Rituximab Therapy for Membranous Nephropathy: A Systematic Review

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Background and objectives: The treatment of membranous nephropathy (MN) remains controversial. Rituximab, which selectively targets B cells, has emerged as a possible alternative treatment option with limited toxicity.

Design, setting, participants, & measurements: The available data on rituximab therapy for MN were reviewed using the MEDLINE database (inception to August 1, 2008), Google Scholar, and selected reference lists. English-language studies investigating the use of rituximab in idiopathic and secondary MN, in native and transplanted kidneys, were included. Study design, subject number, clinical characteristics (diagnosis, previous and concomitant treatment courses, baseline proteinuria, baseline renal function), rituximab protocol, follow-up period, achievement of complete or partial remission, changes in proteinuria and renal function, and adverse effects of therapy were extracted.

Results: Twenty-one articles were included for review; all were either case reports or case series without controls. More than half of the published cases (50 of 85) came from one center where rituximab was used as primary immunosuppression for idiopathic MN. The available data suggest that rituximab, dosed either as 375 mg/m^2 once weekly for 4 wk or as 1 g on days 1 and 15, achieves a 15 to 20% rate of complete remission and a 35 to 40% rate of partial remission. The drug was well tolerated with minimal adverse events.

Conclusions: Although rituximab may prove to be a better treatment option for MN than alkylating agents or calcineurin inhibitors, the current literature only supports using the drug in research protocols. Whether, when, how, and why to use rituximab in MN remains to be determined.

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Membranous nephropathy (MN) remains a leading cause of nephrotic syndrome in adults (1,2). In most patients, an underlying etiology for the lesion is unknown and the disorder is termed idiopathic. About one-quarter of cases are felt secondary to a predisposing disease (*e.g.*, systemic lupus erythematosus), infection (*e.g.*, hepatitis B), or medical therapy (*e.g.*, nonsteroidal anti-inflammatory drugs).

The treatment of MN depends on patient presentation and disease progression after diagnosis is made by biopsy (3). In general, most patients are given a trial of conservative therapy with renin-angiotensin system (RAS) blockade. If partial or complete remission is not achieved with 6 mo of conservative management, immunomodulatory therapy is then initiated. The two leading immunomodulatory therapies used are alkylating agents (cyclophosphamide or chlorambucil) and calcineurin inhibitors (cyclosporine or tacrolimus), both typically given alongside oral or intravenous corticosteroids (4,5). Given the limited efficacy, high rate of relapse, and toxicities of alkylating agents, calcineurin inhibitors, and corticosteroids, other therapies for MN are needed.

Recently, rituximab has surfaced as a potential treatment option for MN. This monoclonal antibody directed against the B cell antigen CD20 may be beneficial in MN on the basis of experimental evidence that B cell activation is a key step in the pathogenesis of MN (6,7). Furthermore, rituximab is generally well tolerated with a limited short-term toxicity profile.

A small but growing body of literature is emerging on the benefits of rituximab in MN as primary treatment and as treatment for lesions refractory to other immunomodulatory regimens. We therefore performed the first systematic review of the available literature on rituximab therapy for MN. Specifically, we asked when and how rituximab has been used, how effective treatment has been, and what toxicities of therapy have been reported.

Materials and Methods

Data Sources and Search Strategy

Two authors (ASB, VKD) independently searched MEDLINE from inception to August 1, 2008 for English-language studies that reported treatment of MN with rituximab using the search terms "membranous" and "rituximab." These results were cross checked with a secondary search of Google Scholar using the same search terms. We also com-

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pared our search results with the references of all identified publications, including previous narrative reviews.

Study Selection

Any study, case report, or case series that reported the use of rituximab in biopsy-proven MN was eligible for review. We included publications with both idiopathic and secondary MN, as well as publications of disease in both native and transplanted kidneys. We excluded studies of rituximab in non-MN glomerular diseases.

Data Extraction

The following information was extracted by the principal investigator (ASB) and confirmed by two other investigators (VKD, JGM): study design, subject number, subject clinical characteristics (including diagnosis, previous treatment courses, baseline proteinuria, baseline renal function), rituximab treatment protocol (including use of concomitant therapy), follow-up period, achievement of complete or partial remission (including investigators' definitions of remission), changes in proteinuria and renal function, and any adverse effects of therapy. When studies reported outcomes of interest at different times (*e.g.*, proteinuria at 3, 6, and 12 mo), we included data from the latest point of follow-up. Differences over inclusion of studies and interpretation of data were resolved by consensus discussion.

