Rituximab, Cyclophosphamide, and Corticosteroid Combination in Difficult-to-Treat Membranous Nephropathy

Dear Editor,

Managing resistant or relapsing primary membranous nephropathy is challenging, especially with comorbidities like diabetes or frailty. Clinicians often switch first-line therapies, such as rituximab, with cyclical cyclophosphamide/corticosteroids and vice versa. However, both regimens have issues.[1,2]

Emerging evidence suggests that rituximab with low-dose cyclophosphamide/corticosteroids (hybrid therapy) may be promising for treating treatment naive, relapsing or resistant membranous nephropathy.[3-5] Nevertheless, data on this combination are limited for relapsing and resistant disease.[4,5] Given its broad immunosuppressive effects, this therapy will likely induce remission in this group. We present our experience with this resistant relapsing membranous nephropathy management using this combination. The methodology has been detailed in Supplemental Methods.

Hybrid therapy including oral prednisolone (starting at 60 mg and tapering to 5 mg by month six), oral cyclophosphamide (150 mg for one week followed by 100 mg until month two), and rituximab (a dosage of 1 g was administered day 0, followed by a second dose between days 15-45, and a third dose between days 90-180) was administered to 22 patients [Supplemental Table 1]. Four missed the third dose: three due to financial constraints and one due to a severe complication resulting in death before administration. The follow-up period was at least 12 months. The study comprised three females and 19 males; the average age was 42.33 ± 13.33 years. Prior to therapy, the median proteinuria level was 7.2 g/day (5.72, 12.50), and average serum albumin and creatinine levels were 2.41 ± 0.83 g/dL and 1.42 ± 0.58 mg/dL, respectively. Among 22, 16 cases were positive for anti-PLA2R antibodies by ELISA, two through indirect immunofluorescence only, and one had a history of antibody positivity. Additionally, three (13.63%) patients had pre-existing diabetes mellitus, and 16 (72.72%) had hypertension. The previous treatment consisted of both cyclical cyclophosphamide/corticosteroids and rituximab, cyclical cyclophosphamide/corticosteroids alone, and rituximab alone in 13 (59.09%), 5 (22.73%), and 4 (18.18%) patients, respectively. Seven and 15 patients had relapsing and resistant disease, respectively. Ten patients presented with kidney dysfunction (eGFR<60 mL/min/1.73m^2), seven showing eGFR <45 mL/min/1.73m^2.

At the last follow-up (median 18-months), out of the total 22 patients, 14 (63.6%) achieved remission, with 05 (22.7%) attaining complete remission (CR) and 9 (40.9%) achieving partial remission (PR). At 6 and 12 months, 10 (02 CR and 08 PR) (45.5%) and 12 (04 CR and 08 PR) (54.5%) patients achieved clinical remission.

In the subset of patients with resistant disease, 05 (33.33%), 07 (46.44%), and 09 (60%) achieved remission at 6, 12, and 18-month follow-up, respectively. In patients with relapsing disease, 05 (71.42%), 05 (71.42%), and 05 (71.42%) achieved remission at 6, 12, and 18 months, respectively. Three patients (2 with resistant disease and 1 with relapsing disease) experienced nephrotic syndrome relapse after achieving remission. Proteinuria, serum albumin, and creatinine in patients with resistant, relapsing, and chronic kidney disease are shown in Table 1. Ten (71.4%), 13 (92.8%), and 16 (100%) patients achieved serological remission at the 3, 6, and 12-month follow-ups. Four patients showed clinical-serological dissociation, as detailed in Supplemental Table 2.

Table 2 shows that 12 patients (54.54%) experienced one or more complications during therapy, five (22.73%) of which qualified as serious adverse events (SAEs).

There is no well-defined approach to treating relapsing or resistant membranous nephropathy. Hybrid therapy resulted in two-thirds of patients with difficult-to-treat membranous nephropathy showing a reasonably safe response. Previously, this combination has been employed to treat patients who are treatment-naïve, relapsing, or resistant to standard therapy [Supplemental Table 3]. The study by Zonozi *et al.,* included 60 patients; 29 with relapsing nephropathy and 9 with resistant nephropathy.[5] While detailed information about relapsing and refractory cases is unavailable, the hybrid regimen achieved a 90% remission rate in the total cohort at the final follow-up. However, the study required the administration of 8 g of rituximab over 18 months, one of the highest doses reported for any nephrological condition. In this study, 68% of the cases were refractory to previous immunosuppressive therapy. Despite the challenges, two-thirds (60% for refractory disease and 71% for relapsing disease) of patients responded to therapy. The response rates differ from Zonozi *et al.*'s study, likely due to variations in patient profiles (i.e., predominantly treatment-naïve patients in prior studies, compared to the resistant cases in our cohort) and the use of higher rituximab doses.[5] The lower complete remission rates may be attributed to the nature and duration of the disease. Most patients had refractory or relapsing disease, with kidneys more prone to chronic changes, unlike those with treatment-naïve disease, who typically have a shorter disease duration [Supplemental Table 3].

