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Low-Dose Rituximab in the Treatment of Primary Membranous Nephropathy – A Systematic Review and Meta-Analysis

In depth review

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ABSTRACT

Introduction. Rituximab (RTX) holds promise as a treatment for idiopathic membranous nephropathy (IMN). While effective in standard regimens, the application of RTX is hampered by cost burdens and severe side effects. To address these issues, low-dose RTX has been proposed as an intervention strategy. Yet, the efficacy of this approach in treating IMN remain subject of debate. This systematic review and meta-analysis seek to examine the effectiveness of low-dose RTX in adult patients with IMN.

Methodology. A literature search was conducted using PubMed, Wiley Online Library, ScienceDirect, Cochrane Library, Springer and other sources, published between 2004 and 2024. Specifically, articles reporting the intravenous application of RTX at doses lower than four weekly infusions of 375 mg/m² or two infusions of 1 gram each on day 0 and day 15 were considered for inclusion. The primary outcomes were complete response (CR) and partial response (PR) rates at last follow-up. Secondary endpoints included serum creatinine levels, serum albumin levels, 24-hour proteinuria levels, protein-creatinine ratio (PCR), estimated glomerular filtration rate (eGFR) and anti-PLA2R antibody levels.

Results. Sixteen articles were included in this meta-analysis. The pooled analysis of odds ratios (OR) revealed that both main-line (OR = 0.48, 95% CI = 0.30-0.75, p = 0.001) and second-line (OR = 0.27, 95% CI = 0.11-0.67, p = 0.005) RTX treatments induced complete remission (CR) in IMN patients. At the last follow-up, patients treated with both main-line (mean difference [MD] = 1.45, 95% CI = 1.00-1.91, p < 0.00001) and second-line (MD = 0.88, 95% CI = 0.23-1.53, p < 0.00001) RTX treatments showed a significant increase in serum albumin levels. Conversely, in the analysed second line RTX therapy patients, low eGFR trend was noted in the post treatment arm compared to baseline levels (MD = 10.57, 95% CI = 0.30-20.83, p = 0.04). Moreover, RTX was found to be effective in reducing PCR (MD = 24.10, 95% CI= 1.07 to 47.13, p = 0.04) and depleting PLA2R antibody levels (MD = 127.36, 95% CI = 14.90-239.81, P = 0.03). However, RTX might be less effective in lowering proteinuria and serum creatinine levels in patients with nephrotic syndrome.

Conclusion. Rituximab in a low-dose regimen is quite effective in treating adult patients with IMN. Therefore, it can be considered a promising treatment for both main-line and rescue therapy. More randomized controlled trials and research on optimizing the low-dose regimen, based on various health factors, are warranted.

KEYWORDS: Low-dose rituximab, primary membranous nephropathy, systematic review, proteinuria, creatinine

Introduction

Membranous nephropathy (MN) is an immune-mediated disorder that negatively affects the kidney glomerulus of humans [1]. Approximately 80% of MN occurs due to unidentifiable reasons, termed as either primary MN (PMN) or idiopathic MN (IMN) [2]. In the remaining 20% of individuals, MN develops secondarily due to various clinical conditions, such as bacterial or viral infections (hepatitis B and C, syphilis), malignancies, drug toxicities (penicillamine, gold salts) and other rheumatological or immunological diseases (rheumatoid arthritis, systemic lupus erythematosus) [3]. Annual prevalence rates vary globally, with higher incidences reported in North America and Europe [4], indicating greater tendencies among Caucasians followed by Asians, Blacks and Hispanics [5]. Although membranous glomerulopathy can affect individuals of any age, it predominantly manifests in adults than in children [6], with the average age occurring between 50 and 60 years [7]. Studies suggest a male preponderance in IMN cases, with a male-to-female ratio of 2:1, though the underlying reasons remain elusive [8].

PMN is characterized by B-cell abnormalities and the accumulation of immune complexes along the glomerular capillary walls, leading to membranous thickening [4, 9]. Several potential immunological mechanisms proposed include entrapment of preformed immune complexes in the subepithelial space, localization or implantation of circulating antigens in the subepithelial sites and binding of autoantibodies to podocyte membrane antigens (leading to the subepithelial deposition of immune complexes) [10]. Immune deposits consist of several components, including the immunoglobulin G (IgG) subclass of antigens and the membrane attack complex (MAC) formed from the complement components to create C5b–9 [11]. Figure 1 elaborates the treatment targets and immunological mechanisms in primary membranous nephropathy.

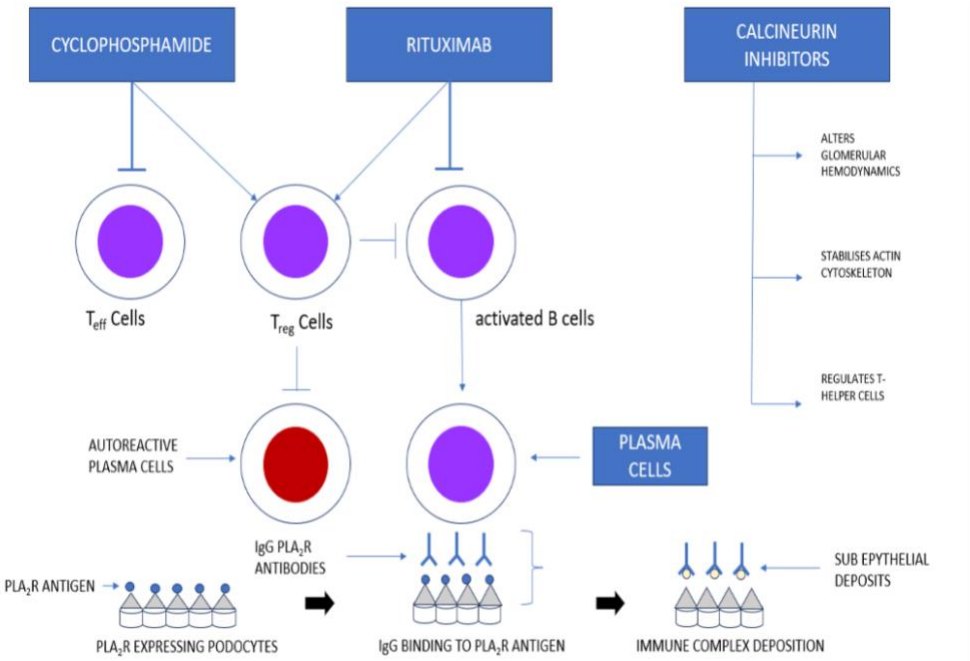

Figure 1. Immunopathogenesis of primary membranous nephropathy along with treatment targets (T eff – T effector cells; T reg – T regulatory cells; IgG – Immunoglobulin G; PLA2R – Phospholipase A2 receptor).

Typically, IgG4 is the predominant IgG subclass deposited in PMN, while other subclasses of IgG (IgG1, IgG2 and IgG3) are observed in MN cases with secondary causes [12]. These deposits, along with the formation of the membrane attack complex (MAC), initiate complement activation, resulting in podocyte structural damage and glomerular dysfunction [2]. Consequently, patients

diagnosed with MN commonly exhibit significant protein loss (>3.5g/day) in urine (proteinuria), reduced serum albumin levels (hypoalbuminemia), hyperlipidaemia and generalized oedema, which are collectively termed as nephrotic syndrome. In adults, MN is a prominent cause of nephrotic syndrome, accounting for approximately 25% of cases. It is estimated that about 5-30% of IMN patients with nephrotic syndrome experience spontaneous remission within five years, 15-30% encounter relapses and the rest of 14-41% progress to end-stage renal disease (ESRD) over a 15-year period [9].

In 70-80% of IMN patients, circulating antibodies target the M-type phospholipase A2 receptor, a cell surface transmembrane receptor on podocytes [13] Among patients who test negative for anti-PLA2R, approximately 3%-5% exhibit antibodies against anti-thrombospondin type 1 domain-containing 7A (THSD7A) [14]. Novel target antigens including semaphoring 3B (Sema 3B), neural epidermal growth factor-like 1 (NELL1), protocadherin 7 (PCDH7) and high-temperature requirement A1 (HTRA1) have been identified in the rest of patients [15]. In rare instances, proteins, such as aldose reductase, alpha-enolase, cationic bovine serum albumin and superoxide dismutase, serve as autoantigens for MN in children [16].

Treatment of primary membranous nephropathy

The identification of anti-PLA2R antibody has demonstrated a sensitivity of about 80% and specificity of 100% for PMN [2]. Moreover, a correlation is found between levels of circulating anti-PLA2R antibodies and disease progression, treatment response and outcomes in patients [15]. These findings collectively establish the role of anti-PLA2R antibody as a biomarker, aiding not only in the diagnosis of the disease but also in guiding treatment strategies for affected individuals. Given the potential presence of anti-PLA2R antibodies several months before the development of proteinuria, PMN patients with positive serum anti-PLA2R results but exhibiting <3.5g/day of proteinuria initially receive supportive care (SC) [2]. Following six months of SC, most patients undergo spontaneous remission, with proteinuria reduced to less than 4 g/day and a stable glomerular filtration rate (GFR). However, patients with persistent nephrotic syndrome over six months and continued positivity for serum anti-PLA2R antibodies are considered for immediate immunosuppressive therapy (IST). IST is recommended as the primary treatment for MN patients falling into specific risk categories. Patients classified as moderate-risk (with proteinuria ranging from 4 to 8 g/day and normal renal function) and high-risk (with proteinuria exceeding 8 g/day with or without renal insufficiency) receive IST as first-line therapy [16]. Immunosuppressive agents employed in this context include cytotoxic drugs (cyclophosphamide), monoclonal antibodies (Rituximab), calcineurin inhibitors (CNIs), corticosteroids and adrenocorticotrophic hormone (ACTH) formulations [17]. In 2012, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines for PMN recommended an initial therapy regimen comprising a 6-month course of alternating doses of oral glucocorticoids and oral cyclophosphamide at every month. This treatment protocol has demonstrated efficacy in achieving remission of proteinuria in approximately 50-60% of patients within 12 months and in 70-80% within 24-36 months [18, 19]. Moreover, it is associated with a low relapse rate and a decrease in the incidence of ESRD from 30-40% to ≤ 10% [18, 19].

While the amalgamation of cytotoxic medications and corticosteroids often elicits favourable responses in most patients, they are frequently associated with adverse side effects. These adverse effects include an increased risk of cancer, infertility, myelosuppression, and increased susceptibility to infections [20, 21]. Specifically, cyclophosphamide reduces the synthesis of nephrotoxic antibodies by substantially depleting B cells, albeit in a non-selective manner [22]. In patients who decline this treatment due to contraindications, CNIs present as a viable treatment alternative [23]. The latest KDIGO guidelines confine the use of alkylating agents to patients at high risk of disease progression, while regarding CNIs as an alternative therapeutic option [19]. Whether employed as

monotherapies or in conjunction with low-dose corticosteroids, CNIs have been shown to mitigate proteinuria and decelerate the decline in renal function among patients with IMN [24]. In comparison to cyclophosphamide, cyclosporine has exhibited success in attaining complete remission at an earlier stage and has demonstrated superior efficacy in reducing proteinuria levels [25]. However, the significant toxicity associated with these treatments, including hyperglycaemia, hirsutism, accelerated hypertension, gout and infections, emphasize the necessity for novel therapeutic modalities [26]. Furthermore, concerns regarding long-term nephrotoxicity, need of diligent monitoring of drug levels and the heightened relapse rates are substantial considerations for CNIs [27]. ACTH has also been employed as a therapeutic regimen for patients with PMN. Administered as monotherapy at a dosage of 1 mg twice weekly for one year, ACTH has been shown to decrease anti-PLA2R levels and achieve outcomes (greater than 80% remission at 6 months) like those attained with corticosteroids and cyclophosphamide together, while exhibiting minimal adverse effects [28, 29]. In another study involving 20 patients with MN and nephrotic syndrome, who received subcutaneous doses of 40 or 80 IU ACTH twice weekly, a substantial decrease in proteinuria (from 9.1 g/day to 3.9 g/day) was recorded, along with enhancements in serum albumin and cholesterol levels at 12 months, all without significant adverse effects [30]. Despite these encouraging outcomes, the efficacy of ACTH in PMN has not been thoroughly investigated, likely due to its high cost [31].