Data Analyses

We used authors' definitions of complete and partial remission when provided; otherwise, we used the generally accepted definitions of complete and partial remissions (8,9). Complete remission was defined as most recent proteinuria $\leq$0.3 g/24h with preserved renal function (*i.e.*, estimated GFR $\geq$60 ml/min/1.73m^2), and partial remission as $\geq$50% reduction in proteinuria with proteinuria $>$0.3 g/24 h and $<$3.5 g/24h at last follow-up. If not provided, we calculated percent reduction in baseline urinary protein excretion after rituximab therapy using the following formula: (final proteinuria − baseline proteinuria)/baseline proteinuria. Because none of the included studies used a control arm and there was marked heterogeneity in their participants, interventions, and reported outcome measures, the results of the included studies were not pooled but instead presented qualitatively.

Results

Sixty-two studies were identified by our search strategy (Figure 1). On the basis of review of the title and abstract, 34 studies initially met the inclusion criteria. Review of the full articles led to further exclusion of 13 studies that were either editorials or narrative reviews. Of the 21 studies included in this review (10–30), 12 were single case reports, and the remaining 9 were case series ranging from 2 to 50 patients.

The largest series of patients came from two centers: 15 patients reported by Fervenza's group, and a total of 50 patients reported over a series of 5 articles by Remuzzi and colleagues (Table 1). Half of the studies used rituximab in patients with idiopathic MN; the other half included seven reports on secondary MN after hematopoietic stem cell transplant (typically in the setting of graft *versus* host disease), two reports on lupus-associated MN, and cases of MN in the setting of hepatitis and rheumatoid arthritis. The patients in these reports, regardless of diagnosis or previous treatments, had severe proteinuria (mean 10.5 g/24h, interquartile range 8.6 to 13 g/24 h) with preserved renal function (estimated glomerular filtration rates, when reported, were generally greater than 50 ml/min/1.73m^2).

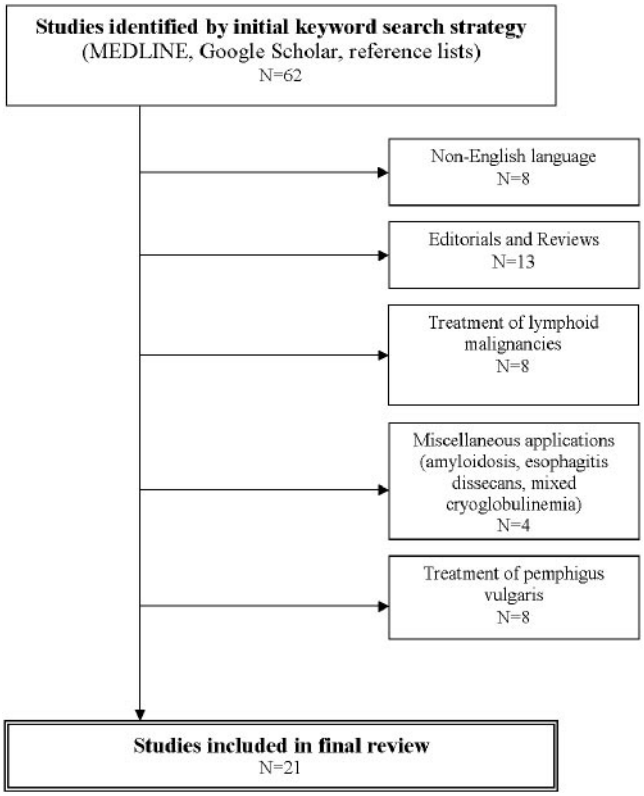

Figure 1. Search results and selection of studies for review.

Patient selection, prior therapy, and rituximab treatment protocols for these reports, even those from the same center, varied significantly and did not allow for a pooled analysis. For example, 7 of 15 patients studied by Fervenza *et al.* had failed prior immunosuppressive therapy, and all patients were on stable doses of angiotensin-converting enzyme inhibitors with an angiotensin II receptor blocker if tolerated (25). Their mean ($\pm$SD) age was 47 $\pm$ 8 yr and estimated creatinine clearance was 85 $\pm$ 25 ml/min/1.73m^2. In the first four series from Remuzzi and colleagues (10,11,21,23), totaling 35 patients, none of the patients had received immunosuppression before rituximab. In at least one study (21), nine patients were selected for rituximab on the basis of the histologic absence of severe tubulointerstitial (TI) scarring (TI score $<$1.7). Compared with previously treated subjects with TI scores $\geq$1.7, these selected patients were younger and had significantly higher creatinine clearances (95.6 $\pm$ 20.3 *versus* 48.6 $\pm$ 17.4 ml/min/1.73m^2, $P <$ 0.001). In another study from this same group (23), no specific histologic selection criteria were mentioned, yet the mean TI score of the 12 reported subjects was low (1.3 $\pm$ 0.4).