Table 1: Baseline and follow-up parameters

	Total (n=22)	Resistant (n=15)	Relapsing (n=07)	eGFR <60 mL/min/1.73m² (n=10)	eGFR ≥60 mL/min/1.73m² (n=12)
Age	41.86±13.19	44.47±14.09	36.90±9.62	42.50±15.70	41.33±11.40
Sex (Female: Male)	03: 19	01:14	02:05	00:10	03:09
Anti-PLA2R	139.30 (67.66,895.20%)	91.21 (54.43,222.60)	739.40 (145.40,1272.00)	95.51 (38.50,336.00)	181.10 (74.80,1088.00)
Baseline					
Proteinuria (g/day)	7.24 (5.86,12.25)	11.08 (6.46,13.01)	6.24 (4.00,7.28)	11.50 (5.89,13.2)	6.84 (5.58,11.36)
Serum albumin (g/dL)	2.41±0.81	2.17±0.49	2.95±1.13	2.34±0.98	2.48±0.69
Serum creatinine (mg/dL)	1.42±0.58	1.53±0.54	1.18±0.65	1.96±0.41	0.98±0.21
6 months					
Proteinuria (g/day)	3.595 (1.54,4.92)	4.22 (1.95,8.18)	2.10 (0.22,3.72)	3.96 (2.18,9.20)	3.29 (0.96,4.69)
Serum albumin (g/dL)	3.651±0.6891	0.35±0.65	4.10±0.61	3.58±0.84	3.71±0.58
Serum creatinine (mg/dL)	1.242±0.4611	1.29±0.45	1.14±0.51	1.58±0.49	0.98±0.20
12 months					
Proteinuria (g/day)	3.000 (0.65,4.42)	3.13 (0.8,4.28)	0.74 (0.27,4.8)	3.02 (2.4,4.78)	0.77 (0.40,3.92)
Serum albumin (g/dL)	3.83±0.64	3.77±0.64	3.95±0.67	3.65±0.73	3.97±0.55
Serum creatinine (mg/dL)	1.31±0.6034	1.31±0.55	1.29±0.75	1.63±0.66	1.07±0.44
Last follow-up (median 18 months)					
Proteinuria (g/day)	1.23 (0.50,4.15)	2.19 (0.77,4.66)	0.45 (0.28,3.99)	1.6 (0.73,7.12)	1.01 (0.40,1.18)
Serum albumin (g/dL)	3.93±0.67	3.87±0.68	4.05±0.70	3.87±0.78	3.97±0.62
Serum creatinine (mg/dL)	1.28 (0.88,1.75)	1.28 (1.04,1.68)	0.86 (0.81,2.30)	1.60 (1.35,2.4)	1.10±0.44
Remission- 6 months	10 (45.45%)	05 (33.33%)	05 (71.42%)	04 (40.00%)	06 (50.00%)
CR	02 (20.00%)	None	02 (40.00%)	01 (25.00%)	01 (16.67%)
PR	08 (80.00%)	05 (100%)	03 (60.00%)	03 (75.00%)	05 (83.33%)
Remission- 12 months	12 (54.54%)	07 (46.66%)	05 (71.42%)	03 (30.00%)	09 (75.00%)
CR	04 (18.18%)	01 (14.28%)	03 (60.00%)	None	04 (44.44%)
PR	08 (36.36%)	06 (85.72%)	02 (40.00%)	03 (100.00%)	05 (55.56%)
Remission- last follow-up	14 (63.63%)	09 (60.00%)	05 (71.42%)	06 (60.00%)	08 (66.67%)
CR	05 (22.72%)	01 (11.11%)	04 (80.00%)	01 (16.67%)	05 (62.50%)
PR	09 (40.91%)	08 (88.89%)	01 (20.00%)	05 (83.33%)	03 (37.50%)

Three patients had a relapse of nephrotic syndrome after achieving remission in between months 6-12. CR: Complete remission, PR: Partial remission, PLA2R: M-type Phospholipase A2 receptor, eGFR: estimated glomerular filtration rate.

Table 2: Side effects

Any side effect	12 (54.54%)
Serious side effect*	05 (22.72%)
New onset diabetes mellitus	03 (13.63%)
Skin and soft tissue infection	02 (09.10%)
Gastro-intestinal bleed	02 (09.10%)
Gastrointestinal infections	02 (09.10%)
Urinary tract infections	01 (04.54%)
Pneumonia	02 (09.10%)
Fatal myocardial infarction	01 (04.54%)

*Pneumonia, Myocardial infraction, gastrointestinal bleeding, diarrhea with acute kidney injury and urinary tract infection

Most cases in this study were anti-PLA2R-related, with nearly 85% achieving immunological remission by 6 months. The anti-PLA2R results are similar to previous reports.[3,5] The potential causes for failure to achieve clinical remission despite immunological remission have been detailed in Supplemental Table 2.

The final aspect is the regimen's side effect profile. SAEs were more frequent and severe than in previous studies.[6] Besides immunosuppression intensity, other contributing factors include nephrotic syndrome's impact, higher diabetes mellitus incidence, poor glycemic control due to high corticosteroid doses, and the cumulative effects of prior immunosuppressive therapy. Although the side effect profile in this study was *similar* to those of Zonozi *et al*.[5] and Vink *et al*.,[3] we must remain mindful that the recording of adverse events in this study may be incomplete due to the retrospective nature of the study, as patients may not have reported minor adverse events that did not necessitate direct medical intervention.

The hybrid therapy offers reduced doses of corticosteroids and cyclophosphamide compared to the cyclical cyclophosphamide/corticosteroids, while incorporating the potential benefits of CD20 inhibitor. Specifically, the cumulative dose of prednisolone (equivalent) in the hybrid therapy is 2520 mg, against 14085 mg for a 70 kg individual receiving cyclical cyclophosphamide/corticosteroids. Similarly, the cyclophosphamide dose is 6350 mg in the hybrid therapy, against 13500 mg for a 70 kg patient receiving cyclical cyclophosphamide/corticosteroids.[6]

Despite encouraging results in challenging situations, the study has several limitations including its short follow-up period, and the absence of pre-therapy kidney biopsies in these patients with kidney dysfunction.

To conclude, the hybrid therapy of rituximab combined with low-dose cyclophosphamide and corticosteroids is effective in difficult-to-treat membranous nephropathy management. However, a well-designed prospective multicenter study with an adequate sample size is essential to validate these findings.

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