Rituximab and primary membranous nephropathy

Rituximab (RTX), a chimeric monoclonal antibody blended with mouse and human immunoglobulin IgG1, selectively targets the CD20 antigen located on surfaces of both normal and abnormal B lymphocytes [32, 33]. Its mechanism of action involves attaching to CD20, resulting in the depletion and subsequent elimination of B-cells. Initially employed in the treatment of lymphoma due to its ability for B-cell depletion, RTX has gained prominence as a therapeutic option for IMN patients, especially after the identification of autoantibodies to podocyte antigens (PLA2R and THSD7A) as diagnostic markers for IMN [34, 35]. Although the effects of RTX on MN have not been extensively studied in animal models, case reports and clinical trials consistently suggest positive remission rates and safety profiles among MN patients following RTX treatment [36]. Several studies have emphasized the potential of RTX as a promising treatment avenue for managing MN, demonstrating improvements in remission rates [37, 38]. RTX facilitates remission induction and proteinuria reduction by eliminating anti-PLA2R autoantibodies and removing subepithelial immune complexes from glomerular capillaries [39]. Moreover, systematic reviews and meta-analyses have highlighted the safety and effectiveness of RTX as both first line and second-line therapy for IMN patients [40, 42]. RTX has been associated with decreased levels of serum creatinine and urinary protein, increased total remission rates with a higher incidence of complete remission and decreased depletion of PLA2R-antibodies [43]. Additionally, adverse events related to RTX treatment have primarily been mild infusion-related reactions, with rare serious contradictions [44].

Objective of the study

In the context of RTX dosage for treating idiopathic membranous nephropathy (IMN), many health centres have adhered the standard dosing regimen, which typically involves either four weekly infusions of 375 mg/m^2 or two 1-gram doses administered on day 1 and day 15, often repeated after six months [45]. However, the extensive use of this high-dose regimen poses several challenges, thereby restricting its widespread acceptance for IMN treatment [46]. Primarily, the high cost of RTX and the logistical challenges associated with its administration make it difficult to afford in middle-income countries such as India. Additionally, a potential risk of infections is associated with the use of RTX [47], particularly in patients with a history of prior treatment with immunosuppressive drugs. Increased doses of RTX can amplify the cumulative immunosuppressive exposure in these patients,

a concern of particular significance in low- and middle-income countries such as India, where the prevalence of infectious diseases is notably high [46]. To mitigate these challenges, a low-dose regimen of RTX has been introduced. Lower doses of rituximab are considered safer and more cost-effective, significantly reducing both drug costs and hospitalization expenses [48]. However, studies have produced conflicting results regarding the clinical outcomes of patients [49, 50], thereby prompting a scrutiny of its efficacy. Hence, this necessitates a systematic review in this area.

The objective of the present study is to conduct an extensive literature review to identify studies that utilized low-dose RTX for IMN management. Subsequently, the collected data were subjected to meta-analysis to investigate the clinical and immunological efficacies of low-dose RTX across various follow-up periods and different stages of IMN. Through this endeavour, the meta-analysis seeks to offer a comprehensive understanding of the application of low dose RTX in the treatment of IMN globally.

Methodology

The present systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This research is registered in Prospero with id no:[[CRD42024522097]].

PICO strategy

In the present study, the population, intervention, comparison/control and outcome (PICO) framework was employed to conduct the search strategy based on the following question:

"How effective is low-dose rituximab in treating patients with primary membranous nephropathy?"

To address this question, the study population referred to the adult patients aged 18 years and older diagnosed with primary membranous nephropathy (MN). The intervention involved administering rituximab intravenously at a low dosage. The outcomes reviewed in the literature encompassed various clinical and immunological measures, achievement of complete or partial remission and the occurrence of relapse, as reported across different research studies and case reports.

Inclusion and exclusion criteria

Publications that met the following inclusion criteria were selected: (1) adult patients (aged ≥ 18 years) diagnosed with primary MN confirmed via renal biopsy; (2) patients experiencing nephrotic syndrome and testing positive for serum anti-PLA2R antibodies; (3) administration of rituximab intravenously at doses lower than standard regimens i.e. less than four weekly infusions of 375 mg/m^2 or two infusions of 1 gram each on day 0 and day 15; (4) studies published in English and; (5) studies published between 2004 and 2024.

The exclusion criteria were as follows: (1) use of rituximab for causes of nephrotic syndrome and primary glomerular diseases other than primary MN; (2) administration of rituximab at a dose of 375 mg/m^2 weekly for four doses or 1 gram each on day 0 and day 15; (3) patients having membranous nephropathy due to secondary causes and (4) presence of contraindications to the use of rituximab.

Search strategy

Based on previous studies concerning the treatment of MN with rituximab, various keywords were identified for use as search terms. These included "rituximab", "anti-CD20 monoclonal antibody", "Antigens, CD20", "primary", "idiopathic", "membranous nephropathy", "glomerulonephritis, membranous" and "membranous glomerulopathy". The literature search was conducted in five electronic databases, namely, PubMed, Wiley Online Library, Cochrane Library, Science Direct and

Springer. Logical combinations of appropriate keywords and medical subject headings (MeSH) terms were employed during the search process. Additionally, relevant studies were manually searched within the identified studies and related review papers. The literature search included peer-reviewed research articles, case reports, case series, randomized or non-randomized controlled trials published in English between 2004 and 2024. Table S1(Supplementary data) provides details of the electronic databases used, search terms, filters and number of results retrieved.

The PRISMA guidelines were followed to facilitate the identification, selection, evaluation and synthesis of studies relevant to the above-mentioned research question. The entire review process and number of studies finalized were illustrated in Figure 1. A total of 610 articles from five electronic databases (PubMed – 44; Wiley Online Library – 177, Science Direct – 205, Cochrane Library – 73 and Springer – 77 articles) and other sources (Google Scholar – 34) were identified. The researcher assessed these articles, resulting in the removal of three duplicates. Further, 548 studies were excluded as they were reviews, abstracts, chapters or editorials or were found non-relevant (studies concerning glomerular diseases other than MN; studies involving drugs other than rituximab; studies administering higher doses of rituximab; studies lacking clarity regarding disease type or drug dose; and studies focusing on adverse effects of rituximab or its application in children). This process yielded 59 full-text studies which were manually screened. Finally, a total of 16 studies that met all the eligibility criteria were selected for inclusion in the qualitative analysis.

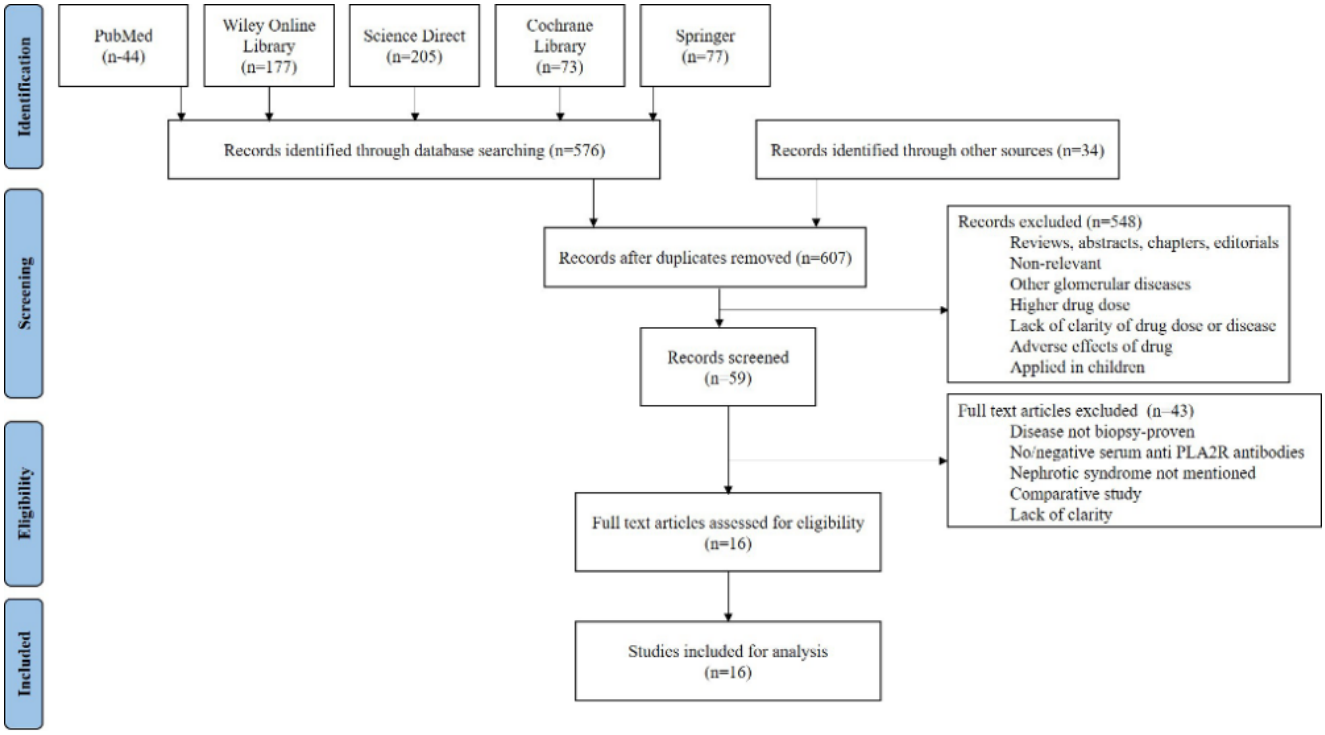

Figure 2. Study selection process.

Study selection and data selection process

During the study selection process, an initial search was conducted across PubMed, Wiley Online Library, Cochrane Library, Science Direct, Springer and Google Scholar (Figure 2) using predetermined search terms. Subsequently, the titles and abstracts of the identified articles were reviewed, and any studies not related to the research question were excluded. Duplicate or repetitive articles were also eliminated at this stage. Following this, full-text documents of the remaining relevant studies were obtained for further review, where they were assessed against pre-established inclusion and exclusion criteria. The references of the selected studies were then chronologically entered into an Excel spreadsheet for organization and analysis.

Data extraction

From each of the included studies, various information was extracted such as name of first author, year of publication, study design, settings, country where the study was conducted, patients' baseline characteristics, treatments administered, rituximab dose, duration of follow-up and study outcomes. The baseline characteristics of patients included total number of patients enrolled, gender, age, baseline values for serum albumin, serum creatinine, 24-hours proteinuria and estimated glomerular rate as well as their anti-PLA2R antibody positivity before rituximab treatment. Data extraction was limited to the rituximab arm of clinical trials or sections of studies that met the selection criteria. Following the data extraction process, a qualitative analysis of the extracted data was conducted.

Types of outcome measures and their definitions

The efficacy of low-dose rituximab in treating adult patients with primary MN was evaluated by extracting data on complete response (CR) rate, partial response (PR) rate, overall response rate, no response (NR) and relapse rate at the last follow-up. These parameters were considered as the primary outcomes of the study. Secondary endpoints included various clinical and immunological outcomes, such as serum creatinine levels, serum albumin levels, 24-hour proteinuria levels, protein-creatinine ratio, estimated glomerular filtration rate (eGFR) and anti-PLA2R antibody levels. As per definitions, CR was referred to as achieving a proteinuria level of 0.5 g/24-hr or less. PR was defined as experiencing a reduction in proteinuria of at least 50% from baseline with the final proteinuria level between 0.5 and 3.5 g/24-hr. Overall response (OR) encompassed both CR and PR whereas NR was characterized when proteinuria level is not reduced to at least 25% from baseline. Relapse was defined as the reappearance of the proteinuria level above 3.5 g/24-hr following CR or PR. Mainline treatment was defined as utilization of low-dose rituximab as a primary treatment strategy for IMN while second line treatment was defined as utilization of low-dose rituximab (rescue therapy) after failure of primary treatment regimen that included glucocorticoids, calcineurin inhibitors, cyclophosphamide or combination of immunosuppressants.

Quality and risk of bias assessment

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality and risk of bias assessment of included studies. This tool assesses quality of studies across three domains: selection (four items), comparability (two items) and exposure or outcome (three items). Each study can be rated between 0 and 9 and based on these scores, studies can be categorized into poor quality (scores 0-2), intermediate quality (scores 3-5) and high quality (scores 6-9). Publication bias was also checked using several methods including the funnel plot, Begg's test, and Egger's test. A two-sided p-value less than 0.05 was considered statistically significant.