Rituximab Treatment Course

In both idiopathic and secondary MN, rituximab was typically used as a second-line immunosuppressive therapy after treatment failure of steroids alone or steroids used in conjunction with either cyclosporine or an alkylating agent. The notable exception is the reports from Remuzzi and colleagues, in

Table 1. Overview of 21 studies included for review[a]

Reference	*N*	Clinical Presentation/Diagnosis	Treatment before Rituximab	Proteinuria before Rituximab (mean g/24h if $n > 1$)	Renal Function before Rituximab (mean if $n > 1$)[f]
Remuzzi *et al.* (2002)	8	Idiopathic MN with persistent NS	Full-dose ACE-I for mean 29.7 mo	8.6	Cr 1.4 mg/dl
Ruggenenti *et al.* (2003)	8[b]	Idiopathic MN with persistent NS	Full-dose ACE-I for mean 29.7 mo	8.6	Cr 1.4 mg/dl
Ratanatharathorn *et al.* (2003)	1	Secondary MN after hematopoietic stem cell transplant	Tacrolimus, methylprednisolone, and MMF over 8 mo	15.0	Not reported
Fra *et al.* (2003)	1	Secondary MN in setting of SLE with persistent NS	High-dose prednisone (cumulative dose 13.7 g) and cyclophosphamide (cumulative dose 15.7 g) over 9 mo	2.0	Cr 0.8 mg/dl
Rossi *et al.* (2005)	1	Idiopathic MN	Methylprednisolone 2 mg/kg/d for 2 wk, then 5 mg/kg/d for 1 wk	11.0	Normal range
Rao (2005)	2	Secondary MN after hematopoietic stem cell transplant	None ($n = 1$); prednisone, MMF, and ARB for 3 mo ($n = 1$)	9.5	Cr 1.1 mg/dl
Srinivasan *et al.* (2005)	2	Secondary MN after hematopoietic stem cell transplant	Cyclosporine ($n = 2$) and prednisone ($n = 1$)	21.0	CrCl 47.9 ml/min
Jacobson *et al.* (2006)	1	Secondary MN in setting of SLE with persistent NS	Cyclophosphamide, prednisolone, cyclosporine, and MMF over >33 mo	5.3	Cr 2.7 mg/dl
Cobo *et al.* (2006)	1	Idiopathic MN with persistent NS	ACE-I + ARB for 8 mo, then steroids and chlorambucil for 5 mo	7.3	Cr 1.0 mg/dl
Gallon and Chhabra (2006)	1	Recurrent idiopathic MN after kidney transplant	Full-dose ACE-I for 1 mo on top of maintenance immunosuppression with MMF and tacrolimus	16.0	Cr 1.8 mg/dl
Reddy *et al.* (2006)	1	Secondary MN after hematopoietic stem cell transplant	Methylprednisolone	8.0	Not reported
Ruggenenti *et al.* (2006)	23[c]	Idiopathic MN with persistent NS	ACE-I for at least 6 mo	9.1	Cr 1.4 mg/dl
Terrier *et al.* (2007)	1	Secondary MN after hematopoietic stem cell transplant	ACE-I, corticosteroids, and MMF	8.2	CrCl 57 ml/min
Cravedi *et al.* (2007)	12[d]	Idiopathic MN with persistent NS	ACE-I for at least 6 mo	10.3	Cr 1.4 mg/dl
Pansini *et al.* (2007)	1	Secondary MN in setting of HCV with relapse on NS	Full-dose ACE-I	10.4	Cr 0.8 mg/dl
Fervenza *et al.* (2008)	15	Idiopathic MN with persistent NS	ACE-I + ARB for at least 4 mo ($n = 15$); prednisone alone ($n = 2$); prednisone and alkylating agent ($n = 2$); cyclosporine ($n = 2$); MMF ($n = 1$)	13.0	Cr 1.4 mg/dl
Ferrannini *et al.* (2008)	1	Secondary MN after hematopoietic stem cell transplant	Methylprednisolone 1 g/d for 3 d, then prednisone decreased until 0.5 mg/kg/d	35.2	Cr 0.9 mg/dl

