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Low-dose Rituximab Monotherapy or in Combination with Tacrolimus Is Effective in Primary Membranous Nephropathy

Vivek Pathak,[1] Madhav Venkatesan,[1] and Renu Regunathan-Shenk[2]

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Introduction

The Membranous Nephropathy Trial of Rituximab study demonstrated that rituximab was noninferior to cyclosporine in inducing complete remission (CR) or partial remission (PR) of primary membranous nephropathy (MN) using an induction dose of 1000 mg on day 1 and another 1000 mg on day 15 (1). Prior studies of rituximab demonstrated remission using lower doses (2,3). We present 22 patients who received low-dose rituximab monotherapy or in combination with tacrolimus to achieve CR or PR for MN.

Materials and Methods

Retrospective chart review was conducted for 22 patients aged 28–72 years who underwent treatment for MN from 2014 to 2019. Patients whose GFR was <40 ml/min per 1.73 m^2 were excluded. Five patients previously received immunosuppression. Patient 14 received modified Ponticelli regimen without response. His medications were stopped 2 months before starting rituximab therapy. Patient nine and Patient 17 were treated with tacrolimus and steroids without response. Patient 17 stopped his medications 6 months before starting rituximab therapy. Patient 9 stopped his medications 2 months before starting rituximab therapy. Patient 11 and Patient 22 achieved remission with steroids and tacrolimus but relapsed. Patient 11 relapsed 1 year after stopping medications and Patient 22 relapsed 1 month after stopping medications. Patient 11 started rituximab 1 year after stopping medications, and Patient 22 started rituximab 3 months after stopping medications.

There were two treatment groups: in Group 1, 15 patients received a fixed-dose 500 mg of rituximab as induction with a repeat dose of 500 mg and the addition of tacrolimus at 3 months for nonresponders. On follow-up, patients were given third and fourth doses of rituximab (500 mg) at 6 months and 9 months, respectively, if the reduction of proteinuria was not considered adequate, for a maximum of four doses.

In Group 2, seven patients received a fixed dose of rituximab 500 mg with simultaneous tacrolimus at induction. This group also received second, third, and fourth doses on follow-up on the basis of response to treatment. Tacrolimus was continued for 18 months as tolerated. CR was defined as reduction in proteinuria to 0.3 gms and PR defined as <3 gms or >50% reduction in proteinuria.

This is a retrospective analysis of data and exempt from Review Board approval. Informed consent was obtained from the patients.

Results

In Group 1, six patients achieved CR in a median of 6 months without addition of tacrolimus (Table 1). Among these patients, three needed one dose of rituximab (500 mg) to reach remission, whereas two needed a total of 1 g, and one needed 1.5 g. In the remaining nine patients, tacrolimus was added after 3 months; four patients achieved CR in a median of 9.5 months, and one had no response. (This patient on follow-up responded to combination of cyclophosphamide and steroids.) Four patients developed tacrolimus toxicity on addition of tacrolimus, and it was discontinued. Among these, one patient achieved PR with four doses (2000 mg) of rituximab, whereas three patients did not show response. Among the patients in Group 1 who achieved CR, there were two relapses (Patients one and 11) and both responded to an additional 500 mg of rituximab.

In Group 2, all seven patients achieved CR in a median of 10 months. Five patients received additional doses of rituximab (median dose 500 mg, range 500–1500 mg). Two patients relapsed (Patients 17 and 18) and responded to an additional 500 mg rituximab dose.

The serum phospholipase A2R antibody (PLA2R-Ab) level normalized in 11 out of 12 patients who attained CR in both groups. PLA2R-Ab was available for 13 patients at start of the treatment (Group 1, seven out of 15 and Group 2, six out of seven). Among the seven patients in Group 1, five had positive PLA2R-Ab values, and two had negative PLA2R-Ab values. However, two patients who had negative PLA2R-Ab values in serum had positive PLA2R staining in renal biopsy. Besides these seven patients, three out of the remaining eight patients had positive PLA2R staining in renal

[1]Nephrology, Kovai Medical Center and Hospital, Coimbatore, Tamil Nadu, India
[2]George Washington University School of Medicine and Health Sciences, Washington, DC

Correspondence: Vivek Pathak, Nephrology, Kovai Medical Center and Hospital, Coimbatore, Tamil Nadu, 641014, India. Email: bq.hanu@yahoo.com