Statistical analysis

The gathered data underwent thorough examination utilizing RevMan software (version 5.3, The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). Relapse-free survival was scrutinized employing the log odds ratio (OR), standard error (SE), and their respective 95% confidence intervals (CI). Meta-analysis was conducted utilizing both fixed-effect and random-effect methodologies depending on the I2 values. I2 statistic was classifies as (i) I2 = 0%–25% referring to no heterogeneity (ii) I2 = 25%–50% as moderate heterogeneity and (iii) I2 = 50%–75% as high heterogeneity and (iv) I2 = 75%–100% extreme heterogeneity. When the studies had high or extreme heterogeneity, random-effect model was employed for statistical analysis. No or moderate heterogeneity was treated with fixed-effects model.

Results

Characteristics of included studies

A total of 16 studies identified from literature search were found appropriate and included in this meta-analysis. Out of them, there were six retrospective studies [50, 55], two prospective studies [56, 57], four case reports [58, 61] one case series [62] and three cohort studies [63, 65] (Table 1). Eight studies [50, 51, 54, 57, 62, 63, 65] were performed in Asia, six studies in Europe [59, 64], and one study in Turkey [53]. All studies were published between 2014 and 2023 and included adult patients, with median or mean ages ranging from 31 to 64 years. Most patients in included studies reported proteinuria ranged from 1.6 to 20 g/day), serum albumin levels: 1.9 to 2.8 g/dL and serum creatinine levels: 0.9 to 1.82 mg/dL as baseline characteristics (Table 1). Nine studies reported estimated glomerular filtration rate (eGFR): 37 to 102 ml/min/1.73 m^2 while only five studies mentioned protein creatinine ratio which were from 6.6 to 9.8. Serum PLA-2R antibody levels were reported in seven studies with a level of 80 to 244 RU/mL.

References	Country	Study type	Gender (M/F)	Age (year)	Proteinuria (g/day)	Serum albumin (g/dL)	Serum creatinine (mg/dL)	eGFR (ml/min/ 1.73 m^2)	Serum PLA-2R antibody (RU/ml)	Protein creatinine ratio
[50]	India	R	14/7	33.3±12.3	6.2 ± 2.2	2.5 ± 0.5	0.9 ± 0.3	95.8 ± 26.9	–	–
[58]	France	CR	1/0	57	20	19	1.42	–	–	–
[59]	Italy	CR	9/5	64.4 ± 10.8	–	–	–	–	–	–
[51]	India	R	18/2	37.7±12.5	7.5±2.15	2.01±0.6	0.9±0.4	86.5±20	–	–
[56, 57]	India	P	4/1	55.2 ± 10.6	10.2±1.8	–	1.3 ± 0.6	>30	–	9.8±1.56
[60]	France	CR	1/0	31	1.6	2.9	1.6	–	194	–
[63]	Korea	C	11/2	55.3	–	2.6	1.7	37	80.1	6.6
[62]	India	CS	3/1	42	8.719- 12.2	2.0-2.7	1.1-1.4	56	108-121	–
[52]	France	R	22/6	44.4	–	1.9	1.10	68.7	–	6.23
[53]	Türkiye	R	11/9	39.9 ± 14.6	6.94	2.73 ± 0.78	–	102.1 ± 35.6	–	–
[64]	France	C	21/6	51	–	2.1	1.1	–	102.5	8.4
[65]	China	C	30/6	47.3±17.6	12.3±5.9	2.19±0.58	1.82 ±1.26	55.7±33.9	244.5±296.1	–
[55]	China	R	5/3	44.0 ± 11.7	8.14 ± 6.05	2.80 ± 0.842	1.09± 0.40	–	>20	–
[54]	China	R	25/7	55 ± 15	8.5 ± 3.6	2.48 ± 0.34	–	88 ± 25	>20	–
[61]	Germany	CR	1/0	34	–	–	–	–	–	8.8

Table 1. Baseline characteristics of included studies. R = retrospective study; CR = case report; CS = case series; p = prospective study; C = cohort.

Sample sizes of enrolled studies who received low-dose rituximab ranged from 1 to 32 (Table 2). Seven studies reported the outcomes of low-dose RTX as treatment for IMN patients who had not received prior IST (main-line RTX therapy)[52, 54, 56, 58, 59, 62, 64]; whereas other seven studies investigated the response to RTX as a second-line therapy [50, 53, 55, 60, 61, 63, 65]. Only two studies reported both main-line and second-line therapy among the enrolled patients [51, 62]. The low-dose RTX regimen in these studies were classified as follows: (1) one, two or three infusions of

375 mg/m^2 7 days or 15 days or 20 days apart; (2) single dose of 100 mg; (3) 200 mg once a month; and (4) two doses of 500 mg each given 7-10 days or 30 days apart. The follow-up time ranged from 2 to 24 months.

References	Sample size	Treatment type	Dose	Clinical outcomes					Immunological outcome	CR+PR (%)	CR or PR (%)	CR (%)	Follow-up (months)
				Proteinuria (g/day)	Serum albumin (g/dL)	Serum creatinine (mg/dL)	eGFR (ml/min/ 1.73 m^2)	Protein creatinine ratio	Serum PLA-2R antibody (RU/ml)				
[50]	10	Second-line	two doses of 500 mg each; 7-10 days apart	0.3-15.4	1.7-5.0	0.5-3.3	–	–	–	6/10 (60)	–	–	10-18.8
[58]	1	Main line	Two infusions at 375 mg/m^2 per week	12	1.9	1.86	–	–	378	–	–	–	6
[59]	14	Main line	single dose of 375 mg/m^2	7.5 ± 4.8	2.5 ± 0.5	1.05 ± 0.3	68.7 ± 26.6	–	13/14 no PLA2R Ab	13/14 (92.8)	–	–	24
[51]	20	65% as second line	two doses of 500 mg, 1 month apart	–	3.31±0.96	1.17±0.6	–	2.95±2.2	PLA2R Ab at 12 months 17.77 ± 21.23 RU/mL in CR and PR patients; 311.67 ± 356.05 RU/ml in NR	12/18 (66.7)	—	–	12
[56, 57]	5	Main line	single dose of 100 mg	1.08±0.5	normal	–	—	4.91±3.11	–	4/5 (80)	–	–	6
[60]	1	Second line	Two infusions at 375 mg/m^2 per week (first course); 1 gm (second course)	0.1	4.0	1.6	–	–	0	1/1 (100)	–	–	9
[63]	13	Second line	two infusions at 375 mg/m^2 per 2 weeks	–	2.3	—	–	7.5	46.1	8/13 (61.5)	–	–	22
[62]	4	3/4 first line 1/4 second line	100 mg	0.12-9.1	–	—	–	—	–	–	–	2/4 (50)	12
[52]	14	Main line	(11/28) two doses of 375 mg/m^2 weekly; (3/28) three doses of 375 mg/m^2 weekly	–	–	–	–	–	–	–	11/14 (78.6)	–	12
[53]	20	Second line	two weekly doses of 375 mg/m^2	4.08	2.07 ± 0.5	–	76.4 ± 22.24	–	–	–	12/18 (66.7%)		24
[64]	27	Main line	two weekly doses of 375 mg/m^2	–	2.9	–	–	3.7	8.3	–	8/27 (29.6)	–	6
[65]	21	Second line	(3/36) one dose of 375 mg/m^2 (11/36) two doses of 375 mg/m^2 (7/36) three doses of 375 mg/m^2	–	–	–	–	–	–	–	–	9/21 (42.8)	12
[55]	8	Second line	200 mg once a month	1.24 ± 1.34	2.093 ± 0.585	1.02 ± 0.225	–	–	–	8/8 (100)	–	–	12
[54]	32	Main line	monthly 100 mg	1.8 ± 3.0	2.93 ± 0.57	–	79 ± 21	–	–	27/32 (84.4)	–	–	18
[61]	1	Second line	two doses of 375 mg/m^2 at d8 and d28	<0.5	–	–	—	–	0	–	–	1/1 (100)	2

Table 2. Efficacy of low-dose rituximab in included studies.

Quality assessment

The quality of included studies was assessed according to the Cochrane Collaboration's "Risk of bias". It was observed that out of seven components, most of the included studies were categorized as "low risk" for five components, while their risks of random sequence generation and allocation concealment were high (Table 3, Figure 3). This suggests that the included studies are of good quality overall (Figure 4).

Study		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias		
Author	Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Total
Bagchi et al. [50]	2018	*	*	–	–	–	–	–	2/7
Dahan et al. [58]	2017	*	*	–	–	*	–	–	3/7
Fenoglio et al. [59]	2020	*	–	*	–	–	–	–	2/7
Gaggar et al. [51]	2023	*	*	–	–	–	–	–	2/7
George et al. [56]	2020	*	*	*	–	*	–	–	4/7
George et al. [57]	2020	*	*	*	–	*	–	–	4/7
Georges et al. [60]	2019	*	*	–	–	*	–	–	3/7
Jeon et al. [63]	2022	*	*	*	–	–	–	–	3/7
Mathew et al. [62]	2023	*	*	*	–	*	–	–	4/7
Michel et al. [52]	2021	*	–	–	–	–	–	–	1/7
Mirioğlu et al. [53]	2023	*	–	–	–	–	–	–	1/7
Seitz-Polski et al. [64]	2019	*	*	*	–	*	–	–	4/7
Wang et al. [65]	2018	*	–	–	–	–	–	–	1/7
Wang et al. [55]	2023	*	*	*	–	–	–	–	3/7
Wang et al. [54]	2023	*	*	*	–	–	–	–	3/7
Wen et al. [61]	2014	*	*	–	–	*	–	–	2/7

Table 3. Risk of bias assessment. * = Presence of the attribute in the study protocol. – = Absence/non-applicability of the attribute in the study protocol.

