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Rituximab in the treatment of PLA2R-associated membranous nephropathy: Insights from a hospital centre experience

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Abstract
Introduction: Rituximab is recommended as the first-line therapy for PLA2R-associated membranous nephropathy in patients at moderate to high risk of progressive loss of kidney function, due to its superior long-term efficacy and improved safety profile. This study aims to assess the use of rituximab for treating PLA2R-associated membranous nephropathy at a tertiary hospital centre.
Methods: A retrospective study was conducted on patients diagnosed with PLA2R-associated membranous nephropathy who underwent their first rituximab administration between 2017 and 2022 at Coimbra Hospital and University Centre. The study assessed the occurrence of immune and clinical remission, relapse, response predictors, and adverse events.
Results: Eleven patients were included, with a mean follow-up time post-rituximab of 36.9±23.1 months. Rituximab was the first immunosuppressive therapy for only 3 patients. Additional immunosuppressive therapies were required for 7 (63.6%) patients. No response was observed in 2 patients (18.2%). Immune remission was achieved in 9 patients (81.8%), at mean time of 3.8±1.4 months. Among them, 5 (55.6%) patients achieved complete remission, 2 (22.2%) experienced partial remission, and 2 (22.2%) maintained nephrotic proteinuria. Immune remission consistently preceded clinical remission. Immune relapses occurred in 5 (45.5%) patients, at a mean time of 20.6±13.7 months. Four patients (36.4%) remained free of relapses throughout the entire follow-up period, with a mean time of 22.8±10.0 months. Patients with lower serum albumin were more likely to experience non-response or relapse ($T(9) = 2.51$, $p = 0.03$). Patients with anti-PLA2R exceeding 150 RU/mL exhibited no response or relapsed.
Within the 6 months following rituximab, 4 patients experienced adverse events.
Discussion: Rituximab demonstrated both efficacy and safety in PLA2R-associated membranous nephropathy. Monitoring disease progression through anti-PLA2R titres may guide clinical decisions. Patients with lower serum albumin levels, higher anti-PLA2R titres (>150 RU/mL) and no proteinuria response, demand closer surveillance.

Keywords: Membranous nephropathy; rituximab; anti-pla2r antibody; treatment response

Introduction

Membranous nephropathy (MN) is the most common cause of primary nephrotic syndrome (NS) in adults, particularly among caucasian males aged between 50 and 60 years [1, 2]. In 80% of cases, MN manifests as a kidney-specific autoimmune glomerular disease, characterized by the accumulation of subepithelial deposits containing immunoglobulins and complement components [1, 3]. Phospholipase A2 receptor (PLA2R) is the most common target in MN [2-4]. Notably, recent findings have identified other target receptors, challenging the use of the terms idiopathic or primary [4-6]. These antibodies are highly specific for the diagnosis of MN and closely linked to disease activity, obviating the necessity for a biopsy to establish the diagnosis [7-9].

The natural history of PLA2R-associated MN is diverse, with approximately 1/3 of patients achieving spontaneous remission and 1/3 entering partial remission. However, another 1/3 may maintain persistent NS, and half of these individuals may eventually progress to end-stage renal disease [2, 3]. Due to the heterogeneous course of the disease and the side effects associated with immunosuppressive therapy (IST), the optimal strategy for managing patients with PLA2R-associated MN remains a subject of ongoing debate.

The KDIGO 2021 [10] recommendations propose the implementation of nephroprotective and cardioprotective measures for all patients, along with the use of IST based on risk stratification for progressive renal injury. The compelling evidence highlighting the pivotal role of B cells in the pathogenesis of MN and the recognized drawbacks of conventional IST have steered the focus towards rituximab (RTX) in managing this glomerular disorder. RTX is a chimeric, IgG1 monoclonal antibody that depletes CD20 B cells, and may also protect podocytes by decreasing actin cytoskeleton disruption and apoptosis [11]. Current prospective studies consistently demonstrate the effectiveness and safety of RTX when compared to classical IST [12-16]. Presently, RTX stands as the first-line therapy for moderate and high-risk patients [10].

Despite all of this, uncertainties persist regarding the optimal long-term monitoring and therapeutic regimen.

