



ORIGINAL ARTICLE

Treatment with rituximab in idiopathic membranous nephropathy

Marco Fiorentino¹, Francesco Tondolo¹, Francesca Bruno², Barbara Infante², Giuseppe Grandaliano², Loreto Gesualdo¹ and Carlo Manno¹

¹Nephrology, Dialysis and Transplant Unit, Department of Emergency and Organ Transplantation, University of Bari, Piazza Giulio Cesare 11, Bari 70124, Italy and ²Nephrology, Dialysis and Transplant Unit, Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy

Correspondence and offprint requests to: Carlo Manno; E-mail: carlo.manno@uniba.it

Abstract

Background: Rituximab represents a valid therapeutic option to induce remission in patients with primary glomerulonephritis. Despite several studies proving its efficacy in improving outcomes in patients with membranous nephropathy (MN), its role in therapeutic protocols is not yet defined.

Methods: We studied 38 patients with idiopathic MN treated with rituximab (in 13 patients as first-line therapy, in the remaining 25 after conventional immunosuppressive therapy). The patients were analyzed for a 15-month median (interquartile range 7.7–30.2) follow-up, with serial monitoring of 24-h proteinuria, renal function and circulating CD19⁺ B cells.

Results: The percentages of patients who achieved complete remission, partial remission and the composite endpoint (complete or partial remission) were 39.5% (15 patients), 36.8% (14 patients) and 76.3% (29 patients), respectively. The 24-h proteinuria was reduced significantly during the entire period of follow-up (from a baseline value of 6.1 to 0.9 g/day in the last visit; $P < 0.01$), while albuminemia increased constantly (from a baseline value of 2.6 to 3.5 g/dL in the last observation; $P < 0.01$). Renal function did not significantly change during the observation period. Circulating CD19⁺ B cells were reduced significantly from the baseline value to the 24-month value ($P < 0.01$); data about anti-phospholipase A₂ receptor antibodies were available in 14 patients, 10 of which experienced a decreasing trend after treatment. No significant adverse events were described during and after infusions.

Conclusions: The present study confirmed that treatment with rituximab was remarkably safe and allowed for a large percentage of complete or partial remissions in patients with MN.

Key words: glomerulonephritis, immunosuppression, membranous nephropathy, nephrotic syndrome, rituximab

Introduction

Rituximab represents a new therapeutic hope for the treatment of primary or secondary glomerulonephritis (GN), such as membranous nephropathy (MN) and other GN. Rituximab is a chimeric

monoclonal antibody specifically directed to the transmembrane protein CD20 on B-lymphocytes [1, 2]. It was first introduced in 1997 for the treatment of B cell lymphoma (four weekly doses of 375 mg/m²) [3] and in 2006 it was approved for the treatment

Received: June 23, 2016. Accepted: July 30, 2016

© The Author 2016. Published by Oxford University Press on behalf of ERA-EDTA.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

of rheumatoid arthritis [4]. In recent years, several studies have shown the efficacy of rituximab in improving the outcome of renal diseases associated with an autoimmune pathology, but the mechanism of action in these diseases is still unclear [5]. In a prospective observational study, Ruggenti *et al.* demonstrated a significant reduction in proteinuria after rituximab treatment in eight patients with MN and persistent proteinuria >3.5 g/24 h [6]. In a follow-up of 1 year, one-quarter achieved complete remission (proteinuria <0.5 g/24 h) while three-eighths had partial remission (proteinuria <3.5 g/24 h). In 2012, Ruggenti *et al.* [7] showed high percentages of complete and partial remission (27 and 38%, respectively) in a larger cohort of MN patients treated with rituximab.

The aim of this study was to describe the efficacy and safety of rituximab in 38 patients with MN prospectively monitored for a median follow-up of 15 months after rituximab administration.

