

Obinutuzumab is Effective for the Treatment of Refractory Membranous Nephropathy



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Received 21 May 2020; revised 22 June 2020; accepted 24 June 2020; published online 3 July 2020

Kidney Int Rep (2020) 5, 1515–1518; <https://doi.org/10.1016/j.ekir.2020.06.030>

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Membranous nephropathy (MN) is a leading cause of nephrotic syndrome in nondiabetic adults. Left untreated, two-thirds of patients with MN can develop nonprogressive chronic kidney disease or progress to end-stage renal disease in 10 years.¹ The recognition of MN as an autoimmune disease has paved the way for the use of anti-B-cell therapy in its management.² Over the last decade, rituximab has been successfully used to treat MN and was shown to be noninferior to cyclosporine in the Membranous Nephropathy Trial of Rituximab study.³ However, 40% of patients with MN do not respond to rituximab.³ Therefore, there is a need for additional treatment options for patients with MN.

Obinutuzumab (Gazyva [Genentech, South San Francisco, CA]) is a humanized and glycoengineered type II anti-CD20 monoclonal antibody that has superior *in vitro* B-cell cytotoxicity compared with rituximab.⁴ Obinutuzumab is directed at a different epitope on CD20 than that recognized by rituximab and can evoke a greater B-cell apoptotic response.⁴ Modification of the glycan tree structure at the Fc fragment of obinutuzumab leads to an increased affinity to FcγRIII and thereby potentiates antibody-dependent cellular cytotoxicity via natural killer cells as well as antibody-dependent cellular phagocytosis via macrophages.⁵ These B-cell depletion mechanisms contrast to the primarily complement-dependent cytotoxicity for rituximab. Combined with chemotherapy, obinutuzumab has been found to be more effective than rituximab in the treatment of patients with certain B-cell malignancies.⁶ Based on these data, the use of obinutuzumab in treatment of patients with MN is an attractive option. Herein, we present our single-center experience of treating MN with obinutuzumab.

RESULTS

Patient Population

Ten patients with MN were treated with obinutuzumab at our center between January 2015 and December 2019. Table 1 shows baseline characteristics of these patients. The work-up for secondary causes of MN was negative except in 2 patients (1 with lupus-associated MN and 1 with *de novo* MN in allograft). Seven patients (70%) had received rituximab within a year before receiving obinutuzumab. Six of these patients were rituximab refractory and 1 had a response to rituximab but was switched to obinutuzumab because of an adverse reaction. Four patients received obinutuzumab after kidney transplant for recurrent MN ($n = 3$) or *de novo* MN ($n = 1$). The median follow-up was 18 months (interquartile range [IQR], 9–24 months).

Outcomes

Urine Protein-to-Creatinine Ratio

At a median follow-up of 6 months (IQR, 6–10.5 months) after obinutuzumab therapy, complete remission was achieved in 4 (40%) and partial remission was achieved in 5 (50%) of patients. The only patient who did not achieve complete or partial remission had 6 months of follow-up and had a 48% decline in proteinuria by that time. All patients who achieved complete or partial remission by 12 months and had longer follow-up ($n = 5$) maintained remission at 24 months. Figure 1 shows the proportion of patients who achieved complete or partial remission over time. Of the 7 patients who had received rituximab before, 4 (57.1%) achieved complete remission and 2 (28.6%) achieved partial remission. The trend of urine protein-to-creatinine ratio (UPCR) in all patients and in rituximab-experienced patients is shown in Figure 2.

Table 1. Patient characteristics

Patient no.	Age (yr)	Sex	Transplant	PLA2R/ THSD7A on Biopsy	Serum Anti-PLA2R (RU/ml)	UPCR (g/g)	Serum albumin (g/dl)	Serum creatinine (mg/dl)	Previous treatment
1	69	F	No	Negative	Negative	14.38	2.9	1.1	Rituximab and ARB
2	66	M	No	Negative	633	11.3	1.7	2.1	Rituximab and ARB
3	41	M	No	PLA2R ⁺	39	10.73	2.7	0.9	Tacrolimus, prednisone, and ARB
4	68	M	No	PLA2R ⁺	261	7.8	2.1	1.3	Rituximab and ARB
5	49	M	No		Negative	4.5	3.9	0.9	Cyclophosphamide, prednisone, and rituximab
6	24	F	No		Negative	3.65	2.5	1.1	Cyclophosphamide, mycophenolate, prednisone, and rituximab
7	76	F	Yes	PLA2R ⁺ , THSD7A ⁺	79	5.8	2.8	1.4	Tacrolimus, prednisone, and ARB
8	67	M	Yes	THSD7A ⁺	57	8.49	2.8	1.5	Rituximab, ARB, tacrolimus, and prednisone mycophenolate
9	69	F	Yes	Negative	Negative	4.7	3.6	2.2	Rituximab, ARB, synthetic ACTH, tacrolimus, prednisone, and mycophenolate
10	50	M	Yes	PLA2R ⁺	Negative	4.5	3.6	1.5	Tacrolimus, prednisone, mycophenolate, and ARB

ACTH, adrenocorticotropic hormone; ARB, angiotensin II receptor blocker; PLA2R, phospholipase A2 receptor; THSD7A, thrombospondin type 1 domain-containing 7A; UPCR, urine protein-to-creatinine ratio.

