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Combination Induction Immunosuppression With Rituximab, Cyclophosphamide, and Prednisone for Fibrillary Glomerulonephritis

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INTRODUCTION

Fibrillary glomerulonephritis (FGN) is a rare type of glomerulonephritis that has a poor prognosis with most studies showing that almost half of the patients progress to end-stage kidney disease (ESKD) within 2 years of diagnosis.[1–4] No treatments for FGN have been shown to slow progression to ESKD. In this retrospective case series, we report the outcomes of 14 individuals with FGN who were treated with the combination of rituximab, cyclophosphamide, and steroids and compare their outcomes with previous published data on FGN.

RESULTS

Baseline Characteristics

Fourteen patients were included in the study and were followed-up with for a median (interquartile range [IQR]) of 3.0 (0.9–5.5) years. Six (42%) were female, the median age at treatment initiation was 60 (range: 38–79) years, and 12 (86%) were non-Hispanic White (Table 1). The median (IQR) time from biopsy to treatment initiation was 44 (7.5–68) days. All 14 patients were treated with rituximab for a median (IQR) of 1.8 (0.7–5.0) years (details are presented in the Supplementary Methods). The median (IQR) time of continuous B cell depletion was 1.3 (0.6–3.3) years. Only 1 patient received rituximab and 13 received combination therapy with rituximab, oral cyclophosphamide, and prednisone (Table 1). The median (IQR) cumulative cyclophosphamide dose was 6500 (5300–9175) mg per person. At the initiation of immunosuppression, the median (IQR) serum creatinine was 2.44 (1.60–2.97) mg/dl, median (IQR) estimated glomerular filtration rate (eGFR) was 29.3 ml/min per 1.73 m^2 (18.9–46.7), and the median (IQR) urine protein-to-creatinine ratio was 4.8 g/g (1.6–7.0).

Biopsy findings are summarized in Supplementary Table S1. Light microscopy showed crescents in 50% (7/14) of biopsies. Mean global glomerulosclerosis was 20% and mean interstitial fibrosis and tubular atrophy was 20%. Seven biopsies were stained for DNAJB9, and all were positive. Congo red staining was performed in 11 biopsies, and all were negative. Thirteen of 14 (93%) of biopsies had polytypic deposits (Supplementary Table S1). The average fibril diameter was 15 nm (range: 10–18).

Outcomes

The cumulative incidence of ESKD was 45% at 5 years by Kaplan Meier analysis (Supplementary Figure S1). At the end of follow-up, 50% (7/14) were nonprogressors; in the other 50% (7/14) who were progressors, 5 developed ESKD (Supplementary Figures S2 and S3). The median (IQR) time between diagnosis and treatment was 35 (8–61) days for nonprogressors, 50 (47–52) days for progressors, and 43 (6–302) days for the ESKD group. In those who developed ESKD, 2

Table 1. Baseline characteristics

Patient	Age (in years)	Gender	Race	Cr (mg/dl)		UPCR (g/g)		Albumin (g/dL)		eGFR[a]		Associated Diagnosis	Treatment	No. of RTX doses	Duration of CBCD	Years of F/u	Outcome
				Baseline	Last F/u	Baseline	Last F/u	Baseline	Last F/u	Baseline	Last F/u						
1[b]	50	M	AA	1.68	7.68	7.2	8.1	3.2	2.8	49	8	HCV, HIV	CBCD[c]	14	0.7	3.9	ESKD
2	64	M	W	2.57	3.24	6.6	3.4	4.0	2.8	27	20	MBL	RCP[d]	14	2.0	6.5	ESKD
3	63	F	W	5.60	1.57	1.2	0.4	3.8	2.8	8	35	AAV	RCP	13	4.5	7.1	Non-progression
4	38	M	W	4.30	5.70	10.1	10.7	2.5	2.9	17	12	-	RCP	2	0.4	0.4	ESKD
5	55	M	W	0.98	0.94	7.1	0.5	3.5	4.2	91	92	DM	RCP	14	2.6	6.1	Non-progression
6	60	M	W	2.31	3.08	4.0	6.3	4.2	4.2	32	22	RA, DM	RCP	3	0.6	0.6	Progression
7	73	M	W	2.67	5.37	5.0	7.1	3.8	3.7	24	10	PS	RCP	9	3.6	3.6	ESKD
8	79	M	W	2.89	2.75	0.2	0.1	4.2	4.0	21	22	ILD	RCP	4	3.6	3.6	Non-progression
9	59	M	H	1.49	1.93	4.5	4.0	4.2	4.2	54	39	DM	RCP	9	0.8	2.5	Progression
10	64	F	W	4.94	4.60	15.3	15.4	2.8	3.5	9	10	-	RCP	6	1.4	1.4	ESKD
11	53	F	W	3.00	1.35	5.4	0.3	2.8	4.4	18	44	-	RCP	13	4.4	9.3	Non-progression
12	53	F	W	1.57	1.08	0.8	1.2	3.8	4.2	39	61	-	RCP	4	1.1	1.1	Non-progression
13	78	F	W	0.77	0.83	2.4	4.3	3.4	3.5	79	72	DM	RCP	4	0.5	0.8	Non-progression
14	54	F	W	1.83	1.42	1.4	0.4	4.1	4.5	32	44	SLE	RCP	3	0.6	0.6	Non-progression