Materials and methods

Patients

Beginning in March 2007, we followed 38 patients with idiopathic MN treated with rituximab referred to two nephrology units (Nephrology, Dialysis and Transplant Unit, Department of Emergency and Organ Transplantation, University of Bari and Nephrology, Dialysis and Transplant Unit, Department of Medical and Surgical Sciences, University of Foggia) with the following inclusion criteria: biopsy-proven MN, nephrotic syndrome characterized by persistent daily proteinuria exceeding 3.5 g/day, hypoalbuminemia and peripheral edema. Patients with secondary forms of MN were not enrolled in this study. Since the drug was off-label, the treatment protocol was approved by the Ethical Committee of the Azienda Ospedaliera-Universitaria Consorziata Policlinico, Bari, Italy. Patients gave written informed consent for rituximab treatment according to the Declaration of Helsinki. Rituximab was supplied by the hospital pharmacy.

Treatment and follow-up

All patients received a conservative therapy characterized by full-dose renin-angiotensin system inhibitors (RASis) with other anti-hypertensive drugs to control blood pressure and proteinuria, loop diuretics to control edema and statins to improve hypercholesterolemia. RASis were used for at least 6 months before starting immunosuppressive treatment in patients for which rituximab was used as first-line therapy and their dosage was titrated on the basis of proteinuria, renal function, blood pressure and adverse effects. Patients who received rituximab as second-line therapy continued treatment with RASis in the period between the different immunosuppressive therapies. Following a baseline evaluation, they received 4 weekly intravenous infusions of rituximab at a dose of 375 mg/m². Two patients received only two infusions of rituximab, because circulating CD19⁺ B cells after the first infusions were $<5/\text{mm}^3$. These infusions were preceded by adequate premedication, based on methylprednisolone 40 mg, antihistaminic drugs (chlorphenamine maleate 10 mg) and adequate hydration (500 mL of sodium chloride solution). Rituximab was reconstituted at the concentration of 1 mg/mL. The infusions were administered at an initial rate of 50 mL/h for 30 min, increasing the rate by 50 mL every 30 min until a maximum rate of 150 mL/h was reached, according to tolerability.

The clinical and laboratory parameters for all patients at baseline and every month for the first 3 months and then every

3 months were evaluated, such as urinary protein excretion, serum creatinine, estimated glomerular filtration rate (eGFR) by the Modified Diet in Renal Disease formula and white blood cell and lymphocyte subpopulation counts. Circulating B cell levels in peripheral blood were evaluated by the detection of CD19⁺ cells. B cell depletion was described as a CD19⁺ cell count $<5/\text{mm}^3$ and $<1\%$ total lymphocytes count. When available, anti-phospholipase A₂ receptor antibodies (anti-PLA₂R Abs) were evaluated before and after the treatment.

Outcomes

The primary outcome of this study was achievement of complete or partial remission. Complete remission was defined as 24-h proteinuria <0.5 g in at least two consecutive visits while partial remission was defined as 24-h proteinuria <3 g or at least 50% reduction versus baseline values. We considered a composite endpoint (complete or partial remission) defined as the presence of at least one of these two events in the study population. Patients who did not achieve these outcomes in the study period were considered nonresponders. A relapse of the disease was an increase in 24-h proteinuria >3.5 g after achievement of complete remission or a novel increment of proteinuria after achievement of partial remission. Secondary outcomes were the evaluation of 24-h proteinuria, albuminemia, renal function and circulating CD19⁺ B cells during the follow-up period. The safety profile of the treatment was analyzed during the follow-up of the study population through the reporting of serious and nonserious adverse events.

Statistical analyses

All patients with at least 3 months of observation were considered for the analysis. Clinical characteristics of the study population in the follow-up period were reported as absolute numbers or percentages for the dicotomic variables, as mean \pm standard deviation (SD) or median and interquartile range (IQR) for the continuous variables with symmetric or asymmetric distributions, respectively. The comparison of clinical parameters during the follow-up period was made using the χ^2 test for dicotomic variables and the Student's *t*-test or the Wilcoxon test for continuous variables as appropriate. The Kaplan-Meier method for censored data was used to analyze the probability of achieving the primary outcomes of complete remission, partial remission or composite endpoint. Survival time was calculated from the beginning of treatment until the date of the event; for the composite endpoint (complete or partial remission), survival time was referred to as the time of partial remission. Patients not achieving remission were considered as censored at the time of the last visit. Statistical analyses were carried out using SPSS software (version 21; IBM, Armonk, NY, USA).

