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Original Paper

Rituximab Treatment for Membranous Nephropathy: A French Clinical and Serological Retrospective Study of 28 Patients

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Key Words
Membranous nephropathy · Proteinuria · Renal failure · Rituximab

Abstract
The development of well-tolerated and effective therapies that target the pathogenesis of membranous nephropathy (MN) would be useful. Our objective was to evaluate the efficacy of rituximab in MN. We analyzed the outcome of 28 patients treated with rituximab for idiopathic MN. Anti-PLA_2R antibodies in serum and PLA_2R antigen in kidney biopsy were assessed in 10 and 9 patients, respectively. Proteinuria was significantly decreased by 56, 62 and 87% at 3, 6 and 12 months, respectively. At 6 months, 2 patients achieved complete remission (CR) and 12 partial remission (PR; overall renal response, 50%). At 12 months (n = 23), CR was achieved in 6 patients and PR in 13 patients (overall renal response, 82.6%). Three patients suffered a relapse

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of nephrotic proteinuria 27–50 months after treatment. Univariate analysis suggested that the degree of renal failure (MDRD estimated glomerular filtration rate <45/ml/min/1.73 m^2) is an independent factor that predicts lack of response to rituximab. Anti-PLA_2R antibodies were detected in the serum of 10 patients, and PLA_2R antigen in immune deposits in 8 of 9 patients. Antibodies became negative in all 5 responsive patients with available follow-up sera. In this retrospective study, a high rate of remission was achieved 12 months after treatment.

Introduction

Membranous nephropathy (MN) is an antibody-mediated disease induced by deposits of immunoglobulins and complement components on the subepithelial layer of the glomerular capillary wall. It is the most common cause of the nephrotic syndrome (NS) in white adults, accounting for 7–20% of NS [1, 2]. In 75% of cases, the etiology of MN is unknown and the disease is referred to as idiopathic. In 25% of cases, MN is associated with autoimmune disease (e.g. systemic lupus erythematosus), exposure to drugs (e.g. nonsteroidal anti-inflammatory drugs), infections (e.g. hepatitis B), or malignancy.

Idiopathic MN has a variable natural course. Although spontaneous remission of NS occurs in about one third of patients [3], end-stage renal failure is observed in about 40% of patients after 10 years [4]. Many patients with MN are treated by conservative therapy with renin-angiotensin system blockade. If partial (PR) or complete remission (CR) is not achieved after 6–12 months, therapy based on steroids and immunosuppressant drugs, such as alkylating agents, calcineurin inhibitors, and mycophenolate mofetil, is considered. Indications for treatment and choice of drugs remain debated because these therapies carry the risk of severe toxic effects, and despite their use for 30 years, controversy still remains about the balance between benefits and safety [5, 6]. Therefore, the development of well-tolerated and efficient pathophysiology-driven therapy is needed.

In the past decade, two major events have occurred. One is the identification of target antigens in human MN. The first is neutral endopeptidase, an alloantigen involved in neonatal MN, found in newborns from mothers deficient in this endopeptidase [7]. The second is the M-type phospholipase A_2 receptor (PLA_2R), the first autoantigen identified in idiopathic MN in adults [8]. Aldose reductase and superoxide dismutase were identified more recently [9]. These findings open new perspectives in the monitoring and treatment of the disease. The second event is the emergence of rituximab as a potential treatment option for MN. Rituximab is an antibody directed against the B-cell antigen CD20. Because B-cell activation is a key step in the pathogenesis of MN, rituximab represents a first step toward specific therapy [10, 11]. Its use was first reported by Remuzzi et al. [12] in a pilot study, and follow-up studies were subsequently published by Remuzzi and Fervenza's groups. However, these studies were uncontrolled and non-randomized [12–17]. A systematic review about the use of rituximab for MN was performed by Bomback et al. [18] in 2009. Rituximab, at a dose of 375 mg/m^2 once weekly for 1–4 weeks, or of 1 g on days 1 and 15, achieved a 10–20% rate of CR and a 40–60% rate of PR at 12 months, which is much more than expected spontaneously. In contrast to classical immunosuppressants, modest side effects and no major adverse events were observed. Though initial results were promising, further studies are needed to confirm the efficacy and safety of rituximab in MN.

