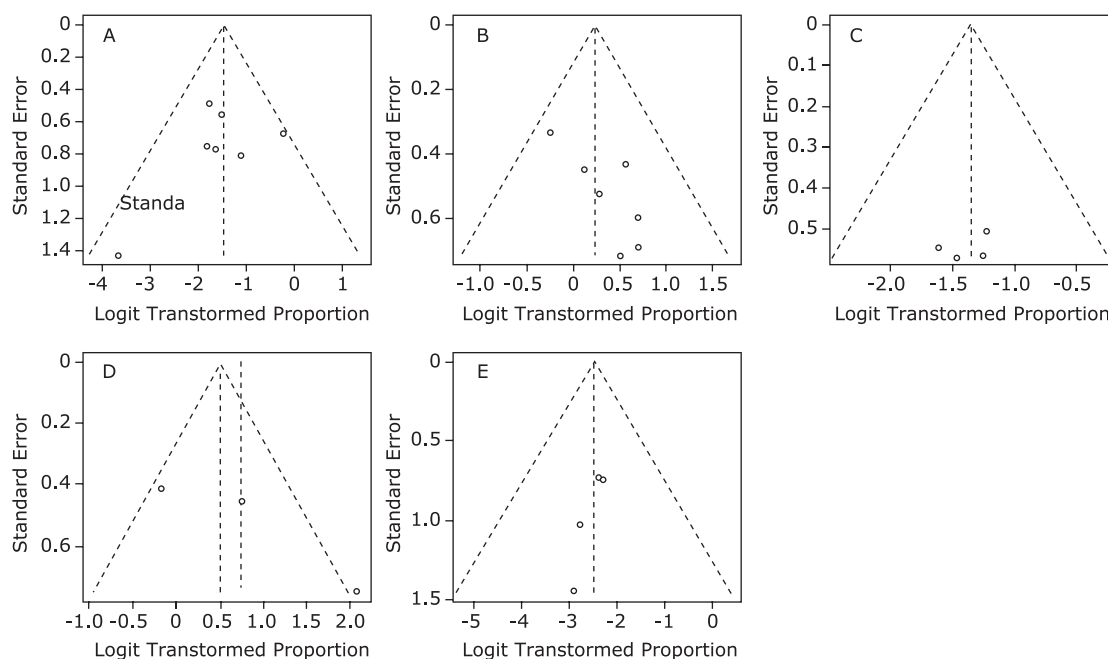


Figure 6. Funnel plots of the meta-analysis. A: 12-month CR rate; B: 12-month CR+PR rate; C: 24-month CR rate; D: 24-month CR+PR rate; E: relapse rate at 24 months.

studies had massive proteinuria, supportive treatment consisted of ACEi, and/or ARB at maximal tolerated dose was conducted with RTX administration. However, most patients selected had a prolonged disease course, proteinuria maintained unchanged despite conservative treatment and even immunosuppressive therapy added for enough time previously. Hence spontaneous remission was unlikely to occur.

Traditional RTX protocol is 375 mg/m² RTX once weekly for 4 weeks, or 1 g RTX on day 1 and day 15. Some nephrologists give a second course routinely or according to the B cell counts (when B cells $\geq 5/\text{mm}^3$) after 6 months. It's confusing whether clinical efficacy is different in different protocols. Limited to the very few study and detail data unavailable, we failed to make a relative meta-analysis. Remuzzi *et al*⁷ firstly demonstrated RTX was efficient in the treatment of IMN, used the four-dose protocol. Segarra *et al*¹³ successfully used the four-dose protocol in 13 IMN patients with long-term calcineurin inhibitors (CNIs) dependence to overcome dependence of CNIs. Studies of Fervenza *et al*¹⁷⁻¹⁸ suggested that four doses of RTX resulted in more effective B cell depletion, but proteinuria reduction was similar to RTX at 1 g every 2 weeks. In addition, there was no difference in proteinuria response between patients who were immunosuppression naive *versus* those who had been previously treated.¹⁷⁻¹⁸ In 2007, Cravedi *et al*¹⁵ con-

ducted a matched-cohort study, concluded that B cell titrated RTX protocol was as effective as standard four-dose RTX treatment in achieving B cell depletion and IMN remission, but cost only a quarter of the standard regimen. Based on their previous finding, these investigators further demonstrated that second-line RTX therapy was equally efficient to first-line RTX therapy in IMN as well.¹⁶ Contrary to Cravedi's opinion, recently in 2016, results from a multi-centric study involving 34 IMN patients (15 patients had been treated with glucocorticoids and immunosuppressive agents) suggested that low-dose RTX was poorly effective, obtained remission in <50% of IMN patients.¹⁹

There was no significant difference between RTX applied as the first-line therapy and the second-line therapy. No conclusion was drawn on which RTX protocol is preferred. Lack of rigorous RCTs, we cannot assert RTX is superior to other treatments commonly applied in clinic. Whether to use RTX combined or continued with other medications include supportive regimes and immunosuppressive agents can induce more remission remain uncertain and needs further study. Luckily there are 2 ongoing multicenter RCTs: the MENTOR study (rituximab *versus* cyclosporine) and the STARMEN study (sequential treatment with tacrolimus-tituximab *versus* steroids plus cyclophosphamide), and we are looking forward to the publication of their results.