Results

Clinical features of the study population

We followed 38 patients with idiopathic MN and nephrotic syndrome for a period of at least 3 months after the first administration of rituximab [median follow-up 15 months (IQR 7.7–30.2)]. Thirteen patients received treatment with rituximab as first-line therapy. The remaining 25 patients showed a relapse of disease after receiving other standard immunosuppressive therapy based on steroids in combination with alkylating drugs (chlorambucil or cyclophosphamide, 14 patients), calcineurin inhibitors (cyclosporine, 7 patients) or other immunosuppressants

Table 1. Baseline clinical parameters of the study population

	First-line therapy	Second-line therapy	P-value
Number of patients	13	25	
Age (years)	56.77 ± 15.44	55.4 ± 19.33	0.82
Gender (M/F)	9/4	14/11	0.42
Follow-up (months)	12 (4.5–23.5)	25 (8–37.5)	0.08
Serum creatinine (mg/dL)	1.1 (0.8–1.48)	1.1 (0.85–1.62)	0.51
eGFR (mL/min/1.73 m ²)	78 (48–100.5)	64 (37.5–98)	0.39
Albuminemia (g/dL)	2.39 ± 0.49	2.64 ± 0.46	0.12
24-h proteinuria (g)	5.4 (4–10.16)	6.3 (4.47–8.2)	0.79
CD19 ⁺ lymphocytes %	10.2 ± 3.45	10.08 ± 4.25	0.93
CD19 ⁺ lymphocytes (n/mm ³)	347.5 ± 423.98	190.88 ± 72.45	0.07

Values are expressed as absolute number, percentage, mean ± SD or median (IQR) as appropriate.

(mycophenolate mofetil, 4 patients). According to our clinical practice, we waited at least 6 months before starting other immunosuppressive drugs. The two groups did not differ in population age (mean 56.7 versus 55.4 years; $P = 0.81$), renal function (median eGFR 78 versus 64 mL/min/1.73 m²; $P = 0.39$), 24-h proteinuria (median 5.4 versus 6.3 g/24 h; $P = 0.79$) and CD19⁺ B cells (mean 10.2 versus 10%; $P = 0.93$) and previous therapies. The main clinical characteristics of the study population are described in Table 1. During study observation, 37 patients did not receive other immunosuppressive treatments; only one ‘nonresponder’ patient received treatment with another immunosuppressant. However, two patients received a second course of rituximab after a relapse of nephrotic syndrome during the follow-up period.

Primary outcome

Over a median follow-up period of 15 months (IQR 7.7–30.2), 15 patients (39.5%) achieved complete remission after treatment with rituximab, while 14 (36.8%) achieved partial remission. The composite endpoint of complete or partial remission was achieved by 29 patients (76.3%; Figure 1). However, nine patients did not present with complete or partial remission after the treatment course. The mean time to complete remission was 5.8 months from the beginning of treatment, while the achievement of partial remission occurred earlier (mean 3.24 months). No statistically significant differences were described in the percentage of patients with complete or partial remission according to gender (men 69.5% versus women 86.6%; $P = 0.35$) and the type of therapeutic approach (patients treated with first-line therapy or after other immunosuppressive drugs; $P = 0.98$). In contrast, the analysis showed a significant difference in renal function between patients who achieved complete or partial remission and nonresponder patients (mean eGFR 74.4 versus 42.1 mL/min/1.73 m²; $P = 0.02$).