(continued)

Table 1. (Continued)

Reference	*N*	Clinical Presentation/Diagnosis	Treatment before Rituximab	Proteinuria before Rituximab (mean g/24h if $n > 1$)	Renal Function before Rituximab (mean if $n > 1$)[f]
Troxell *et al.* (2008)	4	Secondary MN after hematopoietic stem cell transplant	Prednisone alone ($n = 1$); prednisone and MMF ($n = 1$)	10.3	Cr 1.3 mg/dl
Weclawiak *et al.* (2008)	1	Recurrent idiopathic MN after kidney transplant	ACE-I for 18 mo, then ACE-I and ARB for 7 mo, in addition to maintenance immunosuppression with prednisone, MMF, and cyclosporine	10.8	Cr 1.5 mg/dl
Pixley *et al.* (2008)	1	Secondary MN in setting of rheumatoid arthritis	Prednisone, chlorambucil, and MMF over 10 mo	19.5	Not reported
Ruggenenti *et al.* (2008)	7[e]	Idiopathic MN with persistent NS	ACE-I for at least 6 mo	5.5	Cr 1.0 mg/dl

[a]ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Cr, serum or plasma creatinine; CrCl, creatinine clearance; HCV, hepatitis C virus; MMF, Mycophenolate Mofetil; MN, membranous nephropathy; NS, nephrotic syndrome; SLE, systemic lupus erythematosus.

[b]The study reported the long-term (12 mo) follow-up of the 8 patients from the earlier Remuzzi *et al.* (2002) study.

[c]Of the 23 subjects in this study, 8 were included in previous reports by Remuzzi *et al.* (2002) and Ruggenenti *et al.* (2003).

[d]The study used 24 historical reference patients who were previously reported in two previous studies by Ruggenenti *et al.* (2003, 2006).

[e]The study reviews 50 consecutive patients with MN, treated with rituximab from May 2001 to January 2007, but only reports complete data for 7 patients with complete remission who agreed to undergo repeat biopsy. The 50 patients reported in this study include patients previously described in reports by Remuzzi *et al.* (2002), Ruggenenti *et al.* (2003, 2006), and Cravedi *et al.* (2007).

[f]To convert Cr in mg/dl to μmol/L, multiply by 88.4; CrCl in ml/min to ml/s, multiply by 0.0167.

which rituximab was the first-line immunosuppressant used for refractory nephrotic syndrome after at least 6 mo of angiotensin-converting enzyme inhibitor therapy.

Four studies did not report their rituximab protocols. Of the remaining 17 studies, all but 3 gave rituximab at a dose of 375 mg/m^2 once weekly for 4 wk. Cravedi *et al.* followed a protocol in which a second dose of 375 mg/m^2 was given if $\geq$5 circulating B cells/mm^3 were detected 1 wk after treatment; 1 of their 12 subjects received a second dose of medication (23). Fervenza *et al.* gave 1 g rituximab on days 1 and 15; this regimen was repeated at 6 mo if B cells were $\geq 15/\mu l$ and proteinuria was still in the nephrotic range. Of their 15 patients, 10 underwent retreatment with rituximab (25). Pixley *et al.* followed a similar dosing regimen (29).

Rituximab Treatment Outcomes

Outcomes are analyzed separately according to whether MN was idiopathic (Table 2) or secondary (Table 3). Achievement of complete and partial remission depended, in part, on how these entities were defined by investigators and on length of follow-up.

Ten publications focused on patients with idiopathic MN (Table 2), four of which were single case reports. The remaining were uncontrolled case series (of which five emanate from a single center) with a total of 65 patients—specifically, 50 patients reported in the most recent series by Remuzzi's group (30), and 15 patients reported by Fervenza *et al.* (25). Looking only at the case series, 10 of 50 patients (20%) followed by Remuzzi and colleagues over 6 yr and 2 of 15 patients (13%) reported by Fervenza *et al.* achieved complete remission. In separate reports, the rates of partial remission in the studies by Remuzzi's group ranged from 36 to 50%, whereas 6 of 15 patients (40%) followed by Fervenza *et al.* achieved partial remission with subtotal resolution of proteinuria. The median time to complete or partial remission was not reported in these studies, obscuring the effect on remission rates of retreatment with rituximab in B cell-driven protocols (23,25).