This study aims to evaluate the effectiveness, predictors of response, and safety of RTX in a real world population at a tertiary hospital centre for the treatment of PLA2R-associated MN.

Methods

A retrospective study was conducted at the Coimbra Hospital and University Centre, focusing on patients aged over 18 years diagnosed with PLA2R-associated MN, who received their first RTX administration between 2017 and 2022. Eligibility criteria included a documented history of NS alongside positive serum anti-PLA2R, with biopsy not being necessary to establish the diagnosis of PLA2R-associated MN. Exclusion criteria comprised patients with MN associated with other diseases or alloimmune MN, patients who declined treatment, and those lacking a minimum follow-up period of 12 months.

Patients were evaluated concerning the risk of Renal Function (RF) loss following the KDIGO 2021 guideline [10], as well as monitoring RF progression, protein to creatinine ratio (PCR), serum albumin (SAlb), and anti-PLA2R titres. Data collection points included the time of diagnosis, RTX administration, and at 3, 6, and 9 months post-RTX, with subsequent evaluations conducted every 6 months thereafter.

The primary outcomes included both clinical and immune responses post-RTX administration. Secondary outcomes involved the analysis of relapse frequency, identification of response predictors, evaluation of kidney function progression, and documentation of adverse event incidence.

Regarding proteinuria, complete remission (CR) was defined as a proteinuria of no more than 0.3 g/g, accompanied by a SAlb of at least 3.5 g/dL. Partial remission (PR) was defined as a 50% or greater reduction in proteinuria from baseline, with proteinuria levels ranging between 0.3-3.5 g/g, irrespective of eGFR or SAlb. Proteinuria relapse was defined as an increase in proteinuria exceeding 50% from baseline in those who previously achieved CR, or an increase of more than 50%, reaching more than 3.5 g/g in those who previously attained PR.

Concerning anti-PLA2R assessment, a value lower than 14 RU/mL was considered negative, establishing immunological remission (IRM). Following remission, immunological relapse (IRL) was considered to have occurred if the titre exceeded this value.

The absence of response was defined as a proteinuria reduction of less than 25% from baseline without IRM.

Informed consent for anonymized data collection was obtained from all patients.

Statistical analysis was performed using the SPSS program, version 20, and p-values <0.05 were considered statistically significant.

Results

Of the 20 patients diagnosed with MN between 2017 and 2022 and proposed to RTX at the Coimbra Hospital and University Centre, 11 patients met the inclusion criteria, comprising 6 men and 5 women. The mean age at RTX first administration was 60.4±14.7 years, ranging from 43 to 88 years. The median disease duration was 69 [8 – 87] months and the mean follow-up after RTX was 36.9±23.1 months. At the time of first RTX administration, 8 patients were classified as high risk for RF loss, 1 as moderate risk and 2 as low risk, according to the KDIGO 2021 guideline[10] (Table: 1).

All patients initiated antiproteinuric therapy at the time of diagnosis. At the time of RTX administration, 4 patients were on Angiotensin Converting Enzyme Inhibitors (ACEI), 3 were on Angiotensin II Receptor Blockers (ARB), 2 were on ARB and spironolactone, and 2 were on ARB and ACEI. Only 1 patient was taking dapagliflozin.

RTX was the first IST in only 3 (27.3%) patients. The dose of RTX used in the first administrations consisted of 1 g administered twice within 2 weeks, with the exception of 2 patients: one who received 1g three times within 4 weeks and another who received only a single dose of 1 g. Of these 11 patients, 2 received RTX maintenance with 1g every 4-6 months.

Out of the 11 patients, only 2 (18.2%) exhibited no response, evidencing neither immune nor clinical remission. The remaining 9 patients (81.8%) presented IRM. Within this subset of 9 patients, 5 (55.6%) achieved CR, 2 (22.2%) achieved PR and 2 (22.2%) maintained nephrotic proteinuria. On average, patients presented IRM at 3.8±1.4 months, PR at 4.3±1.6 months and CR at 10.8±4.7 months. At the 12-month mark, PR occurred in 7 (63.6%) patients, and 4 (36.4%) experienced CR (Figure 1 and Table: 2).