Secondary outcomes

Table 2 and Figure 2 summarize the main clinical and laboratory parameters of the different follow-up visits of the study population after rituximab treatment. We show a statistically significant reduction in 24-h proteinuria in the first months after rituximab infusions for the entire period of observation (from a median

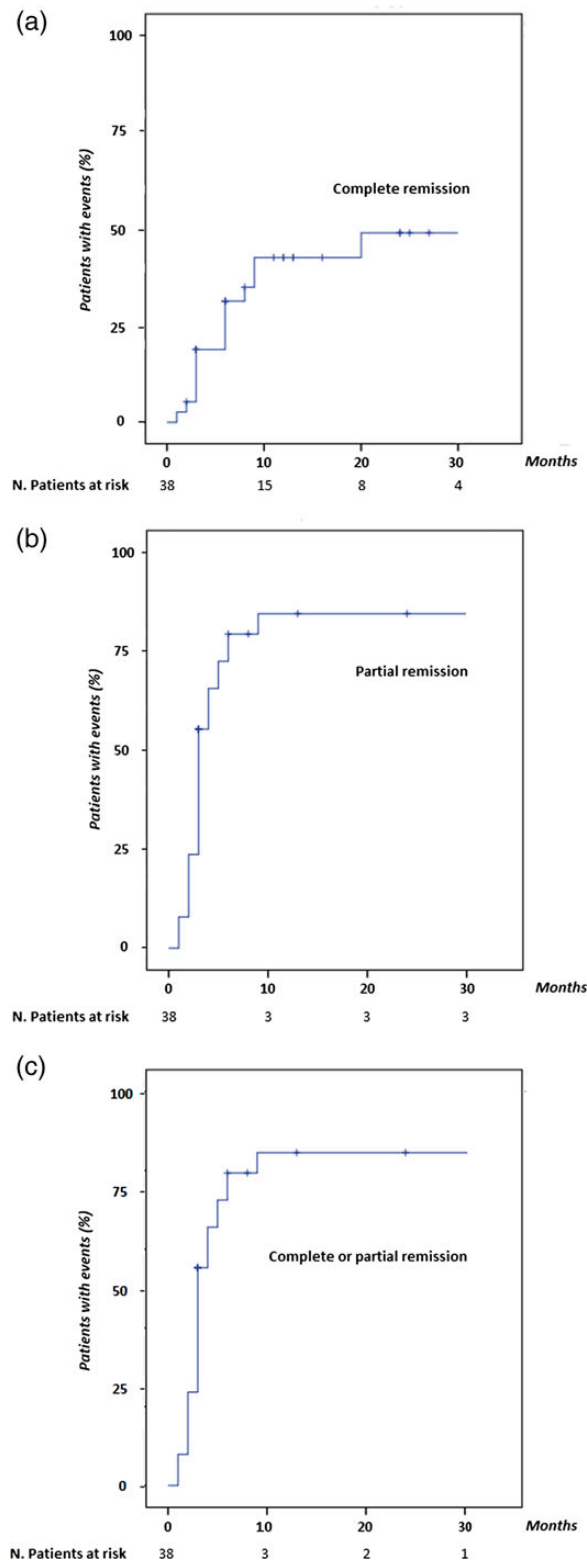


Fig. 1: Kaplan–Meier analysis of the percentage of patients who achieved (a) complete remission, (b) partial remission or the (c) composite endpoint. Patients not achieving remission were considered as censored at the time of the last visit.

24-h proteinuria of 6.15 to 0.9 g at the last visits; $P < 0.01$); this improvement was associated with a significant increase in albuminemia (from a median of 2.6 to 3.5 g/dL at the last follow-up;

Table 2. Clinical and laboratory parameters of the study population during the follow-up period

