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Rituximab in Patients With Primary Membranous Nephropathy With High Immunologic Risk

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INTRODUCTION

The Kidney Disease Improving Global Outcomes guidelines recommend incorporating anti-M-type Phospholipase A_2 receptor (PLA2R) antibody titers in steering treatment decisions for patients with primary membranous nephropathy (PMN).[1]

Various publications suggest patients with high anti-PLA2R titers respond poorly to immunosuppressive treatment.[2,3] In a recent report, van de Logt *et al.*[4] reported poor immunologic response to rituximab in patients with a baseline titer >152 RU/ml. In routine practice, the aforementioned study is widely cited for recommending oral cyclophosphamide and corticosteroids (CYC/CS) in patients with PMN who have high titers of anti-PLA2R. However, there is limited data on the efficacy of rituximab compared to the cyclical CYC/CS in patients with PMN who have high anti-PLA2R titers. Therefore, in the present manuscript, we report the clinical outcomes of patients with PMN who have an anti-PLA2R titer >150 RU/ml treated with either rituximab or cyclical CYC/CS. The details of the study methods are shown in Supplementary Methods along with Supplementary References[S1,S2] and STROBE statement for observational studies.

RESULTS

Participants

In our PMN registry, 33 rituximab-treated patients had baseline anti-PLA2R levels of >150 RU/ml. For comparison, we included the first (consecutive) 33 patients with PMN who were treated with cyclical CYC/CS with anti-PLA2R titer >150 RU/ml.

Descriptive Data

The baseline parameters were comparable in both groups (Table 1). The median age was 40 (IQR 28, 49) years. Of the patients, 23 (69.7%), 2 (6.1%), and 8 (24.2%) received 1 g × 2 (day 0 and 15), CD19-targeted therapy, and 375 mg/m^2 × 4 doses protocol, respectively. One patient was lost to follow-up from each group and was excluded from the outcome analysis. Twelve (37.5%) patients received additional doses of rituximab during follow-up.

Outcome

At 18 months, 21 (65.6%) and 17 (53.1%) patients treated with cyclical CYC/CS and rituximab (risk ratio 1.2; 95% confidence interval, 0.8 to 1.9, $P = 0.4$) achieved remission, respectively. Complete remission was numerically higher in the cyclical CYC/CS-treated patients (complete remission vs. partial remission, 25% vs. 15.6%, risk ratio 1.3; 95% confidence interval, 0.5–3.2, $P = 0.7$). There was no significant difference in the remission rate between the 2 groups in treatment naïve, relapsing, and resistant cases at 18 months (Table 2).

Three (9.3%) patients in the rituximab group progressed to kidney failure by month 18. Two had

Table 1. Baseline and follow-up parameters of the study patients

Parameter	Rituximab[a] (n = 33)	Cyclical CYC/CS[a] (n = 33)	*P*-value
Age (yr)	37 (25–49.5)	41 (28–48.5)	0.75
Sex (M: F)	21:12	17:16	0.45
Treatment naïve/relapse	20 (60.6%)/3(9%)	26(81.8%)/1 (3%)	-
Resistant disease	10 (30.4%)	6 (18.2%)	-
Baseline			
Anti-PLA2R (RU/ml)	295 (224.4–522.8)	378.27 (227.9–733.9)	0.39
Proteinuria (g/d)	5.2 (4.4–9.4)	4.7(4.2–8.0)	0.18
Serum albumin (g/dl)	2.3 (1.9–2.8)	2.3 (1.9–2.7)	0.45
Serum creatinine (mg/dl)	0.9 (0.8–1.1)	0.8 (0.7–0.9)	0.09
eGFR (ml/min/1.73m^2)	94.4 (67.8–120.6)	105.0 (88.0–114.6)	0.36
6-mo			
Anti-PLA2R (RU/ml)	27.5 (0.6,109)	8.6 (1.9,59.8)	0.63
Proteinuria (g/d)	3.7 (2.2–6.9)[a]	0.8 (0.5–3.6)[b]	0.002
Serum albumin (g/dl)	3.06 (2.64–3.7)	3.5 (2.6–3.5)	0.56
Serum creatinine (mg/dl)	0.9 (0.8–1.2)	0.8 (0.8–0.9)	0.06
eGFR (ml/min per 1.73 m^2)	91.3 (73.4–125.0)	105.1 (94.3–121.7)	0.15
12-mo			
Proteinuria (g/d)	2.07 (0.4–4.9)	1.3 (0.2–3.4)	0.25
Serum albumin (g/dl)	3.5 (2.9–4.1)	3.8 (2.9,4.1)	0.71
Serum creatinine (mg/dl)	0.83 (0.76–1.0)	0.8 (0.8–0.9)	0.58
eGFR (ml/min per 1.73 m^2)	107.0 (87.1–127.6)	105.7 (93.5–119.2)	0.90
18-mo			
Proteinuria (g/d)	1.58 (0.385–4.8)	0.6 (0.2–2.5)	0.16
Serum albumin (g/dl)	3.85 (3.4–4.3)	4 (3.4–4.2)	0.98
Serum creatinine (mg/dl)	0.9 (0.8–1.0)	0.8 (0.8–1.0)	0.28
eGFR (ml/min per 1.73 m^2)	103.3 (81.9–120.2)	103.3 (93.6–111.2)	0.66
Remission			
12 mo	15 (46.9%)	20 (62.5%)	0.31
	CR (07 (21.9%))	CR (09 (28.1%))	
	PR (08 (25%))	PR (11 (34.4%))	
18 mo	17 (53.1%)	21 (65.6%)	0.44
	CR (05 (15.6%))	CR (08 (25%))	
	PR (12 (37.5%))	PR (13 (40.6%))	