Serum Albumin and Creatinine

All patients with a serum albumin ≤ 3.5 g/dl at obinutuzumab initiation ($n = 7$) had an improvement in serum albumin (Supplementary Figure S1). The median Chronic Kidney Disease Epidemiology Collaboration estimated glomerular filtration rate at obinutuzumab initiation was 52.5 ml/min (IQR, 35–77.5 ml/min). Kidney function remained stable in all patients (Supplementary Figure S2).

Serum PLA2R Antibody

Five patients had elevated serum PLA2R antibodies. One of these patients (patient 4) achieved immunologic remission without improvement in proteinuria with rituximab and therefore had a normal PLA2R antibody titer at the time of obinutuzumab therapy. All 4 patients who had detectable serum PLA2R antibodies at the time of obinutuzumab administration had a decline in the titer to <14 RU/ml (negative result for our immunology laboratory; Supplementary Table S1).

Safety

One patient had mild wheezing during obinutuzumab infusion that resolved with a dose of methylprednisolone. Four patients developed leukopenia (range, $1.42\text{--}3.0 \times 1000/\text{ml}$) at a median of 39.5 days (IQR, 19.0–62.3 days) after the first dose. Leukopenia resolved within 2 months in 3 patients and persisted for 18 months in 1 patient. Minor infections noted in nontransplant patients included upper respiratory infections ($n = 3$) and urinary tract infections ($n = 2$). One posttransplant patient had multiple urinary tract infections and 1 episode of *Clostridium difficile* infection requiring hospitalization. This patient was found to have a low IgG level and was treated with i.v. immune globulin. Another 2 posttransplant patients developed

cytomegalovirus viremia, 1 of whom died of glioblastoma multiforme 6 months after receiving obinutuzumab.

DISCUSSION

The recognition of nephritogenic autoantibodies in the pathogenesis of MN has defined the key role of anti-B-cell therapy in its management.² In this pilot study, we used obinutuzumab for treatment of 10 patients with MN and showed that 90% patients achieved either partial or complete remission with 2 doses. All patients with detectable serum PLA2R antibody achieved immunologic remission before improvement in proteinuria as seen in previous studies.³ Our patient population was largely rituximab refractory. The other conventional treatment options for these patients are calcineurin inhibitors or cyclophosphamide, which are associated with significant long- or short-term toxicity and high rates of relapse. In addition, the efficacy of these agents in patients who have failed rituximab therapy is unknown. In a recent case series of 3 patients with rituximab-refractory PLA2R MN, obinutuzumab led to complete immunologic remission and improvement in proteinuria in 2 patients.⁷ In our study, obinutuzumab led to complete or partial remission in 85.7% of rituximab-refractory patients.

Obinutuzumab was well-tolerated in our cohort, which included a patient who had previously experienced infusion-related anaphylaxis with rituximab. Rituximab is a chimeric monoclonal with mouse motifs in the antigen-binding region, and therefore immune responses in the recipient could inhibit or diminish efficacy or result in severe allergic reactions as seen in our patient.⁸ Obinutuzumab, on the contrary, is a