An IRL was observed in 5 patients (45.5%), at a mean time of 20.6±13.7 months. Of these 5 patients, 3 patients had experienced partial or complete proteinuria remission and exhibited concomitant proteinuria relapse, both events detected simultaneously, at a mean time of 27.3±14.2 months. The other 2 patients maintained a nephrotic range proteinuria throughout the follow-up period, experiencing the IRL at a mean time of 10.5±2.1 months (Table: 2).

During follow up, 7 (63.6%) patients required new IST, with 4 (36.4%) repeating RTX administration, 2 (18.2%) repeating RTX along with another IST, and 1 (9.1%) receiving a different IST (Table 1). Four patients (36.4%) maintain clinical remission throughout the follow-up time, with a mean duration of 22.8±10.0 months. It should be noted that among these, 1 underwent serial RTX administrations. The remaining 3 patients sustained a response with IRM and CR throughout follow-up, without further RTX administrations.

At the time of the first RTX administration, 3 patients had anti-PLA2R levels above 150 RU/mL. Among this subgroup, 2 patients exhibited no response and the other experienced a relapse.

Patients presenting lower SAlb levels at the time of RTX administration were more likely to experience non-response

or relapse, (T-Test (9) = 2.51, p= 0.03), with a Youden Index cut-off of 3.2 g/dL, demonstrating a sensitivity of 100% and a specificity of 85.7%.

No statistically significant differences were observed in terms of age, disease duration, RF or proteinuria levels at the time of RTX administration regarding the likelihood of non-response or relapse.

Kidney function remained stable during the follow-up period, with only one patient exhibiting an eGFR under 60 mL/min/1.73m2 at the time of RTX administration. This patient did not experienced a recover in kidney function, but was able to maintain a relatively stable eGFR over time. Another patient evolved to an eGFR under 60 mL/min/1.73m2 during the follow-up, however, this decline may be also attributed to age-related changes in kidney, as the patient as already 90 years old at the end of the 2-year follow-up period (Figure 2).

Regarding adverse events, within the 6 months after RTX administration, 2 patients experienced uncomplicated urinary tract infections. One patient experienced an ischaemic stroke, however, it is notable that this patent had a patent foramen ovale. Another patient had an adrenergic crisis secondary to a newly diagnosed pheochromocytoma, nevertheless, it is worth mentioning that he had previously received other IST.