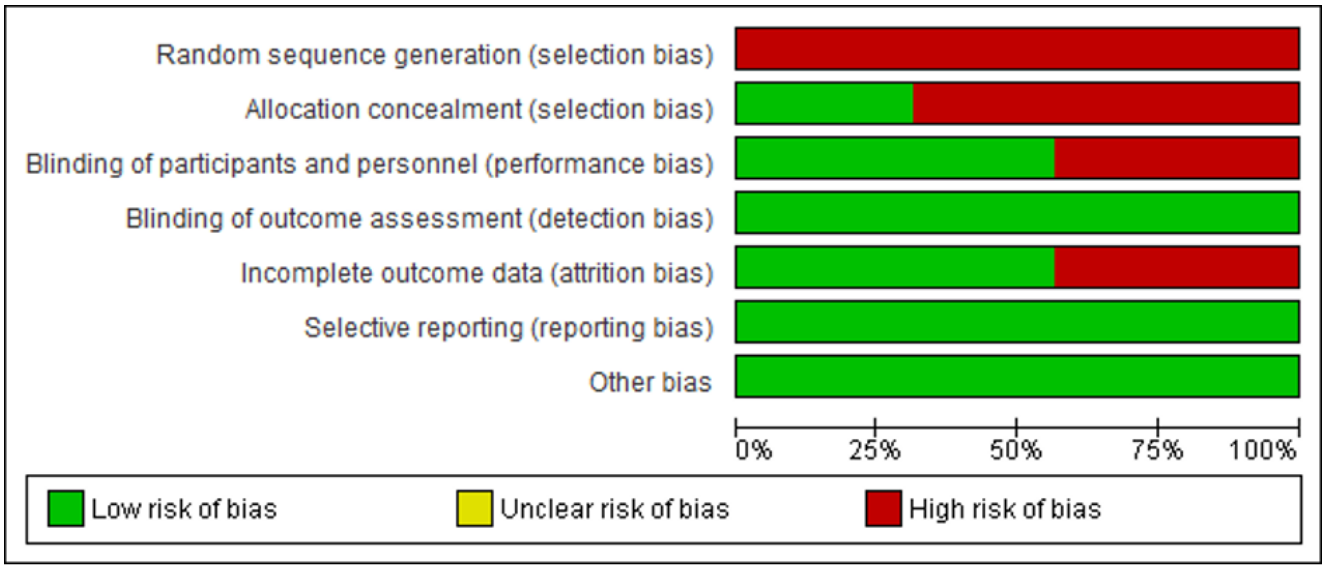

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

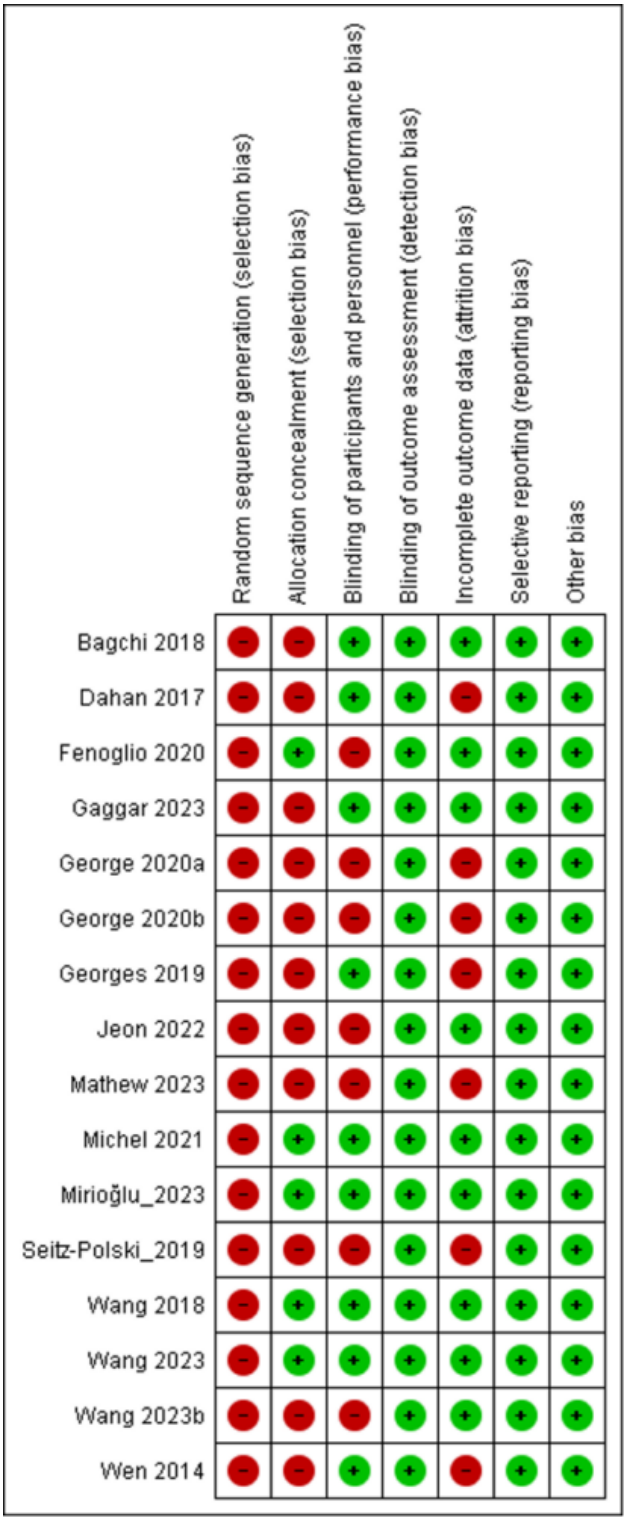

Figure 4. Risk of bias summary: authors' judgements about each risk of bias item for each included study.

Efficacy of low-dose rituximab in adults with MN

Complete and partial remission rates

Nine studies evaluated the complete and partial remission rates of patients following main-line treatment with RTX. The pooled analysis of Odds ratio (OR) revealed that the overall effect favored complete remission (CR) over combined complete and partial remission (CR+PR) in patients receiving RTX as a primary treatment (OR = 0.48, 95% CI= 0.30-0.75, p = 0.001) with no heterogeneity

among the studies (I^2 = 0%, p = 0.64). Five studies assessed the rates of CR and PR in patients following second-line treatment with RTX. The pooled analysis of OR indicated a preference for CR over CR+PR among these patients treated with RTX as a secondary treatment (OR = 0.27, 95% CI = 0.11-0.67, p = 0.005) with no heterogeneity among these studies (I^2 = 0%, p = 0.84). Overall, the subgroup analysis revealed a significant difference in treatment effects between patients undergoing main-line and second line RTX treatments (p < 0.0001), with minimal heterogeneity observed (I^2 = 17.2%, p = 0.27) (Figure 5). For CR, Begg and Mazumdar's test for rank correlation gave p-values of 0.029 and 0.006 for main-line and second-line studies, indicating significant publication bias (Table 4a). However, Egger's test for a regression intercept indicated publication bias for second-line studies (p = 0.001) but not for main-line studies (p = 0.071). For CR+PR, publication bias was not significant for main-line studies (Begg's test: p = 0.484, and Egger's test: p = 0.755). However, for second-line studies, the regression test indicated funnel plot asymmetry (p = 0.014) but not the rank correlation test (p = 0.243).

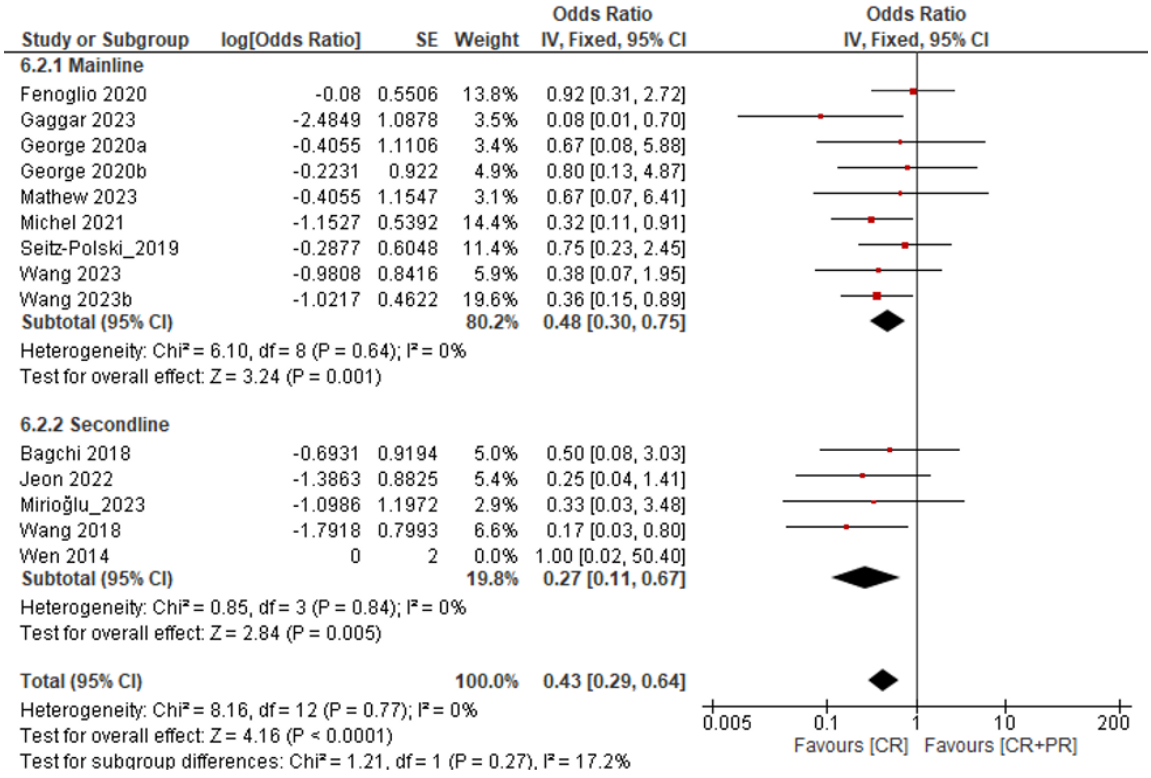

Figure 5. Forest plot of remission rates between main-line and second-line rituximab treatment.

Urinary protein

Nine studies reported the 24-hour urinary protein levels in patients at the end of treatment. Among them, six studies focused on patients undergoing main-line RTX treatment, while only three studies investigated the impact of RTX on proteinuria in patients receiving second-line therapy. The pooled analysis revealed that there is no significant reduction in proteinuria following both main-line (MD = -6.94, 95% CI= -8.65 to -5.24, p < 0.00001) and second line (MD = -6.94, 95% CI= -8.65 to -5.24, p < 0.00001) RTX treatments compared to baseline levels. The subgroup analysis showed a significant difference in proteinuria decrease between patients treated with main-line and second line RTX (MD between post-treatment and baseline values = -6.06, 95% CI= -7.96 to -4.16, p < 0.00001), with minimal heterogeneity observed across included studies (I^2 = 16.9%, p = 0.27) (Figure 6). Neither the rank correlation nor the regression test indicated any funnel plot asymmetry for main-line (p = 0.719 and p = 0.821, respectively) and second-line studies (p = 1.000 and p = 0.730, respectively), indicating no significant publication bias (Table 4a).

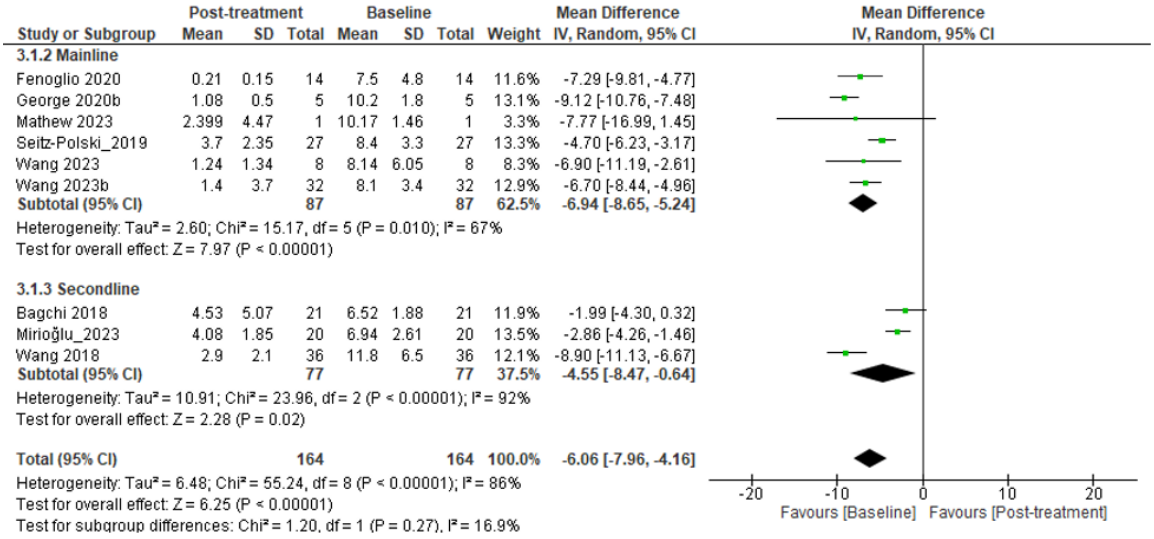

Figure 6. Forest plot of urinary protein between main-line and second-line rituximab treatment.

Serum albumin (g/dL)

Nine studies assessed the serum albumin level after RTX treatment. Among them, five studies focused on patients receiving main-line treatment, while four studies explored the effects of RTX on serum albumin levels in patients undergoing second-line therapy. The pooled analysis of the data demonstrated a significant increase in serum albumin levels in patients treated with both main-line (MD = 1.45, 95% CI= 1.00 to 1.91, $p < 0.00001$, $I^2 = 86\%$) and second line (MD = 0.88, 95% CI= 0.23 to 1.53, $p < 0.00001$, $I^2 = 89\%$) RTX treatments compared to baseline values, with considerable heterogeneity among studies. The subgroup analysis showed significant differences in albumin increment between two patient groups (MD = 1.21, 95% CI = 0.86 to 1.55, $p < 0.00001$), with moderate heterogeneity observed among the included studies ($I^2 = 50.6\%$, $p = 0.15$) (Figure 7). Neither the rank correlation nor the regression test indicated any funnel plot asymmetry for main-line ($p = 0.233$ and $p = 0.279$, respectively) and second-line studies ($p = 0.333$ and $p = 0.359$, respectively), indicating no significant publication bias (Table 4a).