CR, complete remission; CYC/GC, cyclophosphamide and glucocorticoids; eGFR, estimated glomerular filtration rate; F, female; M, male; PLA2R, M-type Phospholipase A2 receptor; PR, partial remission.
[a]One patient in each group was lost to follow-up. Therefore, all the calculation for outcome and other parameters is based on 32 patients in each arm. a × b = 0.02.

extensive tubular atrophy and interstitial fibrosis on biopsy, and the third patient developed coronary artery disease and had a nonrecovering sepsis-induced acute kidney injury. On multivariate analysis, none of the baseline parameters or nature of therapy predicted complete remission or partial remission at 18 months.

Anti-PLA2R Antibody

Eleven (34.4%) and 18 (56.3%) patients in the rituximab and cyclical CYC/CS, respectively, achieved serologic remission at 6 months. Twelve patients had anti-PLA2R positive at 6 months and clinical remission at 18 months; all tested negative or had a significant reduction in anti-PLA2R titers at the 12th month (Supplementary Table S1). Likewise, 2 patients with a negative anti-PLA2R in the sixth month and resistant disease in the 18th month had clinical remission on extended follow-up without additional immunosuppressive therapy (Supplementary Table S1).

Relapse

Five (33%) patients and 1 (5%) patient in the rituximab and cyclical CYC/CS groups, respectively, had a disease relapse after remission at 12 months. All the patients with relapse had either anti-PLA2R positivity at 6 months or a resurgence of anti-PLA2R titer on follow-up.

Safety Profile

Infusion reactions were the most common side effect of rituximab therapy. Besides mild infusion reactions to rituximab, 24 (75%) in cyclical CYC/CS and 6 (18.7%) in the rituximab group patients developed untoward medical events (risk ratio 4.0; 95% confidence interval, 2.0–8.6) to therapy (Supplementary Table S2). Two patients died, 1 in each group, and the cause was pneumonia in both patients.

DISCUSSION

In this study, patients treated with cyclical CYC/CS had numerically higher remission rates than rituximab-treated cases but with a better safety profile in the rituximab-treated patients. The results indicate that rituximab may be a reasonable alternative to cyclical CYC/CS in patients with PMN who have anti-PLA2R titer >150 RU/ml.

A high anti-PLA2R titer at diagnosis suggests a lower probability of immunosuppressive therapy-induced remission.[2,3,5] Van de Logt *et al.*[4] evaluated for immunologic remission following therapy (rituximab [n = 46] vs. CYC/CS [n = 52]) in patients with anti-PLA2R-associated PMN. The authors reported that, at 6 months, rituximab was less effective than CYC/CS in patients with anti-PLA2R >152 RU/ml. The aforementioned study formed the basis for recommending CYC/CS in patients with anti-PLA2R >150 RU/ml.[4] In comparison, in our study, two-thirds of the patients with anti-PLA2R >150 RU/ml treated with cyclical CYC/CS responded, whereas at least 50% of the rituximab-treated patients achieved remission. However, in a multivariate analysis, the nature of the therapy did not predict clinical remission. Variable CYC (2 mg/kg/d × 12 weeks [present study] vs. 1.5 mg/kg/d × 8–24 weeks)[4] and rituximab (cumulative 2000–3000 [present study] mg vs. 1500–2000 mg)[4] dosing may partly explain the discrepancy in the remission rates in the present study with that by van de Logt *et al.*[4] However, a subset of the patients reported by van de Logt *et al.*[4] went on to receive supplemental