	Baseline	3 months	6 months	9 months	12 months	24 months	36 months
Patients (n)	38	38	32	27	26	15	8
Serum creatinine (mg/dL)	1.10 (0.80–1.51)	1.10 (0.80–1.65)	1.10 (0.93–2.03)	1.10 (0.90–2.05)	1.09 (0.87–1.83)	1.05 (0.80–1.61)	1.09 (0.88–1.57)
eGFR (mL/min/1.73 m ²)	73.0 (39.7–98.0)	69.0 (38.8–99.8)	71.0 (32.3–97.5)	78.0 (31.0–98.0)	76.5 (29.8–100.3)	78.0 (55.0–96.0)	69.5 (57.5–82.0)
Albuminemia (g/dL)	2.6 ± 0.5	3.0 ± 0.5*	3.2 ± 0.6*	3.3 ± 0.6*	3.3 ± 0.7*	3.4 ± 0.7*	3.8 ± 0.8*
24-h proteinuria (g)	6.2 (4.3–8.7)	2.2 (0.7–5.7)*	1.2 (0.4–4.8)*	1.0 (0.3–3.9)*	1.4 (0.3–4.7)*	2.0 (0.2–3.6)*	1.0 (0.2–1.7)*
CD19 ⁺ lymphocytes (%)	10.1 ± 3.95	0.61 ± 1.28*	2.11 ± 3.01*	3.43 ± 3.11*	3.62 ± 3.04*	3.48 ± 3.12*	5.92 ± 3.49
CD19 ⁺ lymphocytes (n/mm ³)	244.5 ± 259.6	5.43 ± 12.4*	22.2 ± 51.6*	29.6 ± 47.8*	27.1 ± 49.3*	43.6 ± 44.9*	110.6 ± 70.7

Values are expressed as number, mean ± SD or median (IQR). *P < 0.05 versus baseline values.

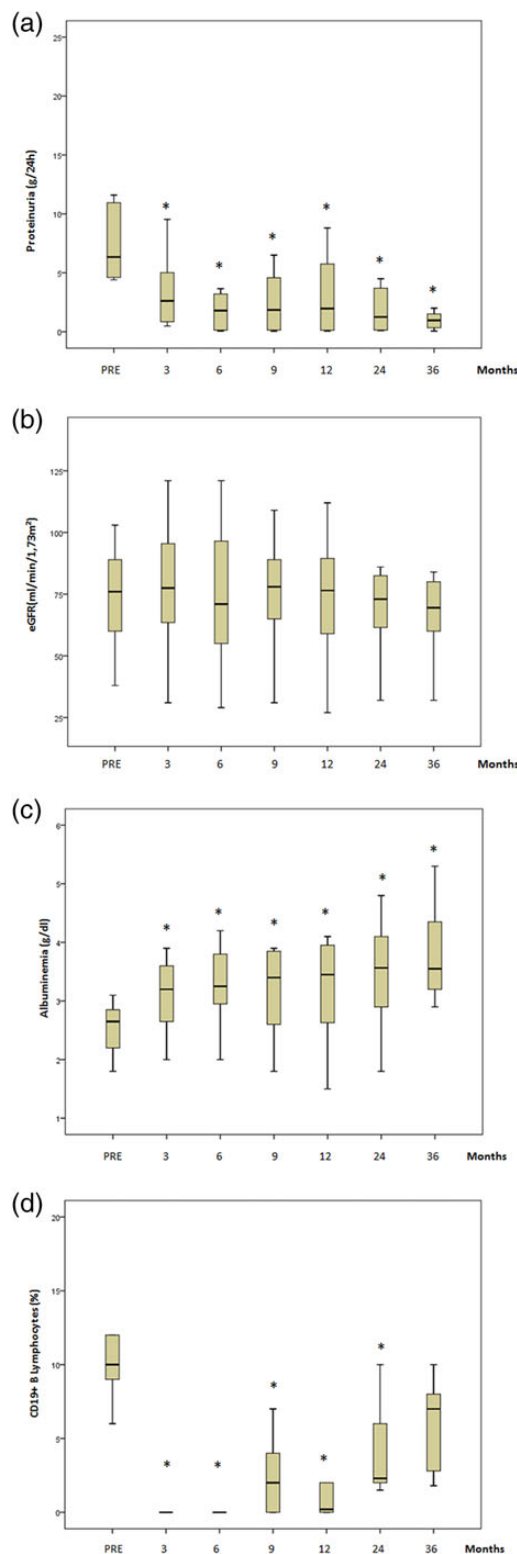


Fig. 2: Follow-up values of (a) proteinuria, (b) eGFR, (c) albuminemia and (d) CD19⁺ B lymphocytes during the period of observation (*P < 0.05 at baseline value).