Table 1. Details of the patients

Patient No.	Proteinuria at Start of Treatment[a]	S. Albumin (g/dl) at Start of Treatment	PLA2R-Ab (RU/ml) at Initiation	Induction Dose of Rituximab (in mg)	Repeat Dose (Y (in mg)/*N*)	Tacrolimus Added	Time to Complete Remission (in Mo)	Urine Protein Creatinine Ratio at 18 Mo	S. Albumin (g/dl) at 18 mo	Follow-up PLA2R-Ab (RU/ml)	CR or PR at 18 Mo
Group 1: Rituximab monotherapy induction											
1	12.4	2.5	NA	500	Y (500)	No	7	0.3	3.9	NA	CR[b]
2	7.9	3.2	110.45	500	No	No	5	0.2	4.2	<0.6	CR
3	7.7	1.2	<0.6[c]	500	Y (1000)	Yes[d]	NA[e]	2.2	3.6	<0.6	PR
4	2.4	2.3	82.9	500	No	No	5	0.3	3.4	<0.6	CR
5	2.1	3.1	NA	500	Y (1000)	No	11	0.2	4	NA	CR
6	19.2	2.8	NA[c]	500	No	No	5	0.3	4.4	<0.6	CR
7	10.2	2.7	492.96	500	Y (500)	No	5	0.2	3.8	NA	CR
8	15.7	2.7	377.48	500	Y (1500)	Yes[d]	NA[e]	7.9	3.3	21.7	NO
9[f,g]	13.1	2.4	NA	500	Y (1500)	Yes[d]	NA[e]	6.2	2.9	<0.6	NO
10	15.8	2.1	NA[c]	500	Y (1000)	Yes[d]	NA[e]	11.7	2.8	NA	NO
11[f,i]	13.6	3	NA	500	Y (1500)	3 M	12	0.2	3.6	21.9	CR[b]
12	14	1.8	170.14	500	Y (1500)	3 M	NA[e]	8.3	4.1	<0.6	NO
13	14.4	2.8	NA[c]	500	Y (500)	3 M	8	0.2	4.1	13.31	CR
14[g,h]	8.4	3.2	NA	500	Y (1500)	3 M	14	0.3	4.4	NA	CR
15	10.97	1.5	4.4[c]	500	Y (500)	3 M	12	0.3	4.3	2.65	CR
Group 2: Simultaneous rituximab and tacrolimus											
16	16.4	2.8	261.92	500	Y (500)	AT START	14	0.3	4.5	<0.6	CR
17[f,g]	5.1	2.3	188.4	500	Y (1000)	AT START	7	0.2	4	12	CR[b]
18	18.8	2.6	NA[c]	500	No	AT START	6	0.2	4.5	<0.6	CR[b]
19	9.9	2	66.9	500	No	AT START	9	0.1	4	<0.6	CR
20	15	2	175	500	Y (1500)	AT START	15	0.3	4.9	<0.6	CR
21	5.8	3.7	78.5	500	Y (500)	AT START	5	0.1	4	4.36	CR
22[f,i]	4.4	3.4	104.1	500	Y (1000)	AT START	13	0.3	4.1	NA	CR

S. albumin, serum albumin; PLA2R-Ab, phospholipase A2R antibody; CR, complete response; PR, partial response; NA, not available.
[a]Urine protein creatinine ratio.
[b]Relapse post-treatment.
[c]Positive PLA2R staining in renal biopsy.
[d]Tacrolimus added at 3 mo but discontinued due to increased creatinine.
[e]Not applicable.
[f]Previously treated with tacrolimus and steroids.
[g]Failed to respond to previous treatment.
[h]Previously treated with cyclophosphamide and steroids.
[i]Relapse after previous treatment.

biopsy. Out of these five patients with positive PLA2R-Ab values, four reached remission and did not have PLA2R-Ab on follow-up. Patient eight did not reach remission with treatment, and the PLA2R-Ab value showed quantitative decrease but did not become negative.

In Group 2, six patients had positive PLA2R-Ab at the time of initiation of treatment, and one had not undergone the test but had positive PLA2R in biopsy (Patient 18). Out of these six patients, all reached CR. On follow-up five patients did not have PLA2R-Ab whereas one (Patient 17) had decreased titer.

Conclusions

In this retrospective study, 18 out of 22 patients achieved CR or PR with low-dose rituximab monotherapy or in combination with tacrolimus. Seven patients achieved CR or PR with rituximab monotherapy with a median cumulative dose of 1000 mg, and three patients achieved CR with a single dose of 500 mg. In total, 11 patients who received low-dose rituximab with tacrolimus achieved CR or PR, with a median cumulative rituximab dose of 1000 mg. We suggest patients may achieve PR or CR using lower doses of rituximab, and certain patients may achieve CR with low-dose rituximab monotherapy, as we saw in three patients who achieved CR after one 500 mg dose, although we are unable to predict which patients will respond to low-dose rituximab monotherapy on the basis of our data. Further research is needed to help differentiate which patients are more likely to respond to low-dose therapy.

Disclosures

All authors have nothing to disclose.

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Author Contributions

M. Venkatesan was responsible for data curation, formal analysis, investigation, methodology, and project administration; R. Regunathan-Shenk was responsible for formal analysis and methodology; V. Pathak was responsible for data curation, formal analysis, investigation, methodology, project administration, and wrote the original draft of the manuscript; and all authors were responsible for conceptualization, and reviewed and edited the manuscript.

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