Table 2. Baseline and follow-up parameters in treatment naïve/relapsing and resistant disease

	Treatment naïve[a]		Relapse		Resistant	
Parameter	**Rituximab $n = 20$**	**Cyclical CYC/CS $n = 26$**	**Rituximab[b] $n = 3$**	**Cyclical CYC/CS[c] $n = 1$**	**Rituximab[d] $n = 10$**	**Cyclical CYC/CS[e] $n = 6$**
Age (yr)	42	44.5	48	22	29.5	33.5
	(31–51)	(28–49)	(25–57)		(20.2–39.7)	(17.5–47.5)
Sex (M: F)	11:9	13:13	1:2	1	9:1	3:3
Baseline						
Anti-PLA2R (RU/ml)	291.6	386.7	221.7	235.18	340.8	238.0
	(247.6–523.0)	(246.1–780.6)	(214.0–731.0)		(215.8–579.5)	(179.1–652.1)
Proteinuria (g/d)	5.9	4.7	5.1	11.5	4.9	4.3
	(4.6–9.5)	(4.2–8)	(4.6–5.9)		(4–17.8)	(3.6–9.3)
Serum albumin (g/dl)	2.3	2.2	3.3	2.62	2.2	2.6
	(1.9–2.9)	(1.8–2.5)	(2.7–3.7)		(1.9–2.3)	(2.3–2.9)
Serum creatinine (mg/dl)	0.9	0.8	0.9	0.8	0.8	0.8
	(0.8–1.1)	(0.7–.9)	(0.7–1.1)		(0.8–1)	(0.8–1.1)
eGFR (ml/min per 1.73 m^2)	86.0	104.4	94.4	127.4	114.1	104.2
	(67.1–114.1)	(86.1–116.0)	(55.7–120.6)		(85.1–127.0)	(84.0–109.0)
6-mo						
Anti-PLA2R (RU/ml)	24.3	8.6	3.3	0.37	57.1	103.3
	(0.6–109.0)	(2.0–33.3)	(1.3–27)		(22.2–169.4)	(0.6–226.6)
Proteinuria (g/d)	4.1[f]	0.78[f]	0.53	0.8	5.0[g]	1.1[g]
	(2.4–5.8)	(0.5–4.9)	(0.3–1.0)		(3.3–11.1)	(0.6–2.6)
Serum albumin (g/dl)	3.2	3.28	3.7	4.1	2.6	3.6
	(3–3.7)	(2.6–3.6)	(3.6–4.3)		(1.9–3.1)	(2.4–3.9)
Serum creatinine (mg/dl)	0.9	0.8	0.8	0.8	1.0	0.8
	(0.7–1.2)	(0.8–0.9)	(0.3–1.1)		(0.8–1.2)	(0.7–1.0)
eGFR	86.2	104.7	90.1	127.4	103.8	109.3
(ml/min per 1.73 m^2)	(69.0–124.3)	(92.8–121.3)	(58.1–160.5)		(79.3–126.4)	(89.4–116.4)
12-mo						
Proteinuria (g/d)	2.0	1.2	0.1	1.09	6.7	2.8
	(0.2–4.2)	(0.21–3.7)	(0.1–0.9)		(3.6–9.9)	(1.7–3.3)
Serum albumin (g/dl)	3.7	3.8	3.8	4.3	3.0	3.15
	(3.1–4.1)	(3.3–4.1)	(3.7–4.7)		(2.5–3.3)	(2.4–4.1)
Serum creatinine (mg/dl)	0.8	0.86	0.8	0.8	0.9	0.8
	(0.6–1)	(0.8–.098)	(0.8–1.1)		(0.8–1.2)	(0.7–1.1)
eGFR	112.6	104.4	87.0	126.6	105.4	104.4
(ml/min per 1.73 m^2)	(85.7–129.1)	(92.3–115.9)	(57.8–121.6)		(93.8–126.3)	(80.6–127.4)
18-mo						
Proteinuria (g/d)	1.4	0.6	0.32	2.6	3.4	3.72
	(0.3–4.8)	(0.17–1.95)	(0.2–0.6)		(1.0–11.6)	(0.2–5.2)
Serum albumin (g/dl)	3.7	4.06	4.6	3.7	3.6	3.4
	(3.3–4.2)	(3.6–4.2)	(3.8–4.7)		(3.1–4.1)	(2.4–4.2)
Serum creatinine (mg/dl)	0.9	0.9	0.8	1.2	1.0	0.8
	(0.7–1.01)	(0.8–1)	(0.7–1.0)		(0.8–1.4)	(0.8–0.8)
eGFR	107.8	101.5	103.4	112.0	97.6	108.0
(ml/min per 1.73 m^2)	(80.4–119.5)	(93.2–111.2)	(64.0–121.6)		(85.4–125.9)	(98.3–109.1)
Remission						
12 mo	10 (50%)	16 (61.5%)	3 (100%)	1 (100%)	0 (0%)	3 (50%)
	CR (5[25%])	CR (8[30.7%])	CR (2[66%])	PR (1[100%])		CR (1[16%])
	PR (5[25%])	PR (8[30.7%])	PR (1[33%])			PR (2[33%])
18 mo	11 (55%)	18 (69.2%)	3 (100%)	1 (100%)	3 (30%)	2 (33%)
	CR (4[20%])	CR (7[26.9%])	CR (1[33%])	PR (1[100%])	PR (3[30%])	CR (1[16.6%])
	PR (7[35%])	PR (11[42%])	PR (1[33%])			PR (1[16.6%])