We conducted a retrospective study in 8 French nephrology centers aimed to establish the rate of remission and to identify factors associated with remission in patients treated with rituximab for idiopathic MN. This clinical study was supplemented with an immunopathological study in 10 patients.

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Patients and Methods

Patients

All renal pathology records of renal biopsies and pharmacological records of rituximab prescription were reviewed over a 6-year period in 8 French nephrology centers to identify patients with idiopathic MN treated with rituximab. A total of 40 patients were identified from October 2005 to October 2009. Twenty-eight patients were included (6 women and 22 men). All of them were nephrotic and treated with angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) for various periods of time prior to the initiation of rituximab. Twelve patients were excluded, including 4 patients with missing data, 2 patients with long-term calcineurin inhibitor dependence who were already in CR at the initiation of rituximab, and 6 patients with MN complicated by systemic lupus erythematosus. Clinical data (medians and ranges) were obtained by review of patient records and included age, gender, height, weight, blood pressure, date of renal biopsy, previous treatment and concomitant immunosuppressive therapy, time and dose of rituximab and follow-up at 3, 6 and (if available) 12 months. We collected the data of urinary protein excretion, serum albumin, serum creatinine and estimated glomerular filtration rate (eGFR) by the MDRD formula before the initial renal biopsy, at initiation of rituximab treatment, and 3, 6 and (when available) 12 months after the first infusion. The stage of MN was also recorded if available.

Immunopathological Study

Circulating antibodies were assessed by a direct immunofluorescence assay with the use of human embryonic kidney 293 (HEK293) cells that were transiently transfected with full-length complementary DNA encoding a PLA_2R1 isoform (Euroimmun AG, Lübeck, Germany), as previously described [19]. PLA_2R in immune deposits was assessed by confocal microscopy in paraffin blocks with affinity-purified specific anti-PLA_2R antibodies (Atlas antibodies) [19].

Statistical Analysis

All continuous variables were expressed as medians and interquartile ranges. The outcome evaluated in this study included serum creatinine, serum albumin and proteinuria rates at 3, 6 and 12 months. CR was defined as proteinuria <0.5 g/day (or protein:creatinine ratio <500 mg/mg) with stable renal function, and PR was defined as proteinuria <3.5 g/day (or protein:creatinine ratio <3,500 mg/mg), reduction in proteinuria >50% and proteinuria ≥0.5 g/day (or protein:creatinine ratio ≥500 mg/mg) with stable renal function. Low response (LR) was defined as a reduction >50% of the basal level of proteinuria and proteinuria >3.5 g/day (or protein:creatinine ratio >3,500 mg/mg) with stable renal function. Treatment success was considered in two different ways, first reaching a CR or PR, and second reaching CR, PR or LR. Values at baseline, and 3, 6 and 12 months were compared using Fischer's exact test. For multivariate analysis, two-way analysis of variance was performed to determine the effect of age and chronic renal disease on response. The statistical significance level was defined as $p < 0.05$.

Results

Patient Characteristics

Twenty-eight patients (6 women and 22 men) with biopsy-proven MN and nephrotic syndrome (median age 44.4 years, range 18.5–82.4) were identified as presumed idiopathic MN (table 1). Twenty patients had stage 2 MN and 8 patients stage 1 MN. Time from renal