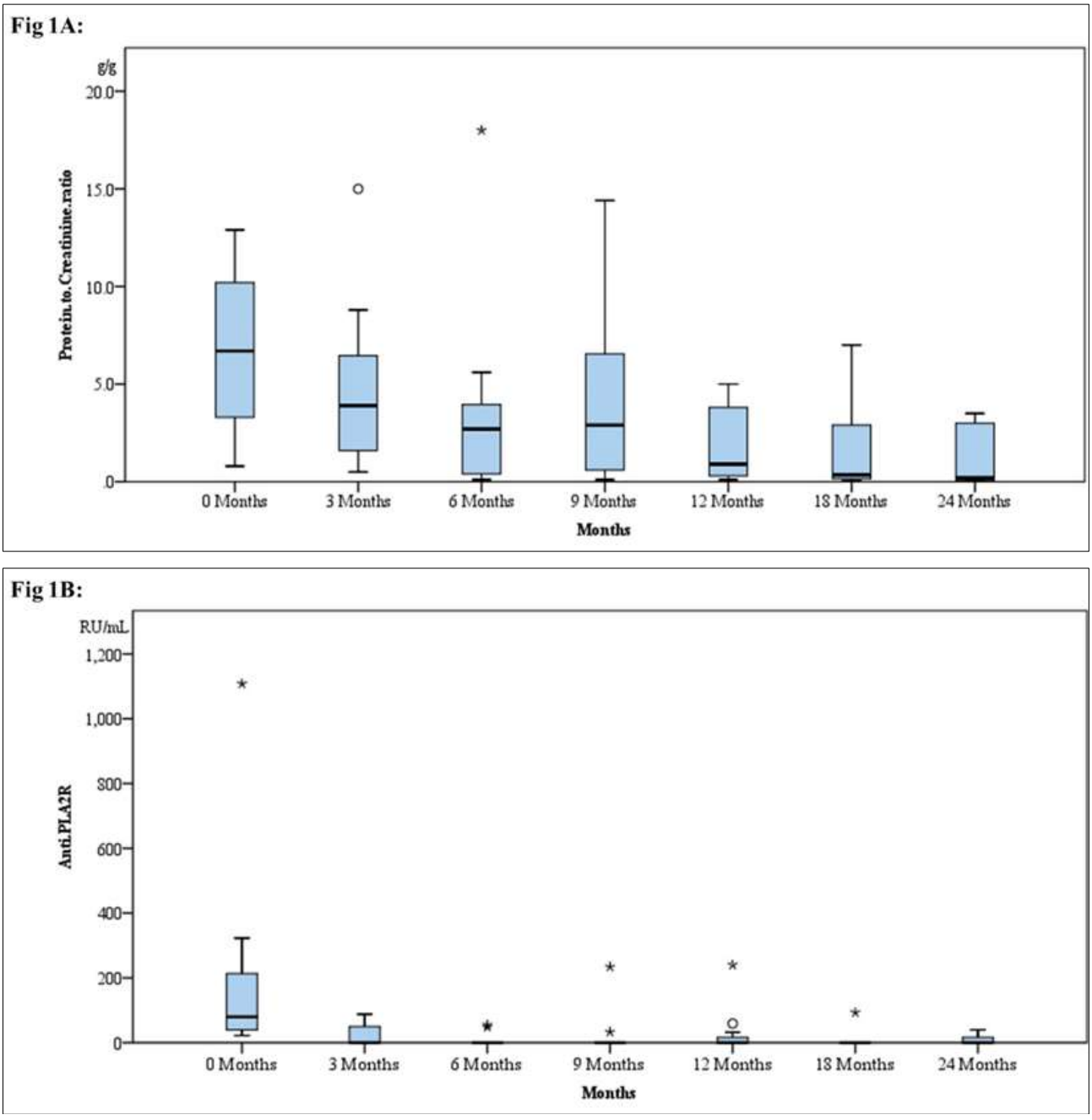
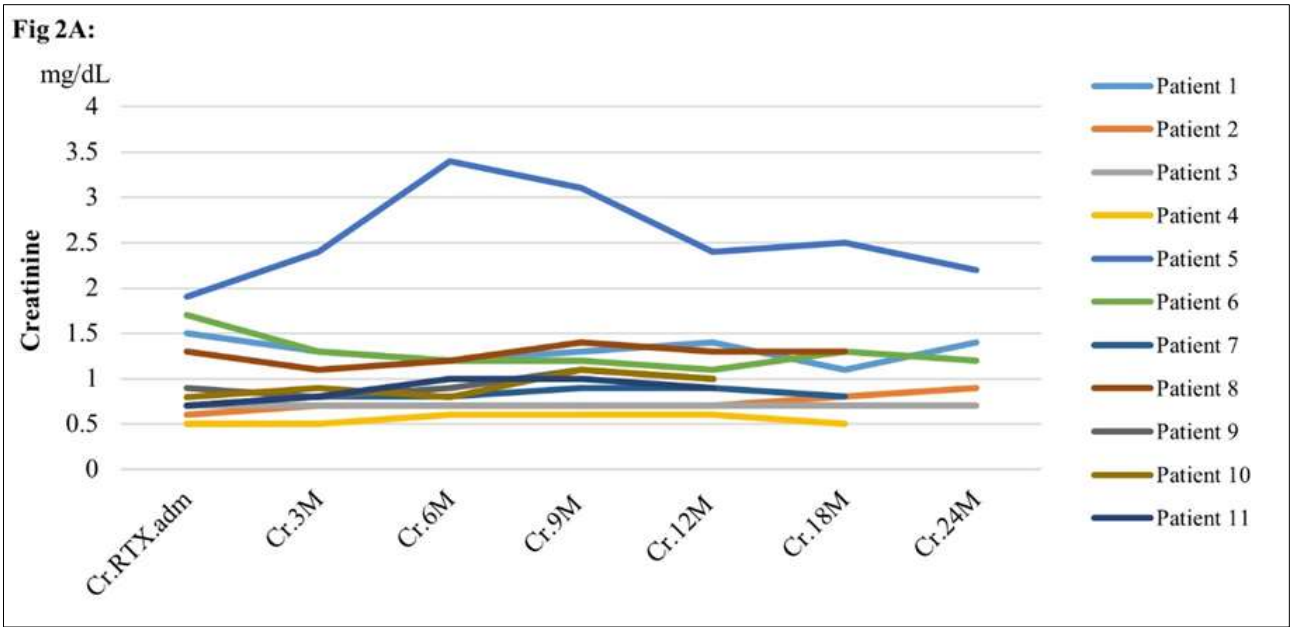