CR, complete remission; CYC/CS, cyclophosphamide and corticosteroids; eGFR, estimated glomerular filtration rate; F, female; M, male; PLA2R, M-type Phospholipase A2 receptor; PR, partial remission.

[a]Two patientsfrom treatment naïve group (1 from rituximab and 1 from CYC/CS) were lost to follow-up. Therefore, all the calculation for outcome is based on 19 patients in rituximab treatment naïve arm and 25 patients in CYC/CS treatment naïve arm.

[b]Previous therapies include cyclical CYC/CS in 2 and rituximab in 1 patient.

[c]Received rituximab previously.

[d]Previous therapies include cyclical CYC/CS in 3 cases, rituximab in 4 cases, tacrolimus and corticosteroids in 2 cases, and tacrolimus and corticosteroids followed by cyclical CYC/CS in 1 case.

[e]Previous therapies include tacrolimus and corticosteroids in all patients.

[f]*P*-value for a × b is 0.01.

[g]*P*-value for c × d is 0.01.

doses of rituximab, which enhanced the immunologic remission to 80%[6]; furthermore, the immunologic remission translated to clinical remission in most cases. In the present study, one-third of the patients received additional rituximab dosing after 3 months for CD19 repletion. The report by Dahan *et al.*[6] emphasizes the vitality of adequate rituximab dosing while treating patients with PMN.

Considering that one-third of the patients in the current study received an additional dosage of rituximab (on CD19 repletion), the relapse is less likely because ofinadequate dosage. The present study's results signal higher relapse rates in patients treated with rituximab than cyclicalCYC/CS.

Like previous studies, the current report confirms the association of the anti-PLA2R with clinical activity.[7] We witnessed a sharper decline in the antibody at 6 months, with greater magnitude in the cyclical CYC/CS group than in rituximab-treated patients.

Another essential consideration when choosing a therapeutic intervention is the safety profile. Though a previous study reported higher adverse events with CYC/CS (Nijmegen protocol) compared to rituximab therapy,[8] the recent randomized trial does not signal any heightened concern with cyclical CYC/CS over rituximab.[9] In the present study, patients treated with cyclical CYC/CS had almost 4 times more untoward medical events than those who received rituximab therapy; however, most were minor, and there was no meaningful difference in the serious adverse events. A lower oral CYC dosing with cyclical CYC/CS compared to the Nijmegen protocol may explain the differences in serious side effects between the present study and the report by Van den Brand *et al.*[4,8]

Although the study's results do not suggest rituximab as a convincing alternative to cyclical CYC/CS in PMN with high anti-PLA2R titer, limited by numbers, the present study adds to the growing literature on treating PMN patients with very-high immunologic titerswith rituximab therapy. The current study is one of the most extensive studies comparing the 2 first-line therapies in PMN cases with high anti-PLA2R titers. A protocolized approach in the registry data is an additional strength. The study limitations include the nature of the study, heterogenous PMN profile, nonavailability of anti-PLA2R levels at follow-up (mainly at 12 to 18 months) in all patients, and variable rituximab protocols. However, to conclude, in patients with anti-PLA2R antibodies >150 RU/ml, cyclical CYC/CS-induced numerically greater but statistically insignificant difference in the remission rates than rituximab. Therefore, with a favorable safety profile, rituximab monotherapy is a reasonable alternative to cyclical CYC/CS in patients with PMN and high anti-PLA2R titers.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary Reference.

Table S1. Patients with discrepancy in anti-PLA2R at 6 months and clinical activity at 18 months.

Table S2. Untoward medical events profile.

STROBE Statement.

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