Table 1. Factors at baseline associated with renal PR or CR at 6 or 12 months

	All patients (n = 28)	Remission (n = 22)	No remission (n = 6)
Demographics			
Age, years	44.4 (18.5–82.4)	43.8 (19.5–78.6)	57.7 (18.5–82.4)
Male gender	22 (78.6%)	19 (86.4%)	3 (50%)
Previous immunosuppression	8 (28.6%)	7 (32%)	1 (17%)
ACEI/ARB before rituximab, months	14.0 (0.5–74)	14.5 (0.5–74)	13.2 (4.6–30.1)
Rituximab infusion protocol			
375 mg/m^2 weekly ×2	11 (39%)	8 (36%)	3 (50%)
375 mg/m^2 weekly ×3	3 (11%)	3 (14%)	0
375 mg/m^2 weekly ×4	13 (46.5%)	11 (50%)	2 (33.3%)
1,000 mg days 1 and 15	1 (3.5%)	0	1 (16.7%)
Clinical parameters			
Body weight, kg	76 (44.9–127)	76.2 (56.0–95.0)	67.5 (44.9–127)
Systolic blood pressure, mm Hg	127.5 (100.0–159.0)	127.5 (100.0–150.0)	130.5 (124.0–159.0)
Diastolic blood pressure, mm Hg	76 (57.0–97.0)	73.5 (57.0–97.0)	80.0 (66.0–93.0)
Laboratory parameters			
Serum creatinine, μmol/l	110.5 (43–231)	106 (43–231)*	141 (76–224)
eGFR, ml/min/1.73 m^2	68.7 (18.8–162.6)	75.5 (18.8–162.6)	38.0 (33.5–122)*
Serum albumin, g/dl	1.9 (0.9–3.5)	2.0 (1.1–3.5)	1.6 (0.9–2.4)
Protein:creatinine ratio, mg/mg	6,230 (1,780–21,021)	6,230 (1,780–21,021)	7,200 (4,040–13,216)

Data are medians (ranges). * $p < 0.05$ vs. without remission.

biopsy to the beginning of treatment with rituximab was 15 months (range: 0.6–76). Eight patients had failed previous immunosuppressive treatment: 1 patient with prednisone alone before treatment with rituximab, 2 patients with prednisone and a cytotoxic agent [(cyclophosphamide (n = 1) and chlorambucil (n = 1)], 3 patients with calcineurin inhibitors (1 of them with a cytotoxic agent after failure of calcineurin inhibitor treatment) and 2 patients with mycophenolate mofetil and prednisone. The 20 remaining patients had received rituximab as first-line immunosuppressive treatment. Two of them were treated with other immunosuppressants combined with rituximab (including 1 receiving tacrolimus and 1 receiving prednisone). The 28 patients were all on ACEI or ARB at initiation of rituximab therapy although the duration of prior treatment was variable. The median time of treatment with ACEI/ARB was 14 months, but 1 patient was treated only for 2 weeks and 1 patient for almost 74 months.

Rituximab treatment differed among hospitals. It was administered weekly at a dose of 375 mg/m^2 of body surface area for 4 weeks in 13 patients, for 3 weeks in 3 patients, and for 2 weeks in 11 patients. Moreover, 1 patient received 2 infusions at a dose of 1,000 mg on days 1 and 15. No patient received an additional infusion of rituximab after 6 or 12 months.

Global Renal Outcome

Median follow-up lasted 11.9 months (range 6–50), and every patient was followed up for at least 6 months. The protein:creatinine ratio decreased from 6,230 (1,780–21,022) to 3,070 mg/mg (160–14,445; $p < 0.00005$, paired t test) 6 months after rituximab treatment (n = 28) and to 828 mg/mg (53–16,465) 12 months after rituximab treatment (n = 23; table 2; fig. 1).

Table 2. Main clinical and laboratory parameters in the 28 study patients with idiopathic MN from rituximab initiation (baseline) to the 12-month follow-up

	Baseline (n = 28)	3 months (n = 28)	6 months (n = 28)	12 months (n = 23)
Systolic BP, mm Hg	127.5 (100–159)	125.0 (96–164)	120.0 (90–170)	123.0 (90–176)
Diastolic BP, mm Hg	76 (57–97)	75.0 (54–87)	70.0 (52–100)	75.0 (60–107)
Serum creatinine, μmol/l	110.5 (43–231)	115 (65–212)	105 (53–204)	111 (65–199)
eGFR, ml/min/1.73 m^2	68.7 (18.8–162.6)	70 (28.3–141.1)	72.6 (29.5–164.9)	61.8 (6–119)
Serum albumin, g/dl	1.9 (0.9–3.5)	2.7 (1.0–3.9)[a]	3.0 (2.0–4.4)[c]	3.7 (2.0–4.5)[c]
Protein:creatinine ratio, mg/mg	6,230 (1,780–21,021)	3,827 (445–13,804)[b]	3,070 (160–14,445)[c]	828 (53–16,465)[b]

Data are medians (ranges). BP = Blood pressure. [a] $p < 0.005$; [b] $p < 0.0005$; [c] $p < 0.00005$, vs. baseline.