Of the 11 publications on rituximab therapy for secondary MN (Table 3), 8 were single case reports, and the largest series reported outcomes for 4 patients. Of the 16 patients comprising these reports, 9 achieved complete remission, whereas 5 met criteria for partial remission. Only one case report described a patient with secondary MN and no response to rituximab whose proteinuria persisted in nephrotic range and renal function continued to decline over 26 mo of follow-up (22).

Adverse Events during Rituximab Therapy

In the studies that reported adverse events, rituximab was generally well tolerated (Table 4). The few reported side effects were typically mild, transient, and thought to be due to an infusion reaction. Rituximab, when administered in these reports, was given with premedications (including steroids) to limit such effects; However, two serious adverse events were noted in these studies. The first, a laryngospasm reported by Remuzzi *et al.*, was in later publications thought to be due to anxiety (11). The second was a lung neoplasm not detected on chest x-ray done 1 yr before enrollment in the study of Fervenza *et al.*; this patient was withdrawn from the study and died (25). Overall, most studies reported no adverse events of rituximab therapy.

Discussion

In this systematic review, we identified 21 reports of rituximab use in idiopathic and secondary MN. *In toto*, these reports include 85 patients, with 50 patients drawn from a single center. With the exception of this one center, which used rituximab as primary immunomodulatory therapy, the drug has principally been used as a second-line immunosuppressant for patients with refractory disease. The response rate in these studies was approximately 15 to 20% for complete remission and 35 to 40% for partial remission, similar to the response rates of alkylating agents (31) and calcineurin inhibitors (8) yet perhaps more heartening given that many of the patients had resistant disease and therapy was very well tolerated. The current data on rituximab in MN, however, are rooted solely in case series and not valid for direct comparisons to the randomized clinical trial-based data on alkylating agents and calcineurin inhibitors. The results of this review, as with the individual studies, suggest that dedicated, well designed, controlled research protocols investigating rituximab as an alternative to alkylating agents and calcineurin inhibitors in the treatment of MN are needed.

MN remains a leading cause of nephrotic syndrome with an incidence and prognosis that have remained quite stable over the last 30 yr (2). The decision to treat with immunosuppressive medications is complicated by the well known natural history of disease: about one-third of patients spontaneously remit, one-third remain proteinuric but with stable renal function, and one-third progress to renal failure over a period of 5 to 10 yr (1,32,33). Recent quantitative systematic reviews have found no significant difference in renal outcomes between immunosuppressive therapy, placebo, and no treatment (4,34), although these analyses antedate a recent, large randomized trial that reported significant improvement in 10-yr dialysis-free survival among patients treated with cyclophosphamide and corticosteroids (35). Speculatively, MN outcomes may not have substantially changed because alkylating agents and calcineurin inhibitors—the current therapies for patients who do not spontaneously remit or respond to RAS blockade—are nonspecific and potentially toxic.

Rituximab, a monoclonal antibody to the CD20 antigen of B cells, offers a new approach to treating MN that may potentially address the pathogenesis of disease. Subepithelial immune deposits in the glomerular basement membrane histologically define MN. B cells likely play an important role in this injury—hypothesized mechanisms include B cell-mediated Ig deposition along the glomerular basement membrane and interstitial infiltration of B cells as antigen-presenting cells (6,7). Presumably, the efficacy of alkylating agents (and, to a lesser extent, calcineurin inhibitors) in treating MN lies in their ability to interfere with B cell function (8,36); therefore, rituximab potentially offers the same interference with greater selectivity in targets.

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Table 2. Treatment courses and outcomes of rituximab therapy for idiopathic MN