Fig 1: Box plots of protein to creatinine ratio (1A) and anti-PLA2R (1B) post-rituximab.



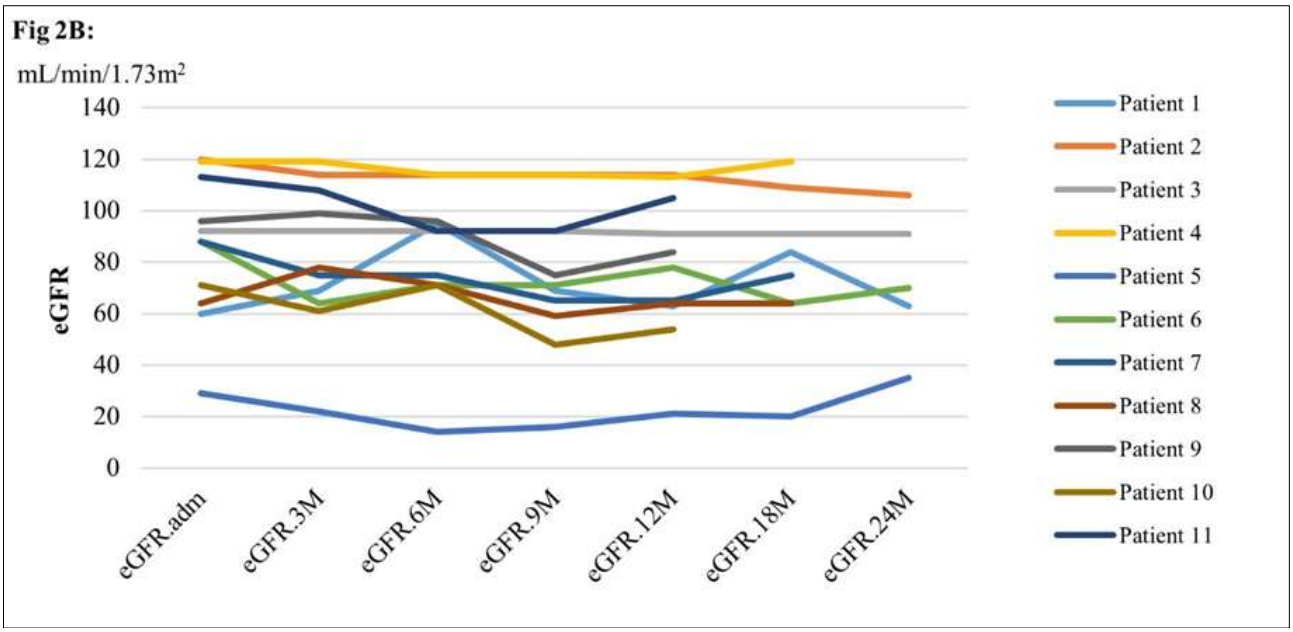


Fig 2: Changes in creatinine (2A) and eGFR (2B) post-rituximab administration. Adm, administration; Cr, creatinine; eGFR, estimated glomerular filtration rate; M, months;

Table 1: Demographic data, risk of kidney function progression and immunosuppressive therapy assessment before and after rituximab.