P < 0.01). Renal function remained stable for the entire period of observation; the monitoring of CD19⁺ B cells showed a significant reduction until 24 months after treatment (10.1 versus 3.5%; P < 0.01), while this difference was not statistically significant at

36 months ($P = 0.22$). Anti-PLA₂R antibody evaluation was available in 18 patients. Among these, 14 patients presented with high levels of antibodies before the treatment: 10 of these patients experienced a reduction of anti-PLA₂R Ab titer, while 3 patients experienced no change after treatment (first patient presented with complete remission, a second patient with partial remission, while a third patient experienced no remission) and in another patient the titer increased (the patient presented with a worsening of renal function without remission of nephrotic syndrome). Treatment with rituximab was well tolerated in all patients; no serious reactions during the infusions were noted, however, one patient presented with dyspnea during the first infusion that resolved after the rate of infusion was decreased. Additionally, an H1N1 viral infection with serious respiratory problems occurred in one patient after the second administration and caused a delay in completing the entire course of treatment.

Discussion

In recent years, the treatment of MN has improved by the identification of pathogenic mechanisms underlying this disease (in particular the role of autoantibodies) and the consequent introduction of targeted therapy based on depleting circulating B cells to induce remission of disease and a reduction of proteinuria [8, 9]. The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that initial therapy consist of the 'Ponticelli regimen', a 6-month course of alternating monthly cycles of oral and intravenous corticosteroids and oral alkylating agents (chlorambucil or cyclophosphamide) [10]. Alternative regimens for initial therapy in MN consist of cyclosporine or tacrolimus, particularly in patients who had contraindications to the Ponticelli regimen, while corticosteroid monotherapy and rituximab was not recommended in first-line therapy [11, 12].

Recently, several studies have been published analyzing the efficacy and safety of rituximab in the treatment of MN [6, 7, 13–16]. The present study showed a significant reduction in 24-h proteinuria and an improvement of albuminemia in a cohort of 38 patients with biopsy-proven idiopathic MN. Among these, 15 patients (39.5%) achieved complete remission after rituximab treatment, while 14 (36.8%) achieved partial remission. The composite endpoint of complete or partial remission was achieved by 29 patients (76.3%). The results of this study were similar to data published by Ruggenenti et al. [7]; in a larger cohort ($n = 100$), rituximab treatment induced complete remission in 27 patients (27%) and partial remission in 38 patients (38%). In our study, there were no statistically significant differences between gender and the rate of complete or partial remission (69.5 versus 86.6%); these data differed from other published data in which female gender was considered an independent factor of disease remission [7]. Also, in our study the percentage of remission does not differ between patients treated with rituximab as first-line therapy and patients treated after previous immunosuppressive therapy. Similarly, Cravedi et al. [14] demonstrated a similar reduction of 24-h proteinuria after treatment with rituximab in first- or second-line therapy. Another important finding in our study is the significant increase in albuminemia and the stability of renal function after treatment with rituximab for the entire period of observation, as Ruggenenti et al. [8, 15] showed previously [6, 7].

The improvement of proteinuria and renal function related to the depletion of CD19⁺ B cells confirms the role of B lymphocytes in MN [14]. This hypothesis was validated by the evidence of immunoglobulin G4 (IgG4) reduction in immunofluorescence and the reduction of dense deposits in electronic microscopy in

renal biopsy performed after rituximab treatment, as reported by Ruggenenti et al. [15]. However, some evidence suggests that the mechanism of action of rituximab is not only related to direct interaction with B cells depleting antibody production, but also by a direct recognition of specific proteins on the podocytes surface [17, 18] and by a modulation of T cell activity [5]. In the present study, renal biopsy was performed before any immunosuppressive treatment, no data about IgG subclasses were collected and electronic microscopy was only available for a few patients. Moreover, CD19⁺ B cell count was determined to monitor the direct effect of the treatment and not to guide clinical management. Hence, patients with an optimal clinical response and the presence of CD19⁺ B cells after treatment did not receive any additional rituximab doses.

Treatment with rituximab was well tolerated in our study population, with limited adverse events after drug administration. Despite the short period of observation, the absence of serious adverse events is suggestive of the safety of rituximab treatment, contrary to what is reported in the scientific literature, where nonserious (fever, skin rash, chills) and serious adverse events (bronchospasm, angioedema, Steven-Johnson syndrome) have been described [9].