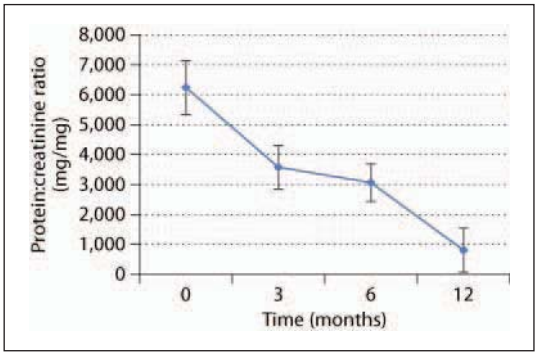

Fig. 1. The protein:creatinine ratio from baseline (month 0) up to the 12-month follow-up in patients who were treated with rituximab. Medians ± SEM.

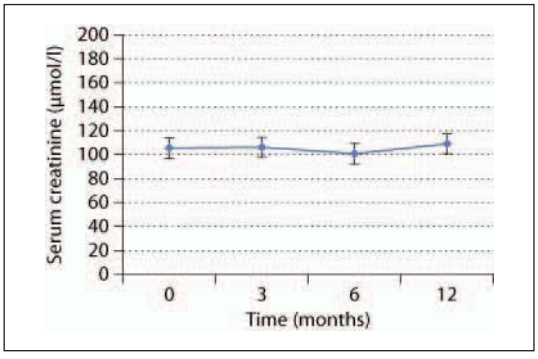

Fig. 2. Serum creatinine from baseline (month 0) up to the 12-month follow-up in patients who were treated with rituximab. Medians ± SEM.

In the meantime, serum creatinine remained stable (fig. 2) and serum albumin increased from 1.9 (0.9–3.5) to 3.0 g/dl (2.0–4.4; $p < 0.0005$, paired t test) after 6 months and 3.7 g/dl (2.0–4.5; $p < 0.00005$, paired t test) after 12 months (table 2; fig. 3). Six months after the rituximab treatment, CR was achieved in 2 patients and PR in 12 patients, corresponding to an overall remission rate of 50%. Three additional patients achieved LR. The overall renal response rate including CR, PR and LR was 60.7%.

Twelve months after rituximab treatment (n = 23), CR was achieved in 6 patients and PR in 13 patients, corresponding to an overall renal response of 82.6%. No patient had LR at 12 months. The median decrease in proteinuria over creatinine ratio was 62.3% at 6 months (–65.3 to 96.8) and 86.8% (–80.3 to 99) at 12 months. Among the 12 patients with PR at 6 months, 4 achieved CR at 12 months, 6 maintained PR at 12 months and follow-up data are

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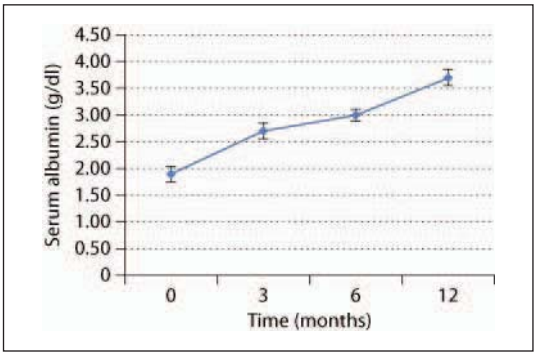

Fig. 3. Serum albumin from baseline (month 0) up to the 12-month follow-up in patients who were treated with rituximab. Medians ± SEM.