Patient	Gender	Dx Year	Age of Dx	Year of 1st RTX	Age of 1st RTX (years)	Time Dx to 1st RXT (months)	Follow-up after 1st RTX (months)	Risk of RF loss at Dx	Risk of RF loss at 1st RTX	Previously IST	New IST after RTX		
											Time since 1st RTX (months)	New RTX administration	Other IST
1[2]	M	2010	37	2017	44	81	77	High	High	CsA+GC/ CYP+GC	4	Yes[1]	No
2	M	2018	47	2018	47	3	63	High	High	No	8	Yes	CYP+GC -> CsA
3	F	2010	64	2018	72	87	60	Moderate	High	CYP+GC	12	Yes	No
4	F	2016	40	2019	43	33	49	Low	Low	No	-	No	No
5	F	2013	60	2020	67	72	42	Very High	High	CsA+GC	6	No	CYP+GC
6[3]	M	2018	54	2020	56	8	36	High	High	CsA+GC	6	Yes[1]	No
7	F	2016	72	2021	78	69	20	Very High	Moderate	CYP+GC	-	No	No
8	M	1995	31	2022	57	324	23	-	Low	CYP+GC	-	No	No
9	M	2022	63	2022	63	6	12	High	High	No	12	Yes	No
10	F	2018	83	2022	88	53	12	High	High	CYP+GC	9	Yes	No
11	M	2010	36	2022	49	150	12	High	High	CsA+GC/ CYP+GC	-	No	No

[1]Patients who were employed RTX maintenance administrations every 4-6 months; [2]First rituximab administration consisted of 3 doses of 1 g within 4 weeks; [3] First rituximab administration dose consisted of a single dose of 1g.

CsA, cyclosporine; CYC, cyclophosphamide; Dx, diagnosis; F, female; GC, glucocorticoids; IST, imunossupressive therapy; M, male; RF, renal function; RTX, Rituximab;

Table 2: Membranous nephropathy evolution after rituximab administration.

Patient	Partial Proteinuria Remission		Complete Proteinuria Remission		Normalisation of Serum Albumin		Imunologic Remission		No Response	Imunologic Relapse		Proteinuria Relapse	
	Time (months)		Time (months)		Time (months)		Time (months)			Time (months)		Time (months)	
1	Yes	3	Yes	18	Yes	9	Yes	Unknown	No	Yes	40[4]	Yes	40[4]
2	No	-	No	-	No	-	No	-	Yes	-	-	-	-
3	Yes	6	No	-	Yes	3	Yes	6	No	Yes	12	Yes	12
4	Yes	3	Yes	6	-	-	Yes	3	No	Yes	30	Yes	30
5	No	-	No		No		No		Yes	-	-	-	-
6	Yes	3	Yes	9	-	-	Yes	3	No	No	-	No	-
7	Yes	3	Yes	9	Yes	3	Yes	6	No	No	-	No	-
8	Yes	6	Yes	12	-	-	Yes	3	No	No	-	No	-
9	No	-	No	-	Yes	9	Yes	3	No	Yes	12	-	-
10	No	-	No	-	Yes	3	Yes	3	No	Yes	9	-	-
11	Yes	6	No	-	Yes	3	Yes	3	No	No	-	No	-

[4]Time considered since the last rituximab administration

Discussions

RTX demonstrated effectiveness in nearly all patients, leading to the achievement of IRM, normal SAlb, proteinuria reduction and maintenance of a relatively stable RF. The rate of PR or CR at 12 months stood at 63.6%, similar to the rates reported in other studies: 60% in the MENTOR study [14], 62% in the RI-CYCLO study [15] and 64.9% in the GEMRITUX study [13].

Most patients achieved IRM at 3 months, PR at 4 months and CR at 10 months, consistent with findings from previous studies [13, 17, 18]. This pattern emphasizes that IRM precedes both the remission of proteinuria [3, 17, 18] and the recovery of SAlb [6]. Therefore, monitoring anti-PLA2R levels could serve as an early indicator of therapeutic efficacy [19]. In fact, in MN the time gap between the initial detection of serum anti-PLA2R and the onset of proteinuria can span months to years. Furthermore, it is evident that after IST, changes in anti-PLA2R levels precede alterations in proteinuria [8, 17, 20, 21]. This occurs due to the persistence of immune deposits in the subepithelial space despite B cell depletion, along with incomplete remodelling of the glomerular filtration barrier and due to irreversible chronic damage that may exist (glomerular sclerosis and interstitial fibrosis) [19].

