Obinutuzumab in Difficult to Treat Phospholipase A2 Receptor Positive Membranous Nephropathy: Our Experience at a Tertiary Care Center in North India

Abstract

Obinutuzumab is a glycoengineered type II anti-CD20 monoclonal antibody with superior B cell cytotoxicity compared to rituximab. Various case reports suggest that in refractory phospholipase A2 receptor (PLA2R) positive membranous nephropathy (MN) patients, Obinutuzumab led to immunologic remission and improvement in proteinuria. In the present case series, we present six cases of difficult-to-treat PLA2R-associated MN refractory to prednisolone, calcineurin inhibitor (CNI), cyclophosphamide, and rituximab but subsequently responded to Obinutuzumab. Five out of six cases showed partial /complete clinical remission and immunological remission (IR) with normalization of serum albumin and stable renal function. Though this drug's long-term efficacy and impact remain unclear, it is being increasingly considered for PLA2R-associated MN resistant to standard therapy.

Keywords: *Obinutuzumab, Rituximab, Tacrolimus, Refractory membranous nephropathy, Complete remission*

Introduction

Primary membranous nephropathy (MN), the most common cause of idiopathic nephrotic syndrome in non-diabetic adults worldwide, accounts for 20%–37% of most kidney biopsy series.[1] B-cell anomalies play a crucial role in both the pathogenesis and management of MN. As per the Mentor Trial, rituximab, a type 1 anti-CD20 antibody was non-inferior to cyclosporine in inducing complete or partial remission of proteinuria at 12 months. It was considered superior in maintaining proteinuria remission (60% vs. 20%) for up to 24 months. There was no response to rituximab in 40% of patients with MN.[2] A more aggressive approach is needed for these rituximab-refractory patients to understand the causes of treatment failure and to seek available alternative treatment options. Various mechanisms through which resistance to B-cell depletion by type I anti-CD20 antibodies may occur are Fcγ receptor IIB (FcγRIIB)-mediated internalization of CD20, ineffective complement-dependent cytotoxicity, decreased engagement of effector cells due to Fc receptor polymorphisms, and acquired deficiencies in antibody-dependent cellular phagocytosis. The unique advantage of Obinutuzumab is that it does not elicit CD20 redistribution to membrane-bound lipid rafts or activate FcγRIIB resulting in reduced CD20 internalization. The clinical superiority of this drug to rituximab for treating chronic lymphocytic leukemia (CLL), follicular lymphoma, and lupus nephritis has already been demonstrated in various clinical trials available in the literature.[3] It is a humanized and glycoengineered type II anti-CD20 monoclonal antibody that has superior in vitro B-cell cytotoxicity compared with rituximab.[4] The increased affinity of this drug to FcγRIII is due to the modification of the glycan-free structure at the Fc fragment. It also potentiates antibody-dependent cellular cytotoxicity via natural killer cells and antibody-dependent cellular phagocytosis via macrophages.[4] In diseases like CLL and non-Hodgkins lymphoma (NHL) with high levels of circulating malignant B cells, there is a greater risk for infusion-related reactions due to rapid lysis of B cells releasing proinflammatory cytokines.[5] Few case reports indicate that in refractory/relapsing phospholipase A2 receptor positive (PLA2R) membranous nephropathy patients, the drug Obinutuzumab led to immunologic remission, significant improvement in proteinuria, and normalization of serum albumin.[6–9]

In this case series, we present our experience of treating anti-phospholipase A2 receptor (PLA2R) positive membranous nephropathy with Obinutuzumab (manufactured by E. Hoffmann-La-Roche Ltd, Germany) refractory to rituximab, cyclical cyclophosphamide, calcineurin inhibitors (CNIs), and corticosteroid therapy. The need for putting these patients on this drug was overt nephrotic syndrome despite the continuation of conventional treatment and sufficient observation period after Inj rituximab. Since these data were retrospective, they did not have a regular follow-up with investigations as per a defined protocol. Ethics approval was obtained from Institutional ethics committee and individual patient consent was taken.