Despite the strong results described, some issues have not been resolved. First, the timing to initiate immunosuppressive therapy is still not defined, considering the possibility of spontaneous remission [17]. KDIGO guidelines suggest a 6-month observation period without immunosuppressive therapy for patients with spontaneous reduction of proteinuria and low risk of progression [10]. Polanco et al. [20] described a high percentage of spontaneous remission (32%) in a cohort of 328 patients with MN [19]. Another important issue is the efficacy of rituximab for inducing remission in patients with idiopathic MN compared with other immunosuppressive drugs: the ongoing MENTOR study will evaluate for the first time the noninferiority of rituximab compared with cyclosporine for inducing complete or partial remission of proteinuria in this setting [20].

However, the cost of rituximab treatment is considerably higher than other immunosuppressive agents and strategies to optimize the use of rituximab should be encouraged. Cravedi et al. [13] compared two different therapeutic approaches with rituximab (the first group's treatment was guided by B cell count, while the second group received the standard four doses) and described a similar rate of complete and partial remission. Similarly, the potential to reduce the number of infusions with a reduction in cost and the incidence of adverse events should be considered.

Finally, evaluation of parameters that define the response to treatment with rituximab is necessary to monitor disease activity. Ruggenenti et al. [21] analyzed 132 MN patients treated with rituximab, monitoring 24-h proteinuria and anti-PLA₂R antibodies. The lower baseline anti-PLA₂R titer and a complete antibody reduction 6 months after the treatment were found to be the best predictors of disease remission. Moreover, the reduction of antibody titer preceded the improvement of 24-h proteinuria, as well as the increase of anti-PLA₂R after a complete or partial remission preceded the worsening of proteinuria [21]. For these reasons, anti-PLA₂R can be an excellent indicator of disease relapse and its use may optimize and personalize treatment in patients with MN [22]. In the present study, the scarce availability of data about anti-PLA₂R antibodies limited the ability to speculate on the role of anti-PLA₂R antibodies in our cohort and to correlate these data with outcomes (complete or partial remission). Nevertheless, a reduction in antibody titer after the treatment was evident in the majority of patients. Recently, a

multicenter, randomized controlled trial evaluated the achievement of complete or partial remission between patients with nonimmunosuppressive antiproteinuric treatment (NIAT) and patients treated with rituximab and NIAT. At month 6 there was no significant difference between the two groups according to the remission rate (21.1 versus 35.1%; $P = 0.21$), while anti-PLA₂R antibody depletion was predominant in the NIAT-rituximab group (56 versus 4.3%; $P < 0.001$) [23]. These data suggest that anti-PLA₂R antibodies could be an early marker of rituximab treatment.

In conclusion, B cell depletion with rituximab therapy induces remission or stabilization of disease and renal function in MN patients with a high risk of progression of renal damage. The limited adverse events described in our study suggest its efficacy and safety. In the future, the results of randomized clinical trials should confirm these results and better define the role of rituximab treatment in MN.

Acknowledgement

We thank Dr Marilina Tampoia for helping to assay anti-PLA₂R antibodies.

Authors' contributions

M.F. and C.M.: research idea, study design, statistical analysis and writing of the paper. F.T., F.B. and B.I.: collaborated in data collection and follow-up of patients. G.G. and L.G.: collaborated on the research idea and drafting of the paper.

Conflict of interest statement

The present study has not been published previously in whole or part. All the authors approved the final version of the submitted manuscript and have declared no competing interest.