Reference	Rituximab Treatment Dose	Concomitant Therapy	Follow-Up Period	Complete Remission (definition per study, otherwise proteinuria ≤0.3 g/24h)	Partial Remission (definition per study, otherwise ≥50% reduction in proteinuria with proteinuria <3.5 g/24h)	Mean Percent Reduction in Proteinuria
Remuzzi *et al.* (2002)	375 mg/m^2 once weekly × 4	Full dose ACE-I	20 wk	2/8 (proteinuria ≤1 g/24h)	3/8 (proteinuria >1 g/24h and ≤3.5 g/24h)	−57%
Ruggenenti *et al.* (2003)[a]	375 mg/m^2 once weekly × 4	Full dose ACE-I	12 mo	2/8 (proteinuria ≤1g /24h)	3/8 (proteinuria >1 g/24h and ≤3.5 g/24h)	−65%
Rossi *et al.* (2005)	375 mg/m^2 once weekly × 4, then 375 mg/m^2 once monthly × 5	Methylprednisolone, slowly tapered and discontinued	1 yr	1/1	0/1	−98%
Cobo *et al.* (2006)	375 mg/m^2 once weekly × 4	ARB	18 mo	1/1	0/1	−97%
Gallon and Chhabra (2006)	375 mg/m^2 once weekly × 4	ACE-I and maintenance immunosuppression	2 yr	1/1	0/1	−97%
Ruggenenti *et al.* (2006)[b]	375 mg/m^2 once weekly × 4	ACE-I titrated to maximum tolerated dose, with ARB added after 3 mo	12 mo	6/23 (proteinuria <1 g/24h)	6/23 (proteinuria <3 g/24h)	−71%
Cravedi *et al.* (2007)	375 mg/m^2 × 1 (n = 11), 375 mg/m^2 × 2 (n = 1)	ACE-I titrated to maximum tolerated dose	12 mo	2/12 (proteinuria <0.3 g/24h)	6/12 (proteinuria <3 g/24h with a >50% reduction from baseline)	−60%
Fervenza *et al.* (2008)	1 g × 2, on days 1 and 15; repeated at 6 mo if proteinuria >3 g/24h and CD19+ B cells >15/μl (n = 10)	ACE-I + ARB	12 mo	2/15 (proteinuria <0.3 g/24h)	6/15 (proteinuria <3 g/24h with a >50% reduction from baseline)	−48%
Weclawiak *et al.* (2008)	375 mg/m^2 once weekly × 4, then 375 mg/m^2 every 3 mo × 4	ACE-I, ARB, and maintenance immunosuppression	42 mo	1/1	0/1	−99%
Ruggenenti *et al.* (2008)[c]	375 mg/m^2 once weekly × 4	ACE-I titrated to maximum tolerated dose	7 to 59 mo	7/7[c]	0/7	−95%

[a]The study reported the long-term (12 mo) follow-up of the 8 patients from the earlier Remuzzi *et al.* (2002) study.
[b]The study included 8 patients from the previous reports by Remuzzi *et al.* (2002) and Ruggenenti *et al.* (2003).
[c]The study reviews 50 consecutive patients with MN, treated with rituximab from May 2001 to January 2007, of whom 10 went into complete remission by 1 yr. The study only reports complete data for 7 patients with complete remission who agreed to undergo repeat biopsy. The 50 patients reported in this study include patients previously described in reports by Remuzzi *et al.* (2002), Ruggenenti *et al.* (2003, 2006), and Cravedi *et al.* (2007).

Table 3. Treatment courses and outcomes of rituximab therapy for secondary MN[a]

Reference	Rituximab Treatment Dose	Concomitant Therapy	Follow-Up Period	Complete Remission (definition per study, otherwise proteinuria ≤0.3 g/24h)	Partial Remission (definition per study, otherwise ≥50% reduction in proteinuria with proteinuria <3.5 g/24h)	Mean Percent Reduction in Proteinuria
Ratanatharathorn *et al.* (2003)	375 mg/m^2 once weekly × 4	Methylprednisolone and sirolimus	9 mo	0/1	1/1	−73%
Fra *et al.* (2003)	375 mg/m^2 once weekly × 4	IV cyclophosphamide 20 mg/kg every 28 d × 3, oral prednisone, ACE-I	12 mo	1/1	0/1	−92%
Rao (2005)	375 mg/m^2 once weekly × 4	Prednisone 1 mg/kg/d, ACE-I or ARB	6 to 12 mo	0/2	2/2	−71%
Srinivasan *et al.* (2005)	Not reported	Prednisone, plasma exchange, IV Ig	Not reported	0/2	1/2	Not reported
Jacobson *et al.* (2006)	375 mg/m^2 once weekly × 4	Prednisolone, IV cyclophosphamide 0.5 g/m^2 × 2	36 mo	1/1	0/1	−100%
Reddy *et al.* (2006)	Not reported	Methylprednisolone	Not reported	1/1	0/1	−96%
Terrier *et al.* (2007)	Not reported	ACE-I, corticosteroids, cyclosporine (3.5 mg/kg/d tapered down to 1 mg/kg/d)	26 mo	0/1	0/1	−33%[b]
Pansini *et al.* (2007)	375 mg/m^2 once weekly × 4	ACE-I	24 mo	1/1	0/1	−98%
Ferrannini *et al.* (2008)	375 mg/m^2 once weekly × 4	Not reported	7 mo	1/1	0/1	Not reported
Troxell *et al.* (2008)	Not reported	Not reported	6 to 28 mo	4/4	0/4	Not reported
Pixley *et al.* (2008)	1 g × 2, on days 1 and 15; repeated at 6 mo	Azathioprine 100 to 150 mg/d	49 wk	0/1	1/1	−64%