Case Series

The case details are summarized in Table 1.

Case 1

A 47-year-old male, a known diabetic and hypertensive presented with generalized swelling and fatigue 7 years back. Initial evaluation revealed nephrotic syndrome. He underwent a renal biopsy which revealed MN with immunohistochemistry (IHC) – anti-PLA2R Ab-positive. Serum anti-PLA2R Ab was negative. He was put on steroid + tacrolimus for about 1 year with partial response. He stopped all drugs thereafter and subsequently presented with nephrotic syndrome. He was administered four doses of Inj rituximab (500 mg each dose weekly x 4 weeks). He was also put on oral hypoglycemic agents with adequate control of blood sugar. Even after 1 year of Inj rituximab, he had persistent nephrotic range proteinuria and hypoalbuminemia with a serum anti-PLA2R Ab level of 293 RU/mL. He underwent a repeat kidney biopsy

Table 1: Summary of the patient characteristics treated with Inj Obinutuzumab

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age (Years)	47	44	48	33	24	35
Sex	Male	Male	Female	Male	Male	Male
Previous comorbidities if any	Diabetes mellitus 2, hypertension	CAD-Post PCI	Nil	Nil	Nil	Nil
Anti -PLA2R on kidney biopsy at presentation and serum anti-PLA2R	IHC staining positive serum anti-PLA2R Ab-negative	IHC staining Positive. serum anti-PLA2R Ab-Not done	IHC staining-Negative, anti-PLA2R Ab-Not done	IHC staining-Negative, anti-PLA2R Ab-Not done	IHC staining-not done, Serum anti-PLA2 R-16.36 RU/mL	Not done
Immunosuppression received earlier	Steroid +tacrolimus, Inj rituximab	Inj rituximab, tacrolimus	Inj rituximab, tacrolimus	Tacrolimus, modified ponticelli regimen twice, Inj rituximab	Tacrolimus, modified ponticelli, rituximab	Rituximab, tacolimus, modified ponticelli
Serum anti-PLA2R (RU/mL) at administration	293 RU/mL	-	369.01 RU/mL	77.7 RU/mL	246 RU/mL	342 RU/mL
Gap between Ist biopsy and Inj Obinutuzumab	6 years 4 months	2 years 1 month	1 years 2 months	4 years 11 months	3 years 4 months	6 years
Gap between Inj rituximab and inj Obinutuzumab	3 years 2 months	1 year 9 months	1 year 1 month	10 months	1 year 1 month	3 years
24-hour urinary protein creatinine ratio	17.89 g protein/g creatinine	Fluctuation between nephrotic and subnephrotic range	30.72 g protein/g	3.8 g/g	9–10 g/g	10 g/day
Serum creatinine at administration	1.2 mg/dL	0.9 mg/dL	1.36 mg/dL	1.1 mg/dL	0.9 mg/dL	1.2 mg/dL
Follow-up duration after Inj Obinutuzumab	10 months	11 months	10 months	10 months	13 months	18 months
Serum anti-PLA2R ab at last follow-up	132 RU/mL	Negative	Not done	14 RU/mL	Negative	Negative
Serum creatinine at last follow-up	1.3 mg/dL	1.0 mg/dL	1.4 mg/dL	1.2 mg/dL	0.9 mg/dL	0.7 mg/dL
24-hour urinary protein creatinine on last follow-up	10.8 g/g	230 mg/g	540 mg/g	242 mg/g	220 mg/g	150 mg/g
Last serum albumin on follow-up	2.8 g/dL	4.3 g/dL	3.6 g/dL	3.4 g/dL	3.2 g/dL	3.9 g/dL
Absolute CD19 count on the last follow-up	<5 cells/µL	<5 cells/µL	<5 cells/µL	<5 cells/µL	<5 cells/µL	<5 cells/µL

CAD: Coronary artery disease; PCI: Percutaneous coronary intervention; IHC: Immunohistochemistry; PLA2R: Phospholipase A2 receptor.