The mechanism of RTX to MN is unknown. It was supposed that RTX develops its role of reducing urinary proteins and protects renal function by specifically interferes with B lymphocytes and disturbs B cell differentiation. The treatment response may be related to the remaining B cells counts. Unfortunately, different outcomes in patients could not be explained, since all studies recorded circulating B lymphocytes in all patients depleted and maintained below normal range during whole studies after RTX first administration, CD19+ B cells followed an identical trend as well. Most studies reported serum hemoglobin levels, total white blood cells, platelet counts and levels of IgG, IgA, and IgM had no significant difference. However, data from studies of Fervenza *et al*¹⁷⁻¹⁸ showed the not very consistent results of CD19+ B cells recovery and the IgG level, making these conclusions controversial.

Pharmacokinetics and pharmacodynamics analyses showed serum RTX levels in IMN patients were lower than patients with rheumatoid arthritis, and half-life of RTX was also shorter. However, there were no differences in serum RTX levels at any point between responders and non-responders.¹⁸

Human antichimeric antibodies (HACAs) can be induced by repeated or prolonged exposure to RTX.²⁴ The production of HACAs may limit the effect of treatment and increase the risk for hypersensitivity reactions of the immediate type upon drug re-exposure. Six and two patients in two studies of Fervenza¹⁷⁻¹⁸ were detected to have HACAs, but the titers were low and the presence of HACAs was not associated with treatment response.²⁴

Nephrologists never stop looking for factors that can efficiently predict response to RTX in IMN patients. In 2006, a pilot study of Ruggenenti suggested that TI score was the only significant predictor, patients with a TI score of < 1.7 showed better response to RTX.²¹ However, it was not consolidated demonstrated by Cravedi,¹⁵ since average proteinuria reduction on follow-up *versus* baseline tended to correlate with TI score, but the correlation did not reach statistical significance ($P=0.10$). It was reported the CD4+/CD8+ T cell ratio predict response to RTX therapy by Zucchelli *et al*,²⁵ but Fervenza's study¹⁸ failed to certify it. In addition they found there was no relation between the total number of CD20+ or CD3+ cells, the ratio of CD20+/CD3+ cells, or the number of CD20+ cells/mm² present in the diagnostic renal biopsies and the response to rituximab treatment.¹⁷⁻¹⁸ Irazabal *et al*¹²

suggested low- and high-molecular-weight urinary proteins predict response to RTX in IMN patients. Anti-PLA2R lever measuring were commonly developed in clinical works nowadays, levels of anti-PLA2R correlate with the immunological activity of MN and can well predict response to treatment with RTX.²⁶ One study reported that patients with lower serum creatinine, higher estimated glomerular filtration rate, lower proteinuria, lower titer of anti-PLA2R antibodies at baseline showed better outcome to RTX therapy.¹⁹ However, relationship between response and initial proteinuria remains controversial.

RTX is well tolerated and safe in IMN patients. Adverse events were mainly infusion-related reaction and mostly were not serious. Infections were uncommon since RTX targeted on B cells, and caused no significant changes in total white blood cell, lymphocyte counts and in lymphocyte subpopulations, even some studies recorded serum IgG levels increased. Two researches reported one patient happen myocardial infarction 5 and 3 months after RTX administration respectively,^{17, 19} one study reported a patient diagnosed with adenocarcinoma of the lung 3 months after the first RTX infusion.¹⁸ Previous research verified that patients with NS and IMN were at high risk of cardiovascular events.²⁷⁻²⁸ Approximately 10% MN patients had a malignancy (predominantly solid organ cancers, mainly in the lung, colon, or breast) at the time of renal biopsy or within a year thereafter, and the incidence increased up to 20%-25% after age 60.²⁹⁻³⁰ Thus, we should be cautious to conclude that these severe events were due to the RTX administration. Compared to immunosuppressive agents, side effects of RTX are fewer and milder. Most obvious disadvantage of RTX may be its experience cost. Perhaps it's better accepted by wealthy patients who care more about adverse events of glucocorticoid and immunosuppressive drugs. However, the safety of RTX still needs more observation.

There are several limitations in our study. All included researches were small sample prospective observation cohort studies or matched-cohort studies, mainly came from two common centers, one study was multi-centric (4 nephrology units in northern Italy). Only three studies followed up for 24 months, which may weaken the role of meta-analysis of pooled 24-month remission rate. Limited to the very few study and detail data unavailable, we failed to make a relative meta-analysis of clinical efficacy in different RTX

protocols. Prognostic factors specifically to RTX treatment are controversial since each publication came to different conclusions, making a meta-analysis on the prognostic factors unrealistic. More investigations are needed in the future.

In conclusion, RTX provides a new approach for the treatment of IMN, and it can be seemed as a narrow, disease-specific treatment to IMN. Rigorous and large multicenter RCTs still need to be well performed. It is also necessary to further evaluate the long-term outcome, safety, and factors predict treatment efficacy.

Acknowledgements

The authors appreciate Dandan Hu, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College for her kind support in language editing.

Conflicts of interest statement

The authors have no conflicts of interest to disclose.

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