AA, African American; AAV, antineutrophil cytoplasmic antibody–associated vasculitis; CBCD, continuous B cell depletion; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; Cr, creatinine; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; F/u, follow-up; H, Hispanic; HCV, hepatitis C virus; ILD, interstitial lung disease; MBL, monoclonal B lymphocytosis; PS, pulmonary sarcoidosis; RA, rheumatoid arthritis; RCP, rituximab cyclophosphamide prednisone; RTX, rituximab; SLE, systematic lupus erythematosus; W, White; UPCR, urine protein-to-creatinine ratio.

[a]Calculated by CKD-EPI creatinine equation (2021), reported as ml/min per 1.73 m^2

[b]Patient 1 had an undetectable HIV viral load with antiretroviral therapy; however, he had treatment-naïve chronic HCV with viremia.

[c]Continuous B cell depletion is defined as scheduled rituximab infusions to maintain B cell depletion (total B cell count < 5 cells/μl).

[d]RCP is defined as rituximab-induced continuous B cell depletion, low-dose oral cyclophosphamide for approximately 2 months, and a rapid prednisone taper.

remained on dialysis and 3 received a kidney allograft with no recurrence to date. Serious adverse events were identified in 4 patients; 2 were identified in non-progressors and the other 2 were in patients with ESKD. Serious adverse events are summarized in Supplementary Table S2.

Time to ESKD Analysis

To identify whether specific treatment regimens were associated with a lower risk of ESKD, we expanded our cohort by combining it with historical control cohorts from the 2 largest case series of FGN with baseline and follow-up data (Hogan *et al.*[5] *Nephrology Dialysis Transplantation* 2014, and Javaugue *et al.*[6] *Am J Kidney Dis* 2013). The expanded cohort contained 53 patients with FGN. We noted that our cohort had, on average, a significantly lower eGFR compared with the other cohort: 29 in our cohort versus 36 in the Hogan *et al.*[5] cohort vs 49 in the Javaugue *et al.*[6] cohort (Supplementary Table S3). The incidence rate of ESKD (per 100 person-months) was 0.88 for our cohort, 1.48 for the Hogan *et al.*[5] cohort, and 0.82 for the Javaugue *et al.*[6] cohort.

Within the combined cohort, univariate analysis showed that a higher baseline eGFR was associated with a lower risk of ESKD (unadjusted hazard ratio = 0.72 per 10 ml/min per 1.73 m^2 increase, 95% confidence interval: 0.59–0.88, $P = 0.001$, Table 2). No specific treatment regimen was associated with a lower risk of ESKD. Multivariable analysis showed that a higher baseline eGFR (adjusted hazard ratio = 0.57 per 10 ml/min/1.73 m^2 increase, 95% confidence interval: 0.42–0.79, $P < 0.001$) and combination induction immunosuppression (adjusted hazard ratio = 0.17, 95% confidence interval: 0.04–0.74, $P = 0.018$) were both associated with a lower risk of ESKD. Use of any rituximab (with or without cyclophosphamide) and any cyclophosphamide (with or without rituximab) were not associated with a lower risk of ESKD in univariate or multivariable analyses.