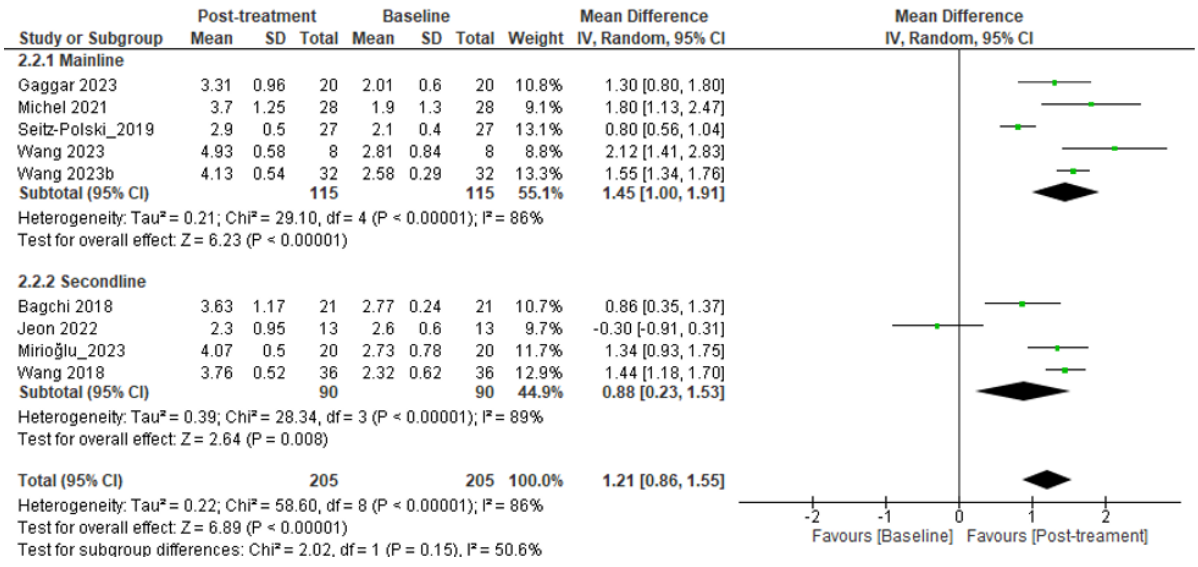

Figure 7. Forest plot of serum albumin between main-line and second-line rituximab treatment.

Serum creatinine (mg/dL)

The serum creatinine level was reported in eight studies. Pooled data from these studies indicated no significant difference in the reduction of creatinine level following both main-line (MD = 0.14,

95% CI= -0.48 to 0.76, p = 0.66, I^2 = 97% indicating heterogeneity) and second line (MD = 0.04, 95% CI= -0.18 to 0.26, p = 0.24, I^2 = 30% indicating no heterogeneity) RTX administration compared to baseline values. The subgroup analysis showed no significant difference in treatment outcome between two patient groups (MD = 0.10, 95% CI= -0.34 to 0.54, p = 0.65), with no heterogeneity observed among the included studies (I^2 = 0%, p = 0.76) (Figure 8). Neither the rank correlation nor the regression test indicated any funnel plot asymmetry for main-line (p = 1.000 and p = 0.123, respectively) and second-line studies (p = 1.000 and p = 0.847, respectively), indicating no significant publication bias (Table 4a).

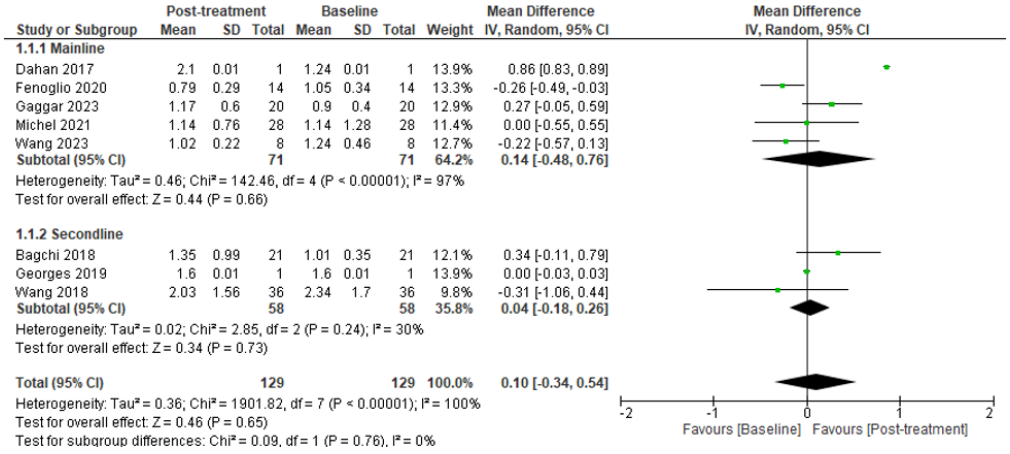

Figure 8. Forest plot of serum creatinine between main-line and second-line rituximab treatment.

Estimated glomerular filtration rate (mL/min/1.73 m^2)

The estimated glomerular filtration rates (eGFR) of patients after RTX treatment was reported in six studies. Pooled data from three studies indicated no significant difference in eGFR level between baseline and post main-line RTX treatment values (MD = 19.79, 95% CI= -6.96 to 46.55, p = 0.15, I^2 = 86% indicating heterogeneity) (Figure 9). Conversely, secondary RTX therapy demonstrated a lower eGFR in the post-treatment arm compared to baseline levels in IMN patients (MD = 10.57, 95% CI = 0.30 to 20.83, p = 0.04, I^2 = 45% indicating no important heterogeneity). The subgroup analysis revealed significant differences in eGFR between IMN patients receiving main-line and second-line RTX treatments (MD = 0.15.66, 95% CI = 3.68 to 27.64, p = 0.01), with no heterogeneity observed among the included studies (I^2 = 0%, p = 0.53). For main-line studies, the regression test indicated funnel plot asymmetry (p < 0.001) but not the rank correlation test (p = 1.000). Neither the rank correlation nor the regression test indicated any funnel plot asymmetry for second-line studies (p = 1.000 and p = 0.461, respectively), indicating no significant publication bias (Table 4a).

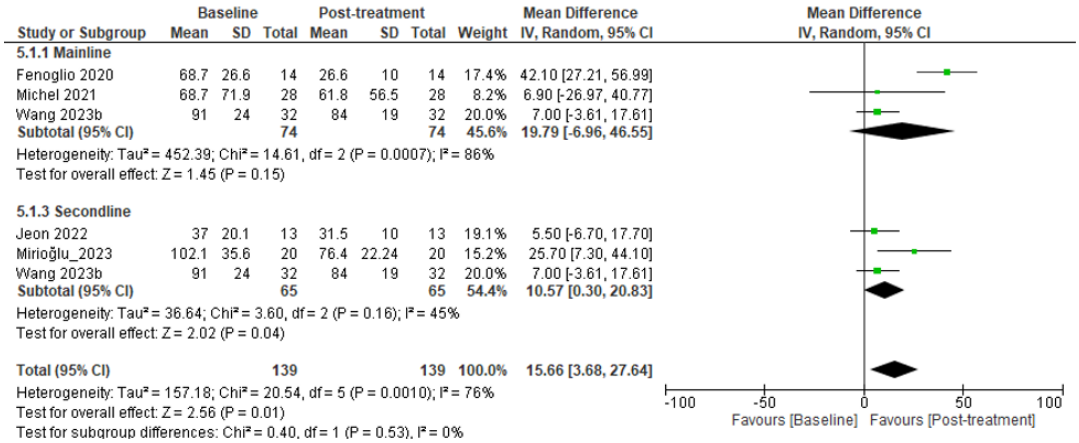

Figure 9. Forest plot of estimated glomerular filtrate rate between main-line and second-line rituximab treatment.

Protein creatinine ratio

Only three studies evaluated the protein creatinine ratio (PCR) in a total of 47 IMN patients treated with RTX. The pooled data from these studies showed a significant difference in PCR before and after RTX treatment (MD = 24.10, 95% CI = 1.07 to 47.13, p = 0.04), with heterogeneity among these studies (I^2 = 86%, p = 0.0008). In other words, individuals with IMN experienced a notable reduction in PCR when treated with RTX (Figure 10). Neither the rank correlation nor the regression test indicated any funnel plot asymmetry (p = 0.136 and p = 0.080 respectively), indicating no significant publication bias (Table 4b).

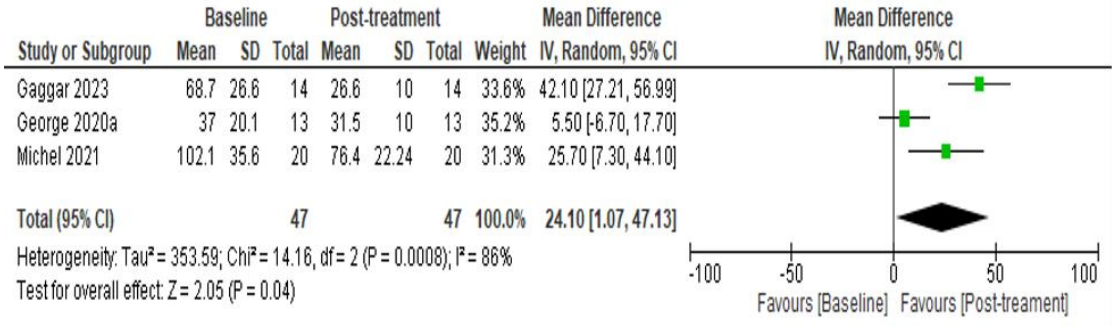

Figure 10. Forest plot of the effect of rituximab on protein creatinine ratio.

PLA2R-Antibody depletion

Four studies addressed PLA2R antibody depletion in a total of 92 IMN patients after RTX treatment. The pooled data from these studies showed a significant difference in PLA2R antibody depletion before and after RTX treatment (MD = 127.36, 95% CI= 14.90 to 239.81, P = 0.03), with heterogeneity among these studies (I^2 = 85%, P = 0.0001). In other words, individuals with IMN experienced a notable reduction in PLA2R-Ab when treated with low dose RTX (Figure 11).

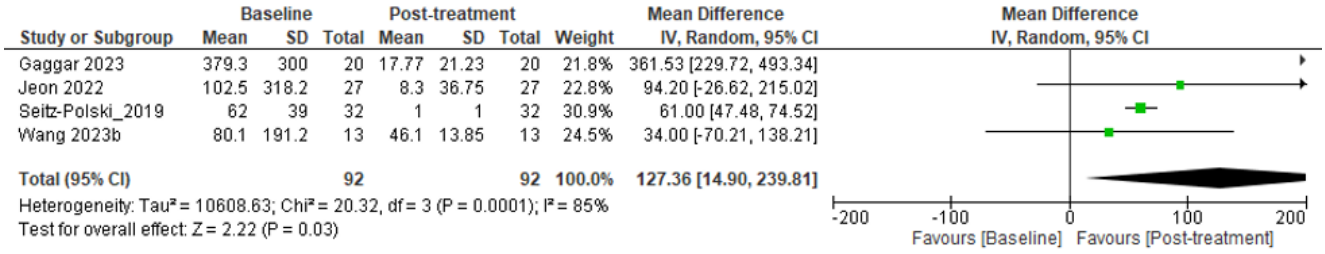

Figure 11. Forest plot of the effect of rituximab on PLA2R-Antibody depletion.

Discussion

A meta-analysis was conducted for evaluating the efficiency of low-dose RTX in the treatment of adult IMN patients in this systematic review. The analysis revealed that a comprehensive remission could be achieved in IMN patients with a low-dose regimen of RTX, which deviates from the standard dosing regimen of either two 1-gram doses administered on day 1 and day 15 or four weekly infusions of 375 mg/m^2. Reduction of protein creatinine ratio and serum albumin levels along with depletion of PLA-2R antibody levels collectively facilitated the remission, thereby underscoring the effectiveness of low-dose RTX. Various challenges related to high dosing regimens, such as potential risk of infections among patients, cumulative immunosuppressive exposure, and high cost, are mitigated by the utilization of low-dose RTX [46, 66, 67].

Test Name	Main-line		Second line	
	value	p	value	p
Complete remission				
Fail-Safe N	374.000	< .001	35.000	< .001
Begg and Mazumdar Rank Correlation	0.556	0.029	1.000	0.006
Egger's Regression	1.803	0.071	3.235	0.001
Complete and partial remission				
Fail-Safe N	1795.000	< .001	121.000	< .001
Begg and Mazumdar Rank Correlation	-0.200	0.484	0.429	0.243
Egger's Regression	-0.312	0.755	2.460	0.014
Urinary protein				
Fail-Safe N	446.000	< .001	65.000	< .001
Begg and Mazumdar Rank Correlation	0.200	0.719	0.333	1.000
Egger's Regression	0.226	0.821	0.346	0.730
Serum albumin				
Fail-Safe N	271.000	< .001	82.000	< .001
Begg and Mazumdar Rank Correlation	-0.600	0.233	0.667	0.333
Egger's Regression	-1.082	0.279	0.917	0.359
Serum creatinine				
Fail-Safe N	1286.000	< .001	0.000	0.348
Begg and Mazumdar Rank Correlation	0.000	1.000	-0.333	1.000
Egger's Regression	1.543	0.123	0.193	0.847
eGFR				
Fail-Safe N	11.000	< .001	1.000	0.034
Begg and Mazumdar Rank Correlation	0.333	1.000	0.333	1.000
Egger's Regression	3.548	< .001	0.737	0.461
PLA2R-Antibody depletion				
Fail-Safe N				
Begg and Mazumdar Rank Correlation				
Egger's Regression				

Table 4a. Publication bias assessment for studies evaluating different clinical and immunological outcomes. Note: Fail-safe N Calculation Using the Rosenthal Approach.