References

- Fervenza FC, Sethi S, Specks U. Idiopathic membranous nephropathy: diagnosis and treatment. *Clin J Am Soc Nephrol* 2008; 3: 905–919
- Pescovitz MD. Rituximab, an anti-cd20 monoclonal antibody: history and mechanism of action. *Am J Transplant* 2006; 6(5 Pt 1): 859–866
- Perez-Callejo D, Gonzalez-Rincon J, Sanchez A et al. Action and resistance of monoclonal CD20 antibodies therapy in B-cell non-Hodgkin lymphomas. *Cancer Treat Rev* 2015; 41: 680–689
- Looney RJ. B cells as a therapeutic target in autoimmune diseases other than rheumatoid arthritis. *Rheumatology (Oxford)* 2005; 44(Suppl 2): ii13–ii17
- Kessel A, Rosner I, Toubi E. Rituximab: beyond simple B cell depletion. *Clin Rev Allergy Immunol* 2008; 34: 74–79
- Ruggenti P, Chiurciu C, Brusegan V et al. Rituximab in idiopathic membranous nephropathy: a one-year prospective study. *J Am Soc Nephrol* 2003; 14: 1851–1857
- Ruggenti P, Cravedi P, Chianca A et al. Rituximab in idiopathic membranous nephropathy. *J Am Soc Nephrol* 2012; 23: 1416–1425
- Nangaku M, Couser WG. Mechanisms of immune-deposit formation and the mediation of immune renal injury. *Clin Exp Nephrol* 2005; 9: 183–191
- Waldman M, Austin HA III. Treatment of idiopathic membranous nephropathy. *J Am Soc Nephrol* 2012; 23: 1617–1630
- Kidney Disease: Improving Global Outcomes Glomerulonephritis Work Group. KDIGO clinical practice guideline for glomerulonephritis. *Kidney Int Suppl* 2012; 2: 139–274
- Cattran DC. Mycophenolate mofetil and cyclosporine therapy in membranous nephropathy. *Semin Nephrol* 2003; 23: 272–277
- Cattran DC, Appel GB, Hebert LA et al. Cyclosporine in patients with steroid-resistant membranous nephropathy: a randomized trial. *Kidney Int* 2001; 59: 1484–1490
- Cravedi P, Ruggenti P, Sghirlanzoni MC et al. Titrating rituximab to circulating B cells to optimize lymphocytolytic therapy in idiopathic membranous nephropathy. *Clin J Am Soc Nephrol* 2007; 2: 932–937
- Cravedi P, Sghirlanzoni MC, Marasa M et al. Efficacy and safety of rituximab second-line therapy for membranous nephropathy: a prospective, matched-cohort study. *Am J Nephrol* 2011; 33: 461–468
- Ruggenti P, Cravedi P, Sghirlanzoni MC et al. Effects of rituximab on morphofunctional abnormalities of membranous glomerulopathy. *Clin J Am Soc Nephrol* 2008; 3: 1652–1659
- Chen Y, Schieppati A, Cai G et al. Immunosuppression for membranous nephropathy: a systematic review and meta-analysis of 36 clinical trials. *Clin J Am Soc Nephrol* 2013; 8: 787–796
- Appel GB. Rituximab in membranous nephropathy: is it a first-line treatment? *J Am Soc Nephrol* 2012; 23: 1280–1282
- Fornoni A, Sageshima J, Wei C et al. Rituximab targets podocytes in recurrent focal segmental glomerulosclerosis. *Sci Transl Med* 2011; 3: 85ra46
- Polanco N, Gutierrez E, Covarsi A et al. Spontaneous remission of nephrotic syndrome in idiopathic membranous nephropathy. *J Am Soc Nephrol* 2010; 21: 697–704
- Fervenza FC, Canetta PA, Barbour SJ et al. A multicenter randomized controlled trial of rituximab versus cyclosporine in the treatment of idiopathic membranous nephropathy (MENTOR). *Nephron* 2015; 130: 159–168
- Ruggenti P, Debiec H, Ruggiero B et al. Anti-phospholipase A2 receptor antibody titer predicts post-rituximab outcome of membranous nephropathy. *J Am Soc Nephrol* 2015
- Beck LH Jr, Fervenza FC, Beck DM et al. Rituximab-induced depletion of anti-PLA₂R autoantibodies predicts response in membranous nephropathy. *J Am Soc Nephrol* 2011; 22: 1543–1550
- Dahan K, Debiec H, Plaisier E et al. Rituximab for severe membranous nephropathy: a 6-month trial with extended follow-up. *J Am Soc Nephrol* 2016