Although the above analysis included individuals who did not receive any immunosuppressive therapy, we reanalyzed the data including only individuals who received rituximab ($n = 32$). The goal was to evaluate whether differences in ESKD risk exist between individuals who received rituximab upfront without cyclophosphamide and prednisone, compared with those who received upfront combination induction with rituximab and cyclophosphamide and prednisone (Supplementary Table S4). Univariate and multivariable analysis both showed that a higher baseline eGFR and a lower urine protein-to-creatinine ratio were associated with a lower risk of ESKD. Multivariable

Table 2. Cox regression for the association between clinical characteristics and time to ESKD in the full combined cohort ($n = 53$)

Characteristics	Univariate		Multivariable	
Age (per 10-year increase)	1.46 (0.98–2.16)	-	-	-
Male gender	0.83 (0.35–1.97)	-	-	-
eGFR (per 10 ml/min per 1.73 m^2 increase)	0.72 (0.59–0.88)	0.70 (0.54–0.89)	0.69 (0.53–0.89)	0.57 (0.42–0.79)
UPCR (per 1 g/g increase)	1.09 (1.00–1.18)	1.04 (0.95–1.14)	1.05 (0.96–1.14)	1.02 (0.94–1.11)
Rituximab	0.99 (0.42–2.34)	0.65 (0.23–1.81)	-	-
Cyclophosphamide	1.19 (0.49–2.89)	-	0.61 (0.21–1.76)	-
Combination induction	0.77 (0.26–2.30)	-	-	0.17 (0.04–0.74)

eGFR, estimated glomerular filtration rate; IQR, interquartile range; UPCR, urinary protein to creatinine ratio.
95% confidence interval for the regression coefficient are shown in parentheses.

analysis showed that combination induction compared with rituximab alone was associated with a lower risk of ESKD (adjusted hazard ratio = 0.08, 95% confidence interval: 0.01–0.95, $P = 0.045$).

DISCUSSION

This is the first case series evaluating combination induction immunosuppression with rituximab, cyclophosphamide, and prednisone for the treatment of FGN. This combination treatment has been used successfully in the treatment of membranous nephropathy.[7] The presence of Ig deposits in FGN biopsies suggests a possible autoimmune etiology of the disease, at least in a subgroup of FGN. The rationale behind using this combination treatment regimen, as opposed to rituximab monotherapy, is that the combined regimen can affect immune cell populations not targeted by rituximab, such as plasmablasts, plasma cells, and T cells.[8]

Previous studies have suggested a role for immunosuppressive treatments for FGN. A study by Andeen *et al.*[9] showed that treatment with rituximab in individuals with FGN was associated with a lower risk of progression to ESKD.[9] The short follow-up period and the absence of a control group make interpretation of the findings difficult. At this time, no immunosuppressive therapies have consistently been associated with a lower risk of ESKD in FGN.

Compared with previous described cohorts (Hogan *et al.*[5] and Javaugue *et al.*[6]), our study cohort had lower eGFR on average at diagnosis; and therefore, would have been expected to reach ESKD sooner.[5,6] The similar or lower incidence rate of ESKD in our cohort despite a significantly lower baseline eGFR suggests that our treatment regimen may be more effective compared with what has been used in these previous studies. When adjusting for baseline eGFR and proteinuria, we were able to show that combination induction was associated with a lower risk of ESKD compared with: (i) any other treatment options, and (ii) compared with rituximab alone. Whether this is due to the concomitant use of prednisone and cyclophosphamide, longer duration of rituximab use, or shorter duration from diagnosis to treatment initiation cannot be determined based on this study.

This study has several limitations because of its retrospective and observational design; specifically because of the following: (i) missing clinical and laboratory data at certain time points, (ii) the need to use historical cohorts as controls because of the lack of available untreated controls at our center, and (iii) potential confounding variables that could affect associations between clinical factors and outcomes.

In conclusion, this is the first case series evaluating combination induction with rituximab, cyclophosphamide, and prednisone for FGN. Our results suggest that early combination treatment is associated with a lower risk of ESKD in FGN compared with other treatment strategies. A randomized clinical trial is needed to confirm these findings.

DISCLOSURE

All the authors declared no conflicting interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Figure S1. Kaplan-Meier estimate for incidence of the primary outcome of end-stage kidney disease.

Figure S2. Progression of kidney disease at the end of follow-up.

Figure S3. Kidney function and proteinuria changes in individuals with fibrillary glomerulonephritis after treatment.

Table S1. Biopsy information of individuals with fibrillary glomerulonephritis.

Table S2. Adverse events.

Table S3. Baseline characteristics of fibrillary glomerulonephritis cohorts included in multivariable analysis.

Table S4. Cox regression for the association between clinical characteristics and time to end-stage kidney disease in those who received rituximab upfront or as part of combination therapy ($n = 32$).

STROBE Checklist.

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