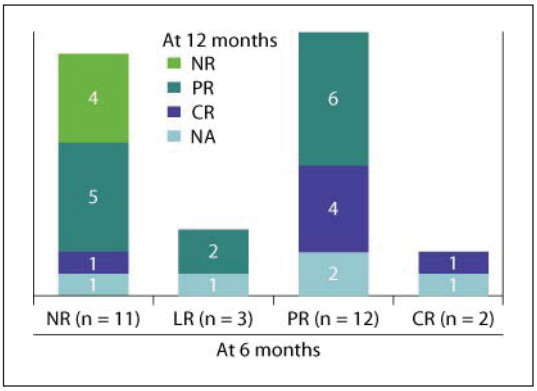

Fig. 4. Response 12 months after rituximab treatment in the 11 patients with no response (NR), 2 with LR, 12 with PR and 2 patients with CR at 6 months. NA = Not available.

lacking for 2 patients. Among the 2 patients with CR at 6 months, 1 maintained CR and follow-up data are not available for 1 patient. Among the 3 patients with LR at 6 months, 2 patients achieved PR and data are missing for 1 patient. Of note, among the 11 patients who showed no response at 6 months, 1 achieved CR at 12 months, 5 achieved PR at 12 months, 4 showed no response and follow-up data are lacking for 1 patient (fig. 4).

During the follow-up, 3 patients relapsed 27, 39 and 50 months after the initial rituximab treatment, respectively. Two of them were retreated with rituximab. The 1st patient experienced a relapse (proteinuria 6.8 g/day) 50 months after the first rituximab treatment. He was retreated with rituximab 375 mg/m^2 weekly for 2 weeks. Six months later, proteinuria decreased to 0.7 g/day and serum albumin increased from 2.9 to 3.7 g/dl. The 2nd patient experienced a relapse 39 months after the initial rituximab treatment. Treatment with rituximab was resumed at 375 mg/m^2 weekly for 2 weeks. Three months later the protein:creatinine ratio decreased from 5,162 to 3,560 mg/mg and serum albumin increased from 2.2 to 3.1 g/dl.

Factors Predicting Renal Response

Univariate Analysis

Response rates (CR and PR) were significantly associated with MDRD eGFR >45 ml/min/1.73 m^2 (p = 0.02). Age >60 years and female gender were associated with lower response rates (p = 0.05 and p = 0.05). However, response rates were not associated with previous immunosuppressive treatment or treatment dosage (table 3). The patients who did not respond to rituximab tended to have more proteinuria [protein:creatinine ratio 7,200 mg/mg (4,040–13,216)] and lower serum albumin [1.6 g/dl (0.9–2.4)] than those who responded to rituximab [(protein:creatinine ratio 6,230 mg/mg (1,780–21,021) and serum albumin 2.0 g/dl (1.1–3.5)],

Table 3. Factors associated with renal PR or CR at 6 or 12 months (univariate analysis)

	Remission (n = 22)	No remission (n = 6)	p value
Demographics			
Age			0.05
<60 years	19	3	
>60 years	3	3	
Gender			0.05
Male	19	3	
Female	3	3	
Protocol of rituximab infusion			1.0
Low dose[1]	8	2	
High dose[2]	14	4	
Laboratory parameters			
eGFR			0.02*
<45 ml/min/1.73 m^2	3	4	
>45 ml/min/1.73 m^2	19	2	
Proteinuria/creatininuria			1.0
<10,000 mg/mg	15	4	
>10,000 mg/mg	7	2	

[1] Two infusions of rituximab weekly at a dose of 375 mg/m^2.
[2] Three or 4 infusions of rituximab weekly at a dose of 375 mg/m^2 or 1,000 mg on days 1 and 15.

but the difference did not reach statistical significance (p = 0.32 for proteinuria and 0.52 for the serum albumin).

Multivariate Analysis

In multivariate analysis, MDRD eGFR >45 ml/min/1.73 m^2 was associated with a higher response rate (CR and PR), with an odds ratio (OR) of 8.08 and a 95% confidence interval (CI) of 0.8–86.1, but no significant difference was found (p = 0.08). For age <60 years, OR was 1.70 (95% CI 0.1–21.3) and for male gender, OR was 3.7 (95% CI 0.4–39.3).

B-Cell Depletion

In 10 patients, B-cell depletion was complete 1 month after rituximab infusion (CD19 lymphocytes <1%), while data were lacking for the 18 other patients. Remission occurred in 70% of the patients with CD19 monitoring and in 83.3% of the remainder (p = 0.46).