Test Name	value	p
Fail-Safe N	21.000	< .001
Begg and Mazumdar Rank Correlation	0.524	0.136
Egger's Regression	1.750	0.080

Table 4b. Publication bias assessment for studies evaluating protein creatinine ratio. Note: Fail-safe N Calculation Using the Rosenthal Approach.

Increment in serum albumin levels among IMN patients and complete remission were found to be substantially associated with both main-line and second line RTX treatments in the present meta-analysis. The KDIGO guideline for glomerular disease recommended RTX as the first-line therapy of high-risk IMN patients in 2021 [68]. The efficacy of rituximab in the management of IMN as both first line and second-line immunosuppressive therapy in such patients was demonstrated by Fenoglio et al.[59]. In a comparison between IMN patients treated with alkylating agents and steroids but failed to respond and those who had not been previously exposed to immunosuppressive drugs, the pooled OR rates for both main- and second-line treatment groups revealed that the low dose RTX regimen was more effective in inducing a total remission with a relatively better level of serum albumin among the former group of patients than the latter. Substantial toxicity, specifically infertility, malignancy, and infections, is found to be associated with the usage of immunosuppressive agents [21]. Consequently, diminished rates of adverse scenarios and non-requirement of steroids resulted in the reduction of hospitalization costs and medication expenses, thereby rendering the main-line RTX therapy to be more efficient than the second-line therapy. Conversely, patients who were naive to treatment were not affected by the efficiency of RTX that was evident in the reduction of eGFR among patients who were priorly subjected to immunosuppressants. You et al. [41] found that the usage of RTX was more efficient in comparison to other immunosuppressive treatments in the treatment of IMN patients, who were resistant to other immunosuppressive therapy agents and those who relapsed.

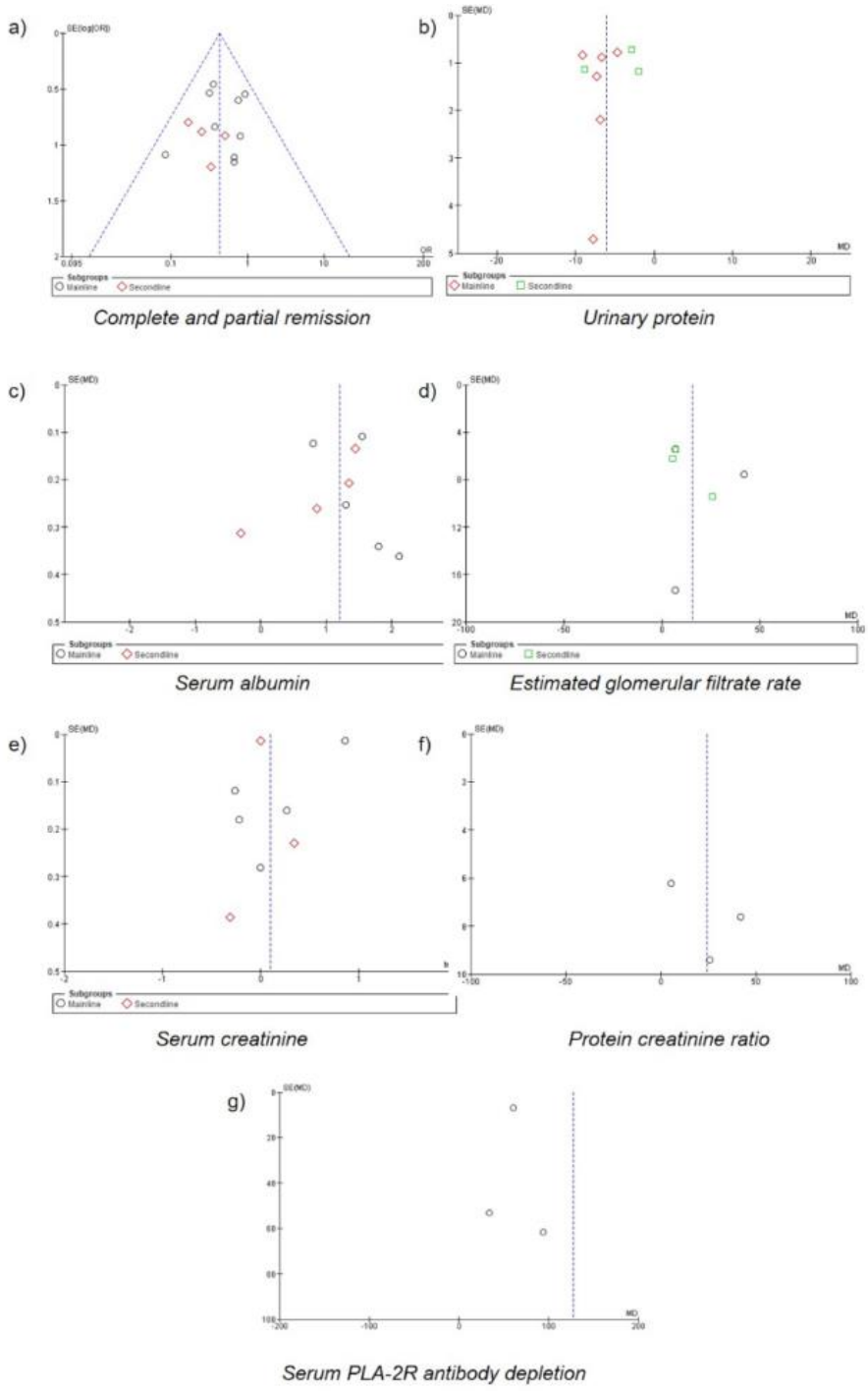

Figure 12. Funnel plots showing the visual outcomes of publication bias assessment.

Transient or incomplete depletion of autoreactive B cells might be responsible for the failure of prior non-selective immunosuppressive treatments. In such cases, pathogenic B cells are depleted sustainably and completely due to the capability of RTX. Such a mechanism could explain the resultant decrease in proteinuria that is systematically preceded by continuous and immediate depletion of circulating B cells [41, 69].

However, serum creatinine levels and urinary protein levels were not reduced through either main-line or second line RTX treatments in the present study. The low eGFR trend noted especially in the second line treatment with low dose rituximab was probably because of the inclusion of high-risk

cases of membranous nephropathy , irreversible glomerular and interstitial damage due to the disease process, incomplete depletion of autoreactive B cells and nephrotoxicity of long term immunosuppressants like calcineurin inhibitors [49, 51].

It was also found that PLA-2R antibody levels were depleted and the protein creatinine ratio was reduced in IMN patients due to RTX. In a study conducted by Wang et al. [54], B-cell depletion was observed with a progressive decrease in anti-PLA2R concentrations among enrolled patients who received two monthly doses of rituximab (100 mg). Likewise, depletion of CD19 caused by a single dose of rituximab 100 mg was reported by Ramachandran et al. [70]. It is evidenced that administration of small doses results in profound depletion of CD19+ B-cell within few hours [71], and such depletion is beneficial for the negative conversion of anti-PLA2R antibodies and it could be sustained for a minimum of one month [54]. Subsequently, it could be inferred that the production of autoantibodies could be reduced against PLA2R by decreasing the population of B-cells. Further, the counts of CD19+ and CD20+ B-cells are closely associated with the response rate to RTX among IMN patients [58, 64]. Although B-cell depletion was not particularly addressed in the present study, the remission rate found among IMN patients with low-dose RTX was possibly due to the induction of B-cell depletion by RTX, resulting in the reduction of PLA2R antibody levels.

Despite the efficacy of low-dose RTX being evident in the decline of immunological and clinical results [62, 63], an argument exists between standard treatment regimens and low-dose regimens of rituximab among IMN patients. In the treatment of PMN, Fenoglio et al. [59] found that the effects of rituximab 375 mg/m^2 were the same for one-time administration and four-time administration. Conversely, Moroni et al. [49] proposed that longer treatment durations and higher doses were required for inducing and sustaining responses among patients with high titers of anti-PLA2R antibodies because they found that clinical remission could not be efficiently achieved through low-dose RTX. Consequently, it is recommended that factors, such as patient's immune status, comorbidities, primary disease, and age, should be considered for customizing the specific dosing regimen. Mini-dose regimen must not be adopted for PMN patients with high anti-PLA2R titer, but it might be suitable for the susceptible subset of the PMN population, such as patients with low anti-PLA2R antibody titer, patients with very low serum immunoglobulin, patients who have recovered from severe infections, patients susceptible to infection, or elderly people [54].

The studies included in the meta-analysis ascertain the safety and tolerance of low dose RTX among most of the IMN patients. Provision of minor supportive treatment or adjustment of the drug infusion rate could resolve the transfusion-related reactions, which were the primary adverse events that were associated with RTX treatment [43]. However, the scope of the present study does not cover this topic.

Limitations

The inclusion of case series, case reports and observational design studies, due to paucity of well-designed randomized controlled trials, may have marginally skewed the bias risk assessment in this systematic review and metanalysis.

Conclusion

Low-dose rituximab demonstrates its effectiveness in treating adult patients with IMN, supporting its use as both a main-line and rescue therapy (second line) for achieving clinical outcomes. Nevertheless, the lack of B-cell count data due to limited availability could have offered valuable insights into the therapeutic efficacy of rituximab, thus constraining the scope of this meta-analysis.

The heterogeneity in patient populations with varying antibody statuses in one study, where some tested positive for serum anti-PLA2R antibodies while others were negative or had unavailable data, led to inconsistency in results regarding the efficacy of RTX in PLA2R antibody depletion. This study emphasizes the importance of conducting further research and clinical trials to optimize the low-dosing regimen of rituximab based on patients' health factors to position it as a promising avenue for the future of IMN therapy.

Electronic Database PubMed	Final search terms	Filters	N° of hits
Search 1	((Rituximab [[MeSH Terms]]) OR (Antigens, CD20[[MeSH Terms]])) OR (RTX[[Title/Abstract]])	2004-2024; Case Reports, Classical Article, Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Randomized Controlled Trial	8866
Search 2	((primary [[Title/Abstract]]) OR (idiopathic [[Title/Abstract]])) AND (Glomerulonephritis, Membranous [[MeSH Terms]])	2004-2024; Case Reports, Classical Article, Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Randomized Controlled Trial	364
Search 3	((((((Rituximab [[MeSH Terms]]) OR (Antigens, CD20[[MeSH Terms]])) OR (RTX[[Title/Abstract]])) AND (primary [[Title/Abstract]])) OR (idiopathic [[Title/Abstract]])) AND (Glomerulonephritis, Membranous [[MeSH Terms]])	2004-2024; Case Reports, Classical Article, Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Randomized Controlled Trial	44
Search 4	((((Rituximab [[MeSH Terms]]) OR (Antigens, CD20[[MeSH Terms]])) OR (RTX[[Title/Abstract]])) OR (Anti-CD20 monoclonal antibody [[Title/Abstract]])) OR (monoclonal antibody to B-cell antigen CD20[[Title/Abstract]]) AND ((primary [[Title/Abstract]]) OR (idiopathic [[Title/Abstract]])) AND (Glomerulonephritis, Membranous [[MeSH Terms]])	2004-2024; Case Reports, Classical Article, Clinical Study, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Randomized Controlled Trial	44
Wiley Online Library			
Search 1	"Primary OR idiopathic" anywhere and "membranous nephropathy OR membranous glomerulonephritis OR membranous glomerulopathy" anywhere and "Rituximab OR Antigens, CD20 OR RTX"	2004-2024; journals; medical science	279
Search 2	"Primary OR idiopathic" anywhere and "membranous nephropathy OR membranous glomerulonephritis OR membranous glomerulopathy" anywhere and "Rituximab OR Antigens, CD20 OR RTX" anywhere and "dose" anywhere and "case OR comparative"	2004-2024; journals; medical science	270
Search 3	"Primary membranous nephropathy OR idiopathic membranous nephropathy OR primary membranous glomerulonephritis OR idiopathic membranous glomerulonephritis OR primary membranous glomerulopathy OR idiopathic membranous glomerulopathy" anywhere and "Rituximab OR Antigens, CD20 OR RTX" anywhere and "case report OR case series OR comparative study OR clinical trials" anywhere and "remission OR treatment OR efficacy OR safety"	2004-2024, journals, medical science	207
Search 4	"Primary membranous nephropathy OR idiopathic membranous nephropathy OR primary membranous glomerulonephritis OR idiopathic membranous glomerulonephritis OR primary membranous glomerulopathy OR idiopathic membranous glomerulopathy" anywhere and "Rituximab OR Antigens, CD20 OR RTX OR Anti-CD20 monoclonal antibody OR Rituximab CD20 Antibody OR Mabthera"	2004-2024, journals, medical science	179
Search 5	"Primary membranous nephropathy OR idiopathic membranous nephropathy OR primary membranous glomerulonephritis OR idiopathic membranous glomerulonephritis OR primary membranous glomerulopathy OR idiopathic membranous glomerulopathy" anywhere and "Rituximab OR	2004-2024, journals, medical science	177