which revealed membranous nephropathy again along with interstitial fibrosis and tubular atrophy (IFTA) around 10%–15%. IHC for anti-PLA2R was negative. He was put on modified ponticelli (cyclical steroid + cyclophosphamide x 6 months). He had partial remission post ponticelli regimen with 24-hour urinary protein of 1.1 g and serum albumin 3.8 g/dL. His repeat PLA2R Ab was <0.6 RU/mL. He had a relapse 2 years post ponticelli with 24-hour urinary protein 17.8 g and serum albumin 1.7 g/dL. His total cholesterol was 353 mg/dL and serum anti-PLA2R Ab was 193 RU/mL. He was again put on tacrolimus with no response even after 6–7 months of tacrolimus. He had serum albumin 1.8 g/dL with 24-hour urinary protein 17.89–19 g/day. Serum creatinine was 1.2 mg/dL. He was administered Inj Obinutuzumab 1 g IV intwo doses at 14 days interval. 10 months post Obinutuzumab his 24-hour urinary protein creatinine ratio was still 10.8 g/g with serum albumin 2.0–2.2 g/dL. His anti-PLA2R Ab is 123 RU/mL. He is on angiotensin receptor blocker (ARB) + SGLT2 inhibitor and mineralocorticoid receptor antagonist at present. Repeat Inj Obinutuzumab dose was not administered as the absolute CD19 count was within the target range.

Case 2

A 44-year-old male had a history of coronary artery disease – post percutaneous intervention (PCI) 4 years back. One year post-PCI, he had features suggestive of nephrotic syndrome (24-hour urinary protein – 5.8 g, serum albumin – 2.6 g/dL, total cholesterol – 324 mg/dL). Renal biopsy revealed MN with IHC staining for anti-PLA2R–positive along the glomerular capillary wall. He was initially treated with ARB followed by four doses of Inj rituximab. He achieved partial remission 3 months post-completion of the dose. However, he developed nephrotic syndrome about 8 months after Inj rituximab. He was put on tacrolimus but did not respond to tacrolimus even after 1 year with proteinuria fluctuating between the nephrotic and sub-nephrotic ranges. Because of persistent proteinuria with thrombotic risk on the background of CAD-post PCI, it was planned to offer him the best available drug useful in relapsing and resistant MN. He was administered Inj Obinutuzumab in two doses 1 g each 15 days apart. He attained complete remission about 3 months after the dose. His 24-hour urinary protein at the last follow-up 11 months post-Obinutuzumab is 230 mg and serum albumin is 4.1–4.3 g/dL. His repeated serum anti-PLA2R antibody is negative.

Case 3

A 48-year-old lady presented with features suggestive of nephrotic syndrome (24-hour urinary protein – 32.4 g, serum albumin – 1.6 g/dL, total cholesterol – 324 mg/dL). Renal biopsy revealed MN with staining for anti-PLA2R-negative along glomerular capillary walls. She was initially treated with Inj rituximab 500 mg IV weekly in four doses along with standard treatment in the form of ARB and SGLT2 inhibitors. Six months post-rituximab she still had nephrotic range proteinuria (24-hour urinary protein – 30.72 g/24 h, serum albumin – 2 g/dL, serum creatinine – 1.36 mg/dL). She was thereafter put on oral tacrolimus + steroid (0.5 mg/kg/day) for about another 6 months with no improvement in proteinuria with the creeping rise in serum creatinine. Tacrolimus was discontinued. She had persistent features of nephrotic syndrome for about 1 year post-biopsy even after Inj rituximab and tacrolimus. Her anti-PLA2R Ab done this time was 369.01 RU/mL (<14 IU/mL). Inj Obinutuzumab was planned thereafter and two doses of 1 g IV each were administered at 15 days intervals. She noticed an improvement in her generalized swelling and fatigue. After 3 months, her 24-hour urinary protein was 2.82 g/day and after 7 months it improved to 0.54 g/day. There was a significant rise in serum albumin after 7 months with a serum albumin level of 3.6 g/dL. She is in complete remission with mild renal dysfunction after 10 months of Inj Obinutuzumab and is on standard care in the form of ARB.