Immunopathological Study

In this retrospective study, anti-PLA_2R autoantibodies could be assessed in 10 patients, all from the Department of Nephrology at the Tenon Hospital in Paris. Sera were sampled at the time of biopsy before rituximab treatment. Follow-up sera were available in 5 patients, including 3 patients with iterative samples. Search for PLA_2R in immune deposits was performed in 9 of the patients.

Anti-PLA_2R autoantibodies were found in the serum of the 10 patients but at variable titers before rituximab treatment (table 4). Search for PLA_2R antigen in immune deposits was strongly positive in 5 patients, weakly positive in 2 patients, very weakly positive in 1 patient and negative in 1 patient (table 4). Interestingly, 1 patient (patient 7) with very high titer of anti-PLA_2R antibody had no PLA_2R detectable in immune deposits.

Table 4. Assessment of anti-PLA_2R autoantibodies in the serum, PLA_2R in the biopsy and response at 12 months in 10 of the 28 patients

Patients	PLA_2R in immune deposits	Anti-PLA_2R autoantibodies in the serum		Response at 12 months
		before treatment	after treatment	
1	positive	1:100	not available	CR
2	positive	1:1,000	not available	PR
3	positive	1:320	negative	CR
4	positive	1:100	negative	PR
5	weakly positive	1:320	negative	PR
6	positive	1:320	not available	no response
7	negative	1:3,200	1:1,000[1]	PR
8	very weakly positive	1:320	not available	PR
9	weakly positive	1:10	negative	CR
10	not available	1:10	negative	PR

[1] Early sampling at 4 weeks (no additional follow-up sample).

PR or CR was associated with disappearance of anti-PLA_2R antibodies in all patients. Disappearance of anti-PLA_2R autoantibodies was noted 5–48 months after initiation of rituximab therapy, but kinetics could not be established in the absence of early samples.

One patient had a relapse in the absence of detectable anti-PLA_2R antibody (patient 9).

Adverse Events

Screening for adverse events during rituximab treatment was not exhaustive. Rituximab was generally well tolerated. The few reported side effects were typically mild, transient, and thought to be due to infusion; no serious adverse events were reported.

Discussion

In this first French multicenter retrospective study, we analyzed the clinical course of 28 proteinuric patients with idiopathic MN. Four important observations were made. First, rituximab appears to be effective in reducing proteinuria in the majority of patients. Second, the reduction in proteinuria was gradual, with 3 of the 9 non-responders after 6 months achieving remission after 12 months (fig. 4). Third, the only parameter that seems to be associated with rituximab response is the initial level of renal function. Fourth, anti-PLA_2R autoantibodies were detected in all 10 patients studied and became negative after rituximab therapy in all 5 patients with available follow-up sera.

In our series, remission rates were 50 and 82.6% at 6 and 12 months, respectively, being apparently superior to those published by Cravedi et al. [14], Fervenza et al. [16, 17] and others [12, 13, 15], who reported global remission rates at 12 months of 65 and 60%, respectively. Several potential confounding factors should be discussed. First, given the heterogeneous course of the disease and the absence of a control group, we cannot rule out that part of the beneficial effect observed was due to spontaneous remission rather than to a therapeutic effect of rituximab. Indeed, the rate of spontaneous remission averages at 30% [3, 4]. However, although the majority of spontaneous remissions occurs within the first 2 years after initial presentation, we did not find an association between response to rituximab and the duration of MN before treatment [mean duration 14.5 months (range: 0.6–76.6) in re-

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sponders versus 13.2 months (range 4.6–30.1) in non-responders]. Second, 9 patients were given rituximab before completion of a 6-month conservative therapy with ACE/ARB, however we did not observe a greater reduction in proteinuria in those patients treated with ACE/ARB during <6 months (data not shown). Third, at 12 months, 5 of 28 patients (18%) were lost to follow-up. Although these 5 patients showed a remission rate of 60% (1 CR and 2 PR) at 6 months, which was superior to that observed in the other patients, we cannot rule out an overestimation of the response to rituximab at 1 year. Fourth, 1 patient received rituximab despite proteinuria levels below the nephrotic range (protein:creatinine ratio: 1,780 mg/mg; serum albumin: 1.8 g/dl) and had CR at 12 months, which contributed to the particularly favorable response to rituximab observed in our patients. Fifth, 1 patient received tacrolimus with rituximab and had PR, which may be closer associated with tacrolimus than rituximab treatment.