	Antigens, CD20 OR RTX OR Anti-CD20 monoclonal antibody OR Rituximab CD20 Antibody OR Mabthera" anywhere and "case studies OR case study OR case report OR case series OR clinical trial OR comparative study"		
Science Direct			
Search 1	(Rituximab OR Antigens, CD20 OR RTX OR Anti-CD20 monoclonal antibody) AND (primary OR idiopathic) AND (membranous nephropathy OR membranous glomerulonephritis OR membranous glomerulopathy)	2004-2024, research articles, case reports, short communications, medicine & dentistry, immunology & microbiology, English	440
Search 2	(Rituximab OR Anti-CD20 monoclonal antibody) AND (primary OR idiopathic) AND (membranous nephropathy OR membranous glomerulonephritis) AND (case OR clinical trial)	2004-2024, research articles, case reports, short communications, medicine & dentistry, immunology & microbiology, English	397
Search 3	(Rituximab OR Antigens, CD20 OR Anti-CD20 monoclonal antibody) AND (primary OR idiopathic) AND (membranous nephropathy OR membranous glomerulonephritis OR membranous glomerulopathy) AND clinical trial	2004-2024, research articles, case reports, short communications, medicine & dentistry, immunology & microbiology, English	205
Cochrane Library			
Search 1	"rituximab" OR Antigens, CD20 in Title Abstract Keyword AND primary membranous nephropathy OR idiopathic membranous nephropathy in Title Abstract Keyword	2004-2024, trials, English	73
Springer			
Search 1	(Rituximab OR Antigens, CD20) AND (primary membranous nephropathy OR idiopathic membranous nephropathy OR primary membranous glomerulonephritis OR idiopathic membranous glomerulonephritis OR primary membranous glomerulopathy OR idiopathic membranous glomerulopathy)	2004-2024, English, article, Medicine & public health, nephrology, urology, medicine/public health, internal medicine, laboratory medicine	110
Search 2	(Rituximab OR Antigens, CD20 OR immunosuppressive therapy) AND (primary membranous nephropathy OR idiopathic membranous nephropathy OR primary membranous glomerulonephritis OR idiopathic membranous glomerulonephritis OR primary membranous glomerulopathy OR idiopathic membranous glomerulopathy) AND (case)	2004-2024, English, article, Medicine & public health, nephrology, urology, medicine/public health, internal medicine, laboratory medicine	241
Search 3	(Rituximab OR anti-CD20 monoclonal antibody OR immunosuppressive therapy) AND (primary OR idiopathic) AND (membranous nephropathy OR membranous glomerulonephritis OR membranous glomerulopathy) AND (efficacy OR remission OR safety OR treatment)	2004-2024, English, article, Medicine & public health, nephrology, urology, medicine/public health, internal medicine, laboratory medicine	298
Search 4	(Rituximab OR Antigens, CD20 OR anti-CD monoclonal antibody) AND (primary membranous nephropathy OR idiopathic membranous nephropathy OR primary membranous glomerulonephritis OR idiopathic membranous glomerulonephritis OR primary membranous glomerulopathy OR idiopathic membranous glomerulopathy) AND (case OR clinical trial)	2004-2024, English, article, Medicine & public health, nephrology, urology, medicine/public health, internal medicine, laboratory medicine	77

Supplementary table. Electronic database search.

BIBLIOGRAPHY

1. Ponticelli C, Glassock RJ. Glomerular diseases: Membranous nephropathy-a modern view. Clin J Am Soc Nephrol. 2014;9(3):609–16. https://doi.org/10.2215/CJN.04160413.
2. Couser WG. Primary membranous nephropathy. Clin J Am Soc Nephrol. 2017;12(6):983–97. https://doi.org/10.2215/CJN.11761116.
3. Moroni G, Ponticelli C. Secondary Membranous Nephropathy. A Narrative Review. Front Med. 2020;7(December):1–13. https://doi.org/10.3389/fmed.2020.611317.
4. Ronco P, Beck L, Debiec H, Fervenza FC, Hou FF, Jha V, et al. Membranous nephropathy. Nat Rev Dis Prim [[Internet]]. 2021;7(1). https://doi.org/10.1038/s41572-021-00303-z.
5. Cattran DC, Brenchley PE. Membranous nephropathy: integrating basic science into improved clinical management. Kidney Int [[Internet]]. 2017;91(3):566–74. https://doi.org/10.1016/j.kint.2016.09.048.
6. Ayalon R, Beck LH. Membranous nephropathy: not just a disease for adults. Pediatr Nephrol. 2015;30(1):31–9. https://doi.org/10.1007/s00467-013-2717-z.
7. Rychlík I, Jančová E, Tesař V, Kolský A, Lácha J, Stejskal J, et al. The Czech registry of renal biopsies. Occurrence of renal diseases in the years 1994-2000. Nephrol Dial Transplant. 2004;19(12):3040–9 https://doi.org/10.1093/ndt/gfh521.
8. Hogan SL, Muller KE, Jennette JC, Falk RJ. A review of therapeutic studies of idiopathic membranous glomerulopathy. Am J Kidney Dis. 1995;25(6):862–75. https://doi.org/10.1016/0272-6386(95)90568-5.
9. Hoxha E, Reinhard L, Stahl R. Membranous nephropathy: new pathogenic mechanisms and their clinical implications. Nat Rev Nephrol. 2022;18(7):466–78. https://doi.org/10.1038/s41581-022-00564-1.
10. Lai WL, Yeh TH, Chen PM, Chan CK, Chiang WC, Chen YM, et al. Membranous nephropathy: A review on the pathogenesis, diagnosis, and treatment. J Formos Med Assoc [[Internet]]. 2015;114(2):102–11. https://doi.org/10.1016/j.jfma.2014.11.002.
11. Ronco P, Debiec H. Pathogenesis of membranous nephropathy: Recent advances and future challenges. Nat Rev Nephrol [[Internet]]. 2012;8(4):203–13. https://doi.org/10.1038/nrneph.2012.35.
12. Doi T, Mayumi M, Kanatsu K, Suehiro F, Hamashima Y. Distribution of IgG subclasses in membranous nephropathy. Clin Exp Immunol [[Internet]]. 1984;58(1):57–62.
13. Beck L, Bonegio R, Lambeau G, Beck D, Powell D, Cummins T, et al. M-Type Phospholipase A2 Receptor as Target Antigen in Idiopathic Membranous Nephropathy. N Engl J Med. 2009;361(1):11–20. https://doi.org/10.1056/NEJMoa0810457.
14. Tomas NM, Beck LH, Meyer-Schwesinger C, Seitz-Polski B, Ma H, Zahner G, et al. Thrombospondin Type-1 Domain-Containing 7A in Idiopathic Membranous Nephropathy. N Engl J Med. 2014;371(24):2277–87. https://doi.org/10.1056/NEJMoa1409354.
15. Gu Y, Xu H, Tang D. Mechanisms of primary membranous nephropathy. Biomolecules. 2021;11(4):1–21. https://doi.org/10.3390/biom11040513.
16. Keri KC, Blumenthal S, Kulkarni V, Beck L, Chongkrairatanakul T. Primary membranous nephropathy: Comprehensive review and historical perspective. Postgrad Med J. 2019;95(1119):23–31. https://doi.org/10.1136/postgradmedj-2018-135729.
17. Scolari F, Alberici F, Mescia F, Delbarba E, Trujillo H, Praga M, et al. Therapies for Membranous Nephropathy: A Tale From the Old and New Millennia. Front Immunol. 2022;13(March). https://doi.org/10.3389/fimmu.2022.789713.
18. Ponticelli C, Altieri P, Scolari F, Passerini P, Roccatello D, Cesana B, et al. A randomized study comparing methylprednisolone plus chlorambucil versus methylprednisolone plus cyclophosphamide in idiopathic membranous nephropathy. J Am Soc Nephrol. 1998;9(3):444–50. https://doi.org/10.1681/ASN.V93444.
19. Cybulsky A V., Walsh M, Knoll G, Hladunewich M, Bargman J, Reich H, et al. Canadian society of nephrology commentary on the 2012 KDIGO clinical practice guideline for glomerulonephritis: Management of glomerulonephritis in adults. Am J Kidney Dis [[Internet]]. 2014;63(3):363–77. https://doi.org/10.1053/j.ajkd.2013.12.001.
20. Bomback AS, Fervenza FC. Membranous Nephropathy: Approaches to Treatment. Am J Nephrol. 2018;47(suppl 1):30–42. https://doi.org/10.1159/000481635.
21. von Groote TC, Williams G, Au EH, Chen Y, Mathew AT, Hodson EM, et al. Immunosuppressive treatment for primary membranous nephropathy in adults with nephrotic syndrome. Cochrane Database Syst Rev. 2021;2021(11). https://doi.org/10.1002/14651858.CD004293.pub4.
22. Ruggenenti P, Fervenza FC, Remuzzi G. Treatment of membranous nephropathy: Time for a paradigm shift. Nat Rev Nephrol [[Internet]]. 2017;13(9):563–79. https://doi.org/10.1038/nrneph.2017.92.
23. Radhakrishnan J, Cattran DC. The KDIGO practice guideline on glomerulonephritis: Reading between the (guide)lines-application to the individual patient. Kidney Int [[Internet]].