Case 4

A 33-year-old male was detected proteinuria during evaluation for generalized swelling 7 years back. The detailed evaluation revealed 24-hour urinary protein – 14.9 g/day, serum albumin – 2.8 g/dL, total cholesterol – 324 mg/dL, and normal serum creatinine – 0.8 mg/dL. A renal biopsy done at that time revealed MN with IHC positivity for PLA2R showing diffuse and globally distributed uniform granular staining along the capillary walls. He was initially put on tacrolimus and had complete remission. Tacrolimus was tapered and stopped after 1 year. He developed features of nephrotic syndrome again after about 8–9 months of stopping tacrolimus. He was then prescribed a modified ponticelli regimen. Post ponticelli, he achieved partial remission with 24-hour urinary protein (24-hour urinary protein – 1.1 g/day). He was kept on ARB and his repeat anti-PLA2R Ab was negative. Nine months post-completion of the ponticelli regimen, he had relapsed again. His 24-hour urinary protein was 4.7 g/day and he had a rise in serum anti-PLA2R – 77.7 RU/mL. He underwent a repeat biopsy which revealed MN with IFTA 8%–10% of the sampled cortex. Staining for PLA2R shows diffuse granular positivity along glomerular capillary walls. He was again put on a modified ponticelli regimen. Six months post ponticelli, he remained to have nephrotic syndrome (24-hour urinary protein creatinine ratio of 3.8 g/g, serum albumin – 2.4 g/dL). He was put on Inj Rituximab in four doses of 500 mg IV weekly thereafter. His 24-hour urinary protein remained around 3.5–3.8 g/day after about 10 months of Inj Rituximab. Considering refractory to conventional treatment, Inj Obinutuzumab was administered in two doses of 1 g IV at 14-day intervals. He was noticed to have a partial response after 3 months of Inj Obinutuzumab in the form of subnephrotic proteinuria and is in complete remission with 24-hour urinary protein 242 mg about 10

months after therapy. His anti-PLA2R Ab titer is 14 RU/mL. He is only on standard treatment at present.

Case 5

A 24-year-old male developed nephrotic syndrome 3 years back. A renal biopsy revealed MN with IFTA <5%. Serum PLA2R Ab (Quantitative, EIA) was 16.36 RU/mL (<14). He was administered an Inj Rituximab Ist dose and had a severe reaction, so the drug was discontinued. He was subsequently treated with tacrolimus for 3 months but showed a poor response. He was switched to a modified ponticelli regimen. He was in remission for about 1 year and had a relapse with serum PLA2R – 90 RU/mL and 24-hour urinary protein around 7.2 g. He was again prescribed tacrolimus but had no response even after 6 months of therapy with 24-hour urinary protein around 7.7 g. Inj Rituximab (4 doses 500 mg IV weekly) was administered with a continuation of CNI-based therapy. He remained refractory to treatment even after 1 year of Inj Rituximab and continuation of CNI with serum albumin around 1.2–1.4 gm/dL and 24-hour urinary protein around 9–10 g. His PLA2R Ab was 246 RU/mL. Considering the case as refractory to conventional treatment, he was administered Inj Obinutuzumab of 1 g IV in two doses 2 weeks apart. He attained complete remission after 6 months and at present around 13 months after Inj Obinutuzumab he is in complete remission. His anti-PLA2R Ab is negative.