[a]IV, intravenous.
[b]The small decrease in proteinuria may be principally due to a steep decline in CrCl during this time, from 57 to 23 ml/min, as evidenced by no significant change in serum albumin levels (from 1.7 to 1.6 g/dl).

Table 4. Reported adverse events during rituximab therapy for MN

Reference	*N*	Rituximab Treatment Dose	Reported Adverse Events
Remuzzi *et al.* (2002), Ruggenenti *et al.* (2003)	8	375 mg/m^2 once weekly × 4	Generalized chills that spontaneously subsided ($n = 1$), skin rash that recovered after steroid pulse ($n = 1$), questionable laryngospasm that recovered after steroid pulse ($n = 1$)
Ratanatharathorn *et al.* (2003)	1	375 mg/m^2 once weekly × 4	None
Fra *et al.* (2003)	1	375 mg/m^2 once weekly × 4	None
Rossi *et al.* (2005)	1	375 mg/m^2 once weekly × 4, then 375 mg/m^2 once monthly × 5	None
Rao (2005)	2	375 mg/m^2 once weekly × 4	Discontinued rituximab after two doses because of rash and wheezing during infusion ($n = 1$)
Srinivasan *et al.* (2005)	2	Not reported	Not reported
Jacobson *et al.* (2006)	1	375 mg/m^2 once weekly × 4	None
Cobo *et al.* (2006)	1	375 mg/m^2 once weekly × 4	None
Gallon and Chhabra (2006)	1	375 mg/m^2 once weekly × 4	None
Reddy *et al.* (2006)	1	Not reported	Not reported
Ruggenenti *et al.* (2006)	23	375 mg/m^2 once weekly × 4	Not reported
Terrier *et al.* (2007)	1	Not reported	Septicemia
Cravedi *et al.* (2007)	12	375 mg/m^2 × 1 to 2 doses	Nausea, chills, sweating, and face rush ($n = 1$)
Pansini *et al.* (2007)	1	375 mg/m^2 once weekly × 4	None
Fervenza *et al.* (2008)	15	1 g × 2, on days 1 and 15; repeated at 6 mo if proteinuria >3 g/24h and CD19 + B cells >15/μl	Itching, rigors, and skin rash ($n = 3$); sore throat ($n = 3$); muscle pain ($n = 1$); serum sickness-like syndrome ($n = 1$); hair loss/thinning ($n = 2$); community acquired pneumonia ($n = 1$); fatigue and voice loss ($n = 1$); reactivated herpes zoster ($n = 1$); adenocarcinoma of lung with normal chest x-ray 1 yr before enrollment ($n = 1$)
Ferrannini *et al.* (2008)	1	375 mg/m^2 once weekly × 4	None
Troxell *et al.* (2008)	4	Not reported	Not reported
Weclawiak *et al.* (2008)	1	375 mg/m^2 once weekly × 4, then 375 mg/m^2 every 3 mo × 4	None
Pixley *et al.* (2008)	1	1 g × 2, on days 1 and 15; repeated at 6 mo	Not reported
Ruggenenti *et al.* (2008)	7	375 mg/m^2 once weekly × 4	Not reported

promising series of case reports does not mean that this therapy is ready for routine clinical practice. This systematic review highlights that the treatment is still in its infant stage and that well designed clinical trials—in multiple centers with diverse patient populations—are needed. The overwhelming majority of positive case reports in this review is concerning for publication bias. Equally concerning is that the bulk of published experience with rituximab in MN—and, particularly, rituximab as first-line immunosuppression—comes from a single center in Italy and may not be generalizable. Amassed together, the evidence for using rituximab for MN outside of a research setting does not currently exist.