Our univariate and multivariate analyses suggest that creatinine is an independent factor which is negatively correlated with the response to rituximab after 6 months. This supports previous findings indicating that poor renal function and tubulointerstitial changes predict a poor response to rituximab [15, 16]. Although a higher rate of remission was observed in patients with lower basal proteinuria by Fervenza et al. [16], proteinuria did not significantly differ in our patients whether or not they achieved remission after 6 months. We observed only a trend toward higher proteinuria in the patients without response, which might be due to the small number of patients in our study cohort. However, the apparent lower response rate in patients with higher basal proteinuria in the study by Fervenza et al. [16] may also be related to a delay in the efficacy of rituximab. This hypothesis is supported by the observation that in their series, mean serum albumin had approached normal levels (3.5 ± 0.8 g/dl) at 12 months while mean urinary protein excretion was still within the nephrotic range (6.0 g/day).

Because high-grade proteinuria leads to losses of rituximab in the urine and a shortened half-life of the antibody, Fervenza et al. [16] postulated that high-dose rituximab could result in a higher remission rate while maintaining a similar safety profile although no correlation was found between rituximab levels and the degree of proteinuria or response rates [16, 17]. We did not observe either a higher rate of CD19 depletion or a better clinical response in patients treated with high-dose rituximab (3–4 infusions of rituximab weekly at a dose of 375 mg/m^2 or 2 infusions of 1,000 mg on days 1 and 15) compared to patients treated with low-dose rituximab (2 weekly infusions at a dose of 375 mg/m^2). The median decrease in proteinuria over creatinine ratio from baseline was 62 and 87% at 6 months and 12 months, respectively, in patients treated with a high dose (n = 18), and 61 and 86% at 6 and 12 months, respectively, in patients given a low dose (n = 10; p = 0.67 and 0.54 at 6 months and 12 months, respectively). These results support previous titration data suggesting that 1–2 weekly infusions of 375 mg/m^2 are enough to achieve complete B-cell depletion and that a larger dose of rituximab does not provide additional benefits in terms of proteinuria reduction rate [14].

Anti-PLA$_2$R autoantibodies were detected in all of the 10 study patients, and PLA$_2$R antigen was found in immune deposits in 8 of the 9 available biopsies. In the initial report by Beck et al. [8], the prevalence of anti-PLA$_2$R autoantibody was 70%. In a recent study of 42 consecutive patients with biopsy-proven idiopathic MN [20], we reported a lower prevalence of 57% positive sera and 74% positive biopsies compared to the present study, which might be due to the size of the sample. One patient had high-titer autoantibodies but no PLA$_2$R in deposits, which might suggest that antibodies were not nephritogenic or that epitopes were poorly accessible at the time of kidney biopsy.

Anti-PLA$_2$R autoantibodies disappeared under rituximab treatment in the 5 patients with follow-up sera. There was apparently no correlation between the titer of anti-PLA$_2$R

autoantibody at the time of initiation of rituximab therapy and the quality (CR or PR) of the response to the drug. The only patient (No. 6) with no response had high-titer anti-PLA_2R autoantibody. In the patient who relapsed in the absence of anti-PLA_2R antibody (No. 9), antibodies directed against other antigenic specificities might be involved. Because of the high rate of efficacy of rituximab and the small sample size, it was not possible to establish a correlation between anti-PLA_2R autoantibodies and clinical response although this was previously suggested by preliminary studies from Beck and Salant [21].

Our study has important limitations inherent to its retrospective design. The follow-up before and after rituximab administration, the duration of ACEI/ARB treatment and the protocol of rituximab treatment were heterogeneous. However, this kind of study mirrors real practices in the absence of guidelines for rituximab treatment.

In conclusion, rituximab appears to be effective in achieving CR or PR (82.6%) in proteinuric patients at 12 months. Despite accumulating evidence in favor of the efficacy of rituximab from our study data and the previous literature, no definitive conclusion can be drawn. An adequately powered, randomized clinical trial is now needed to assess the benefit-risk profile of rituximab in idiopathic MN as well as the response of anti-PLA_2R antibodies to therapy.

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