Case 6

A 35-year-old male had an initial presentation of 16 years back with nephrotic syndrome. Renal biopsy was suggestive of focal segmental glomerulosclerosis (FSGS). Initial treatment was with oral steroids, and he was in complete remission. He had a relapse after 2 months of stopping steroids. He was put on steroid + tacrolimus which continued for almost 4 years. He had a relapse 7 years back and underwent renal biopsy which was suggestive of MN. He was administered two doses of 1 g each of Inj Rituximab every year for consecutive 3 years. His 24-hour urine protein remained around 5.4 g/day. He was put on modified ponticelli and attained partial remission. Two years before he had massive proteinuria with 24-hour urinary protein – 13.97 g/day. Serum anti-PLA2R Ab was 342 RU/mL. He was started on steroids and tacrolimus thereafter. He underwent rebiopsy which revealed membranous GN with IFTA of about 8%–10% and PLA2R positivity. He continued tacrolimus + steroid for about another year with 24-hour urinary protein around 8–10 g/day. His steroid and tacrolimus were tapered and stopped. Inj Obinutuzumab was administered two doses of 1 g each 14 days apart. His 24-hour urinary protein is 150 mg/day and creatinine is 0.7 mg/dL around 6 months after the last dose of Inj Obinutuzumab. His anti-PLA2R is negative. He has been in complete remission for the last 1 year.

Discussion

Most primary MN patients have antibodies against a conformation-dependent epitope in PLA2R. These autoantibodies are mainly IgG4, the predominant immunoglobulin subclass in glomerular immune deposits.[10] Though cytotoxic therapy is the best therapeutic option against progressive kidney disease, treatment with rituximab may be a reasonable alternative for those patients who wish to avoid these cytotoxic agents. Serial assessment of anti-PLA2R antibody levels may be useful for monitoring the immunological activity of the disease and guiding further treatment decisions in these subsets of patients. Those patients who do not achieve complete or partial remission even after all of the first-line conventional therapies are considered to have refractory/relapsing or difficult-to-treat disease. The persistence of serum anti-PLA2R antibodies despite immunosuppressive therapy is also suggestive of resistant or refractory disease. A repeat kidney biopsy may be required to guide further therapeutic options when it becomes difficult to distinguish between refractory disease and chronic irreversible damage to the renal parenchyma. In the present case series, most of our case phenotypes were relapsing and refractory types rather than purely resistant, because of fluctuating clinical and immunological remission course. The decision to put on Inj Obinutuzumab was based on persistent nephrotic syndrome despite all available conventional therapy and repeat biopsy findings of minimal chronicity.

In recent reports by different authors, Obinutuzumab led to immunologic remission and improvement in proteinuria in difficult-to-treat PLA2R MN patients.[6–9] Out of 10 cases reported so far, where Inj Obinutuzumab was administered, five cases were refractory to multiple regimens of these first-line therapies [Table 2]. Sethi *et al*.[6] found that all those patients who had detectable serum PLA2R antibodies had a decline in the titer to <14 RU/mL after Inj Obinutuzumab. In the present case series, all six cases of PLA2R-associated MN were refractory to prednisolone, CNI, cyclophosphamide, and rituximab but subsequently responded to Obinutuzumab. The drug has been started on all these cases with clinical features of overt nephrotic syndrome even after completing a sufficient duration of immunosuppressive therapy. The time gap between the first renal biopsy and the drug administration was around 2–6 years. Five out of six cases showed immunological remission (IR), normalization of serum albumin, and stable renal function. No partial or complete response with Inj Obinutuzumab in case no.1 on the background of diabetes mellitus type 2 without significant chronicity and diabetic nephropathy is difficult to explain. In this case, there was a 39.6% decline in proteinuria and this response was evident within 3 months which attained its maximum response within 6–7 months. Unlike the study by Sethi *et al.*, no patients in the present study developed any hematological

Table 2: Summary of the published case reports of anti-PLA2R positive membranous nephropathy patients (native kidney) with Obinutuzumab other than the present case series