This review raises several questions that can and should be tested in future, prospective studies. First, should rituximab be a first-line therapy for MN? Although the data presented in this review suggest that the drug is equally efficacious as both primary and secondary immunosuppression, with patients having a 15 to 20% chance of complete remission whether or

not they have failed previous immunomodulatory treatment, the natural history of MN makes this comparison difficult and potentially erroneous. It is unclear, for example, how much of the long-term (*i.e.*, ≥1 yr) response in the studies by Remuzzi's group are attributable to rituximab, concomitant long-term RAS blockade, and/or spontaneous disease remission, given that the 20% of their patients who achieved complete remission had, at baseline, significantly lower proteinuria and serum creatinine values than nonresponders (mean values of 6.1 *versus* 11.1 g/24h and 1.0 mg/dl *versus* 1.5 mg/dl, respectively). In addition, selection criteria based on histopathologic findings that were associated with younger age and better baseline renal function may have potentially skewed outcomes.

Next, what is the optimal dose of rituximab, and should dosing be targeted at B cell response? Most studies in this review used the protocol suggested in the first publication of Remuzzi et al. (10) of 375 mg/m^2 rituximab, once weekly for 4 wk, in MN, which was derived from the standard regimen used in treating lymphoma (37,38). The alternative protocol, used by Fervenza's and Pixley's groups to relatively equal effect, was to give 1 g rituximab on days 1 and 15, with the regimen repeated at 6 mo if B cells were ≥15/μl and proteinuria was still in the nephrotic range. This dosing schedule is potentially easier to administer, less expensive, and, with less drug given, less toxic, although that is not supported by the adverse events reported in the study of Fervenza *et al.*, nor by their own discussion on drug dosing (25). Noting that high-grade proteinuria may lead to losses of rituximab in the urine, a shortened half-life of the drug, and faster B cell recovery compared with nonproteinuric patients (*e.g.*, those with rheumatoid arthritis), these investigators questioned whether the use of 1 g every 2 wk (*versus* 4-wk dosing based on the body surface area) resulted in underdosing and lower treatment response. However, they found no association between B cell numbers and treatment response. Still another treatment regimen, which draws on both strategies, is the one used by Cravedi *et al.*, in which a second dose of 375 mg/m^2 was given only if ≥5 circulating B cells/mm^3 were detected 1 wk after treatment (23). In this study, only 1 of 12 patients received a second dose of drug, leading to a 4-fold decrease in drug cost. Because the times to complete or partial remission were not consistently reported in these studies, it is impossible to infer whether one dosing protocol is superior to another beyond group-averaged reductions in proteinuria. Certainly a study comparing these regimens in their present formats or in other formats titrated to patient response will be beneficial.

Finally, what are the long-term risks and benefits of rituximab therapy in patients with MN? This review and its included studies used proteinuria reduction as the primary outcome. There remains substantial uncertainty about using early changes in proteinuria as a surrogate for longer-term, more clinically relevant outcomes such as renal and overall survival (39); this uncertainty is more pronounced in studies, such as those reported here, with small sample sizes and short follow-up. It must also be stressed that the limited toxicity profile of rituximab is primarily based on short-term data. At present, we do not know whether this treatment will have long-term, unforeseen effects. The recent reports of progressive multifocal leukoencephalopathy as a rare but devastating downstream event after rituximab cannot be overlooked (40,41), although this condition has also been reported in patients with autoimmune diseases not exposed to rituximab and treated with other immunomodulatory drugs, such as natalizumab, azathioprine, and mycophenolate mofetil (42–48).

Conversely, we may also not be aware of long-term benefits of therapy. The most recent study from Ruggenenti *et al.* found that the glomerular changes of MN, detected on initial biopsy, regressed alongside clinical improvement in seven patients who achieved complete remission on rituximab therapy and consented for repeat biopsy (30). There were no controls in this study (such as subjects with refractory disease or subjects who achieved spontaneous remission without therapy), but the authors speculate that rituximab may have led to this morphologic improvement by removing the kidney's exposure to pathogenic antibodies, akin to a well known experiment in which kidneys from rats with Heymann nephritis, when transplanted into nondiseased animals, saw resolution of subepithelial deposits with remission of proteinuria (49). If this is indeed true, then achievement of partial remission with rituximab (*i.e.*, the third of patients who remain proteinuric with stable renal function) may prove beneficial, in the long term, over partial remission with other, nonspecific therapies.

Rituximab may prove to be a viable treatment option for MN, although the current data do not support using this drug in nonresearch settings. This systematic review of the rapidly growing literature not only shows the excitement about its potential uses in MN but also highlights the need for future, well designed, prospective research on how, when, and why the drug should be used.

Disclosures

None.

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