Merely 22.2% (n=2) patients exhibited no response to RTX, displaying neither IRM nor PR, comparable to the finding of Ruggenenti *et al*., who reported a non-response rate of 25% over a median follow up of 30.8 months [18]. However, these patients also demonstrated no response or frequent relapses to subsequent conventional IST. On one hand, the persistence or recurrence of anti-PLA2R may indicate inadequate CD20 B cell depletion or primary resistance to IST, which could stem from various factors such as RTX immunization or underdosing (linked to urinary loss, internalization and destruction by target B-cells, or FcRn polymorphism) [22]. On the other hand, persistence or recurrence of proteinuria may suggest irreversible chronic glomerular damage [22].

A proteinuria relapse was observed in 27.3% of patients, again consistent with the 29.8% relapse rate reported by Ruggenenti *et al*. [18] Ruggenneti *et al*. showed that the likelihood of remission and relapse after RTX was comparable between patients who had received RTX as first line treatment and those who had already received other IST [18]. This scenario aligns with the majority of patients evaluated in this study.

More than a half of patients in our study require additional RTX administrations. We also observed a higher likelihood of non-response or relapse in patients with lower SAlb and a faster IRL in patients with persistent nephrotic proteinuria. This phenomenon may be attributed to the shorter half-life of RTX due to increased urinary loss in the context of glomerular membrane selectivity loss in MN [22-24]. These findings underscore the importance of a closer follow-up for patients with persistent nephrotic range proteinuria.

Patients with anti-PLA2R levels exceeding 150 RU/mL either did not respond or relapsed. Recent reviews [11, 22] have even suggested anti-PLA2R above 150 RU/mL as a threshold for high risk of disease progression, contrasting with the 50 RU/mL suggested by KDIGO 2021. In fact, anti-PLA2R levels are associated with disease activity and should be used for treatment decisions [18, 19, 25] Patients with lower levels are more prone to achieve proteinuria remission, and to attain it more rapidly [17, 18, 26] Patients with higher levels exhibited a diminished immunological response, and the inability to achieve IRM strongly predicts the absence of proteinuria remission [17-28] The significance of anti-PLA2R as an independent risk marker, along with its role as an indicator for the potential necessity of new IST, is noteworthy. However, we observed that a 6-month interval between appointments does not enable the early detection of immunologic relapse before the onset of proteinuria relapse. Similar to the sequence of events where immunologic remission precedes partial remission, the same temporal relationship exists for immunologic relapse, occurring up to 3 months earlier [17]. Consequently, a closer monitoring strategy for patients with higher initial PLA2R levels may bridge this temporal gap.

Regarding adverse events, the administration of RTX was well-tolerated by patients, with no reported complications at the time of administration. The most prevalent adverse event was uncomplicated UTIs, experienced by 2 patients. The risk of malignancy in patients who underwent RTX may be similar to that of the general population [29]. In our study, we reported only a case of a pheochromocytoma, but given the patient's prior history of other IST, the influence of RTX is difficult to assess. Finally, 1 patient had an ischaemic stroke, but he had a patency of the foramen ovale as a risk factor. Overall, studies have consistently demonstrated that the safety profile of RTX is either equivalent to or better than conventional IST [12-15, 30].

Our study has notable limitations. The small sample size raises concerns about the generalizability of our findings. Additionally, variations in treatment approaches for each patient pose a challenge to the uniformity of our results. Notably, not all patients received the same initial dose of RTX, and some were concurrently on other IST during RTX administration. These discrepancies in treatment regimens

may have introduced bias into our data analysis, limiting the robustness of our conclusions.

Conclusion

Our study highlights the efficacy and safety of RTX use in PLA2R-associated MN. The presented cases illustrate the heterogeneity of MN, emphasizing the significant challenge of MN monitoring process. Given the substantial need for additional immunosuppression, tracking disease progression through the measurement of anti-PLA2R titres not only guides clinical decisions but also enables a judicious approach to subsequent RTX administrations. Notably, patients with lower serum albumin levels and higher anti-PLA2R titres (>150 RU/mL) require more frequent monitoring and are at increased risk of non-response/relapse. Also patients with no proteinuria response, despite IRM, demand closer surveillance. This tailored strategy not only mitigates toxicity associated with multiple treatments but also addresses cost considerations.

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