2012;82(8):840–56. https://doi.org/10.1038/ki.2012.280.
24. Howman A, Chapman TL, Langdon MM, Ferguson C, Adu D, Feehally J, et al. Immunosuppression for progressive membranous nephropathy: A UK randomised controlled trial. Lancet [[Internet]]. 2013;381(9868):744–51. https://doi.org/10.1016/S0140-6736(12)61566-9.
25. Lin S, Li HY, Zhou T, Lin W. Efficacy and safety of cyclosporine A in the treatment of idiopathic membranous nephropathy in an asian population. Drug Des Devel Ther. 2019;13:2305–30. https://doi.org/10.2147/DDDT.S204974.
26. Cravedi P, Remuzzi G, Ruggenenti P. Rituximab in primary membranous nephropathy: First-line therapy, why not? Nephron – Clin Pract. 2014;128:261–9. https://doi.org/10.1159/000368589.
27. Angioi A, Lepori N, López AC, Sethi S, Fervenza FC, Pani A. Treatment of primary membranous nephropathy: where are we now? J Nephrol. 2018;31(4):489–502. https://doi.org/10.1007/s40620-017-0427-5.
28. Ponticelli C, Passerini P, Salvadori M, Manno C, Viola BF, Pasquali S, et al. A randomized pilot trial comparing methylprednisolone plus a cytotoxic agent versus synthetic adrenocorticotropic hormone in idiopathic membranous nephropathy. Am J Kidney Dis. 2006;47(2):233–40. https://doi.org/10.1053/j.ajkd.2005.10.016.
29. van de Logt AE, Beerenhout CH, Brink HS, van de Kerkhof JJ, Wetzels JF, Hofstra JM. Synthetic ACTH in high risk patients with idiopathic membranous nephropathy: A prospective, open label cohort study. PLoS One. 2015;10(11):1–12. https://doi.org/10.1371/journal.pone.0142033.
30. Hladunewich MA, Cattran D, Beck LH, Odutayo A, Sethi S, Ayalon R, et al. A pilot study to determine the dose and effectiveness of adrenocorticotrophic hormone (H.P. Acthar® Gel) in nephrotic syndrome due to idiopathic membranous nephropathy. Nephrol Dial Transplant. 2014;29(8):1570–7. https://doi.org/10.1093/ndt/gfu069.
31. Kittanamongkolchai W, Cheungpasitporn W, Zand L. Efficacy and safety of adrenocorticotropic hormone treatment in glomerular diseases: A systematic review and meta-analysis. Clin Kidney J. 2016;9(3):387–96. https://doi.org/10.1093/ckj/sfw045.
32. Rozman S, Grabnar I, Novaković S, Mrhar A, Jezeršek Novaković B. Population pharmacokinetics of rituximab in patients with diffuse large B-cell lymphoma and association with clinical outcome. Br J Clin Pharmacol. 2017;83(8):1782–90. https://doi.org/10.1111/bcp.13271.
33. Rudnicki M. Rituximab for Treatment of Membranoproliferative Glomerulonephritis and C3 Glomerulopathies. Biomed Res Int. 2017;2017. https://doi.org/10.1155/2017/2180508.
34. Beck LH, Fervenza FC, Beck DM, Bonegio RGB, Malik FA, Erickson SB, et al. Rituximab-induced depletion of anti-PLA2R autoantibodies predicts response in membranous nephropathy. J Am Soc Nephrol. 2011;22(8):1543–50. https://doi.org/10.1681/ASN.2010111125.
35. Klomjit N, Zand L. Rituximab Is Preferable to Cyclophosphamide for Treatment of Membranous Nephropathy: PRO. Kidney360. 2021;2(11):1696–8. https://doi.org/10.34067/KID.0002492021.
36. Gauckler P, Shin J Il, Alberici F, Audard V, Bruchfeld A, Busch M, et al. Rituximab in Membranous Nephropathy. Kidney Int Reports. 2021;6(4):881–93. https://doi.org/10.1016/j.ekir.2020.12.035.
37. Fiorentino M, Tondolo F, Bruno F, Infante B, Grandaliano G, Gesualdo L, et al. Treatment with rituximab in idiopathic membranous nephropathy. Clin Kidney J. 2016;9(6):788–93. https://doi.org/10.1093/ckj/sfw091.
38. Fervenza FC, Appel GB, Barbour SJ, Rovin BH, Lafayette RA, Aslam N, et al. Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy. N Engl J Med. 2019;381(1):36–46. https://doi.org/10.1056/NEJMoa1814427.
39. Cravedi P. Rituximab in Membranous Nephropathy: Not all studies are created equal. Nephron. 2017;135(1):46–50. https://doi.org/10.1159/000450659.
40. Huang L, Dong QR, Zhao YJ, Hu GC. Rituximab for the management of idiopathic membranous nephropathy: a meta-analysis. Int Urol Nephrol [[Internet]]. 2021;53(1):111–9. https://doi.org/10.1007/s11255-020-02633-5.
41. You L, Ye P, Xiao G, Liang J, Kong Y. Rituximab for the treatment of idiopathic membranous nephropathy with nephrotic syndrome: a systematic review and meta-analysis. Turkish J Med Sci. 2021;51(6):2870–80. https://doi.org/10.3906/sag-2104-177.
42. Xue C, Wang J, Pan J, Liang C, Zhou C, Wu J, et al. Cyclophosphamide induced early remission and was superior to rituximab in idiopathic membranous nephropathy patients with high anti-PLA2R antibody levels. BMC Nephrol. 2023;24(1):1–13. https://doi.org/10.1186/s12882-023-03307-x.
43. Lu W, Gong S, Li J, Luo H, Wang Y. Efficacy and safety of rituximab in the treatment of membranous nephropathy. A systematic review and meta-analysis. Medicine (Baltimore). 2020;99(16):e19804. https://doi.org/10.1097/MD.0000000000019804.
44. Zou P, Li H, Cai J, Chen Z, Li C, Li X. Therapy of Rituximab in Idiopathic Membranous Nephropathy with Nephrotic Syndrome: A

Systematic Review and Meta-analysis. Chinese Med Sci J. 2018;33(1):9–19. https://doi.org/10.24920/21803.
45. Fervenza FC, Abraham RS, Erickson SB, Irazabal MV, Eirin A, Specks U, et al. Rituximab therapy in idiopathic membranous nephropathy: A 2-year study. Clin J Am Soc Nephrol. 2010;5(12):2188–98. https://doi.org/10.2215/CJN.05080610.
46. Bagchi S, Subbiah AK, Bhowmik D, Mahajan S, Yadav RK, Kalaivani M, et al. Low-dose Rituximab therapy in resistant idiopathic membranous nephropathy: Single-center experience. Clin Kidney J. 2018 Jun 1;11(3):337–41. https://doi.org/10.1093/ckj/sfx105.
47. Kelesidis T, Daikos G, Boumpas D, Tsiodras S. Does rituximab increase the incidence of infectious complications? A narrative review. Int J Infect Dis. 2011;15(1):1–31. https://doi.org/10.1016/j.ijid.2010.03.025.
48. Cravedi P, Ruggenenti P, Sghirlanzoni MC, Remuzzi G. Titrating rituximab to circulating B cells to optimize lymphocytolytic therapy in idiopathic membranous nephropathy. Clin J Am Soc Nephrol. 2007;2(5):932–7. https://doi.org/10.2215/CJN.01180307.
49. Moroni G, Depetri F, Del Vecchio L, Gallelli B, Raffiotta F, Giglio E, et al. Low-dose rituximab is poorly effective in patients with primary membranous nephropathy. Nephrol Dial Transplant. 2017;32(10):1691–6. https://doi.org/10.1093/ndt/gfw251.
50. Bagchi S, Subbiah AK, Bhowmik D, Mahajan S, Yadav RK, Kalaivani M, et al. Low-dose Rituximab therapy in resistant idiopathic membranous nephropathy: Single-center experience. Clin Kidney J. 2018;11(3):337–41. https://doi.org/10.1093/ckj/sfx105.
51. Gaggar P, Madipally R, Raju SB. Rituximab, use and B cell depletion in patients with membranous nephropathy – A retrospective, observational study. Indian J Nephrol. 2023;33:356–61. https://doi.org/10.4103/ijn.ijn_62_22.
52. Michel P-A, Dahan K, Ancel P-Y, Plaisier E, Mojaat R, De Seigneux S, et al. Rituximab Treatment for Membranous Nephropathy: A French Clinical and Serological Retrospective Study of 28 Patients. Nephron Extra. 2011;1(1):251–61. https://doi.org/10.1159/000333068.
53. Mirioğlu S, Akyıldız A, Uçar AR, Uludağ Ö, Özlük Y, Dirim A, et al. Low Versus Standard Dose of Rituximab in Adult Patients with Relapsed or Refractory Primary Membranous Nephropathy: Does It Make Any Difference? Turkish J Nephrol. 2023;32(3):209–15.
54. Wang S, Deng Z, Wang Y, Bao W, Zhou S, Cui Z, et al. Monthly mini-dose rituximab for primary anti-PLA2R-positive membranous nephropathy: a personalized approach. BMC Nephrol [[Internet]]. 2023;24(1):1–10. https://doi.org/10.1186/s12882-023-03206-1.
55. Wang YW, Wang XH, Wang HX, Yu RH. Successful treatment of patients with refractory idiopathic membranous nephropathy with low-dose Rituximab: A single-center experience. World J Clin Cases. 2023;11(3):566–75. https://doi.org/10.12998/wjcc.v11.i3.566.
56. George J, Alex S, Raji R, George M, Gopal A, Thomas A, et al. Sat-398 Low Dose of Rituximab Is Clinically and Cost Effective in Primary Membranous Nephropathy. Kidney Int Reports [[Internet]]. 2020;5(3):S167.
57. George J, Alex S, Thomas ETA, Gracious N, Vineetha NS, Kumar S. Clinical Response and Pattern of B cell Suppression with Single Low Dose Rituximab in Nephrology. Kidney360. 2020;1(5):359–67. https://doi.org/10.34067/KID.0000072020.
58. Dahan K, Gillion V, Johanet C, Debiec H, Ronco P. The Role of PLA2R Antibody in Treatment of Membranous Nephropathy. Kidney Int Reports [[Internet]]. 2018;3(2):498–501. https://doi.org/10.1016/j.ekir.2017.10.013.
59. Fenoglio R, Baldovino S, Sciascia S, De Simone E, Del Vecchio G, Ferro M, et al. Efficacy of low or standard rituximab-based protocols and comparison to Ponticelli's regimen in membranous nephropathy. J Nephrol [[Internet]]. 2020;34(2):565–71. https://doi.org/10.1007/s40620-020-00781-6.
60. Georges E, Johanet C, Plaisier E, Debiec H, Ronco P, Dahan K. Efficacy of Rituximab in a Patient With Partial Clinical Remission and Persistent Circulating PLA2R-Ab. Kidney Int Reports [[Internet]]. 2019;4(7):1027–30. https://doi.org/10.1016/j.ekir.2019.03.002.
61. Wen M, Küchle C, Sarkar O, Renders L, Heemann U, Schmaderer C. Plasmapheresis combined with rituximab for refractory idiopathic membranous nephropathy. Int Urol Nephrol. 2014;46(4):847–8. https://doi.org/10.1007/s11255-014-0673-6.
62. Mathew GG, Varadharajan J, Sailapathy S. Case series of low dose rituximab for membranous nephropathy; a single centre experience. J Nephropathol. 2023;12(3):1–5. https://doi.org/10.34172/jnp.2023.21440
63. Jeon SJ, Kim JH, Noh HW, Lee GY, Lim JH, Jung HY, et al. Treatment of rituximab in patients with idiopathic membranous nephropathy: a case series and literature review. Korean J Intern Med. 2022;37(4):830–40. https://doi.org/10.3904/kjim.2021.155.
64. Seitz-Polski B, Dahan K, Debiec H, Rousseau A, Andreani M, Zaghrini C, et al. High-dose rituximab and early remission in PLA2R1-related membranous nephropathy. Clin J Am Soc Nephrol. 2019;14(8):1173–82. https://doi.org/10.2215/CJN.11791018.
65. Wang X, Cui Z, Zhang YM, Qu Z, Wang F, Meng LQ, et al. Rituximab for non-responsive

idiopathic membranous nephropathy in a chinese cohort. Nephrol Dial Transplant. 2018;33(9):1558–63. https://doi.org/10.1093/ndt/gfx295.
66. Fenoglio R, Baldovino S, Sciascia S, De Simone E, Del Vecchio G, Ferro M, et al. Efficacy of low or standard rituximab-based protocols and comparison to Ponticelli's regimen in membranous nephropathy. J Nephrol. 2021 Apr 1;34(2):565–71. https://doi.org/10.1007/s40620-020-00781-6.
67. Sinha A, Bagga A. Rituximab therapy in nephrotic syndrome: implications for patients' management. Nat Rev Nephrol. 2013 Mar;9(3):154-69. https://doi.org/10.1038/nrneph.2012.289.
68. KDIGO. Kidney Disease Improving Global Outcomes (KDIGO) Glomerular Diseases Work Group. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney Int. 2021;100((4S)):S1–S276. https://doi.org/10.1016/j.kint.2021.05.021.
69. Rojas-Rivera JE, Carriazo S, Ortiz A. Treatment of idiopathic membranous nephropathy in adults: KDIGO 2012, cyclophosphamide and cyclosporine A are out, rituximab is the new normal. Clin Kidney J. 2019;12(5):629–38. https://doi.org/10.1093/ckj/sfz127.
70. Ramachandran R, Yadav AK, Kumar V, Siva Tez Pinnamaneni V, Nada R, Ghosh R, et al. Two-Year Follow-up Study of Membranous Nephropathy Treated With Tacrolimus and Corticosteroids Versus Cyclical Corticosteroids and Cyclophosphamide. Adv Clin Chem [[Internet]]. 2017;81(4):610–6. https://doi.org/10.1016/j.ekir.2017.02.004.
71. Del Vecchio L, Allinovi M, Rocco P, Brando B. Rituximab therapy for adults with nephrotic syndromes: Standard schedules or B cell-targeted therapy? J Clin Med. 2021;10(24). https://doi.org/10.3390/jcm10245847.