Case	Author	76 pt	Initial proteinuria g/day	Final proteinuria	Initial S. albumin	Final S. albumin	Initial PLA2R titer	Final PLA2 R titer	Initial S. creatinine	Final S. creatinine	Treatment prior to Obinutuzumab
1	Sethi, *et al.*[6]	66/M	11.3	1.5	1.7	2.0	633	5.1	2.1	1.582	Rituximab
2	Sethi, *et al.*[6]	41/M	10.73	5.9	2.7	3.7	39	1.8	0.9	0.80	Prednisololne, tacrolimus
3	Sethi, *et al.*[6]	68/M	7.8	0.5	2.1	3.8	261	NA	1.29	1.19	Rituximab
4	Hudson, *et al.*[7]	36/M	17	7.56	1.5	4.2	>1500	<2.1	0.63	1.276	Rituximab (4 g total) cyclosporine, prednisolone, Cyclophosphamide
5	Hudson, *et al.*[7]	33/M	5.17	1.43	2.2	4.3	1235	<2.1	0.99	0.96	Rituximab (2 g total), cyclosporine, steroid, cyclophosphamide
6	Klomjit, *et al.*[8]	54/F	8.6	1.1	3.3	4.3	312	5	2.20	1.29	Rituximab 4 g total
7	Klomjit, *et al.*[8]	61/M	21	6.8	2.0	3.8	100	<2	1.09	1.40	Rituximab (2 g total), cyclosporine, steroid, cyclophosphamide
8	Klomjit, *et al.*[8]	54/M	19.7	1.5	2.2	4.1	170	<2	2	1.69	Rituximab 4 g total
9	Naik S, *et al.*[9]	67/F	12.03	2.05	2.55	3.9	200.7	2.55	2.41	1.62	Rituximab, cyclosporine, cyclophosphamide/steroid
10	Naik S, *et al.*[9]	33/M	9.71	3.39	2.70	4.13	125.13	0.6	4.8	2.53	Rituximab, cyclophosphamide/ steroid

PLAR2: phospholipase A2 receptor antibory, S.: serum

abnormalities in the form of anemia, leukopenia, or thrombocytopenia.[6] Since this is a retrospective study of our patients' data who have received this drug in anti-PLA2R positive MN (either serologically or renal biopsy IHC positive), they were not followed up as per fixed protocol resulting in some lapses.

Though the long-term efficacy and impact of this drug remain unclear, it is being increasingly considered for PLA2R-associated MN resistant to conventional therapy. The safety and efficacy of this drug in this disease are being assessed through two ongoing clinical trials (NCT04629248 and NCT05050214). The limitations of our study include a small sample size, a retrospective study with no control arm, short duration follow-up, and no specified protocol. The minimum gap between the last dose of Inj Rituximab and Inj Obinutuzumab in the present case series was 10 months. The response in those patients with less duration after Inj Rituximab may be confounded by the legacy effect of the drug, but the quick response as early as within 3 months after Inj Obinutuzumab administration requires further study in a large number of these difficult-to-treat PLA2R positive MN patients. These subsets of relapsing/difficult-to-treat disease have an increased risk of end-stage kidney disease (ESKD), stressing the critical need for more effective and alternative safer therapies. Though there is no long-term follow-up in this case series (maximum follow-up of 18 months), no patients attaining complete remission had any relapse due to the possible profound effect of B cell depletion with this drug.

Conclusion

In PLA2R-positive MN, immunofluorescence in the kidney biopsy specimens may demonstrate colocalization of PLA2R with the IgG4 stain. In primary MN, circulating PLA2R antibody titers correlate with disease activity and proteinuria. Obinutuzumab is a newer type II humanized monoclonal antibody against the CD20 molecule which has been glycoengineered to enhance its efficiency of B-cell depletion through various mechanisms. This drug contributes to improved clinical responses without increasing the frequency of serious safety events. The majority of refractory PLA2R positive MN responded to this drug and showed immunological remission with normalization of serum albumin and stable renal function. Ongoing and future clinical trials will test its efficacy further in the treatment of naïve and rituximab-resistant primary MN patients.

Disclaimer

Views expressed in this paper are those of the authors and do not represent the views or positions of the Indian Armed Forces.

Conflicts of interest

There are no conflicts of interest.

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