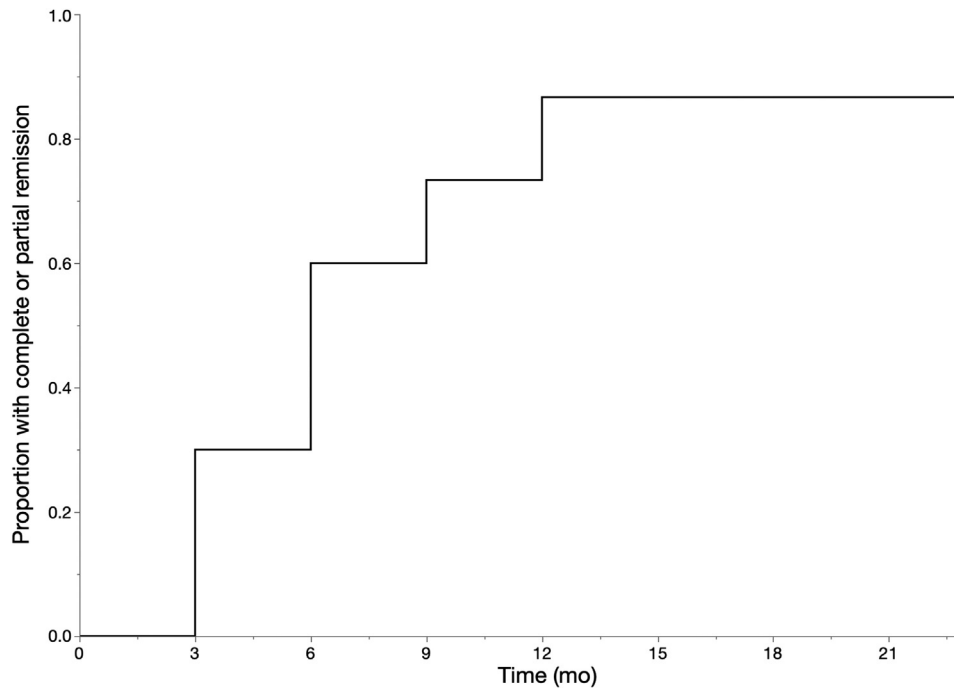


Figure 1. Kaplan–Meier curve for complete or partial remission.

humanized monoclonal antibody with a lower risk of immunogenicity.

The response to obinutuzumab in our study was rapid because 60% of patients achieved complete or partial remission at 6 months compared with the 35% 6-month response rate reported in the Membranous Nephropathy Trial of Rituximab study.³ In addition, obinutuzumab appeared to induce a durable response. All patients who achieved remission at 12 months and who had follow-up data available maintained remission without requiring additional doses of obinutuzumab. On the contrary, a significant proportion of patients treated with rituximab require additional doses to induce remission or treat relapse.³ This may be related to a more profound depletion of B-lymphocytes with obinutuzumab. B-lymphocyte

depletion was seen in both peripheral blood and lymph nodes in a study evaluating the use of obinutuzumab for desensitization in highly sensitized kidney transplant candidates.⁹

The limitations of our study include a small sample size, retrospective nonprotocolled nature, and the lack of a control arm. We also did not check peripheral CD19⁺ or CD20⁺ B-cell counts. Despite these limitations, our study provides a proof of concept of the efficacy and safety of obinutuzumab in treatment of patients with MN. Obinutuzumab is an attractive alternative therapy in patients with resistance or sensitization to rituximab and could potentially be the first-line agent in the treatment of MN. Larger prospective studies are needed to confirm our findings.

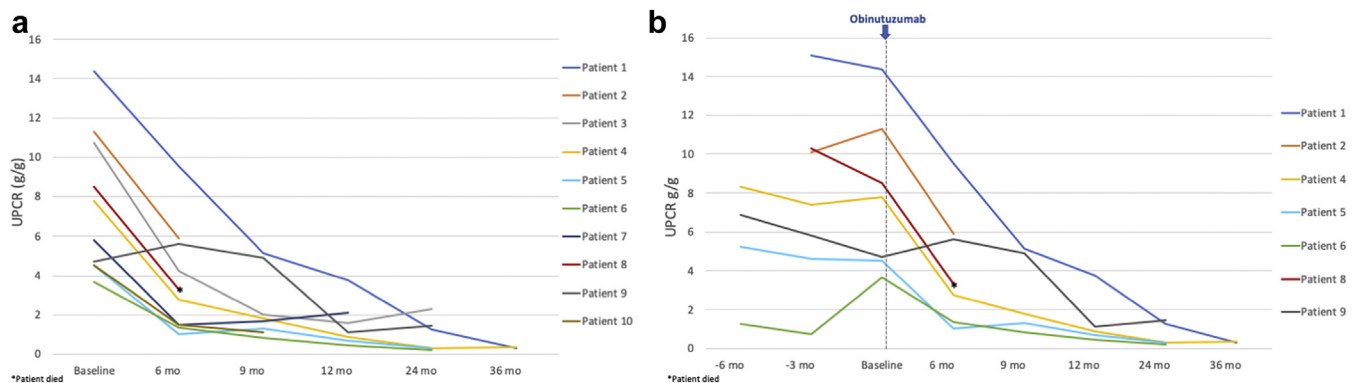


Figure 2. (a) Urine protein-to-creatinine ratio (UPCR) trend after obinutuzumab in all patients. (b) UPCR trend before and after obinutuzumab in rituximab-experienced patients.

DISCLOSURE

SCJ has received grants and consulting fees from CareDx, Vitaeris, Hansa Biopharma, and CSL Behring; consulting fees from Regeneron Pharmaceuticals, Viela Bio, and Amlyx; and grants from Novartis outside the submitted work. All other authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Figure S1. Serum albumin trend after obinutuzumab.

Figure S2. Serum creatinine trend after obinutuzumab.

Table S1. Serum PLA2R antibody titer (RU/ml).

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Nonrecurrent Early Post-Transplantation Focal Segmental Glomerulosclerosis



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Received 7 January 2020; revised 16 May 2020; accepted 8 June 2020; published online 20 June 2020

Kidney Int Rep (2020) 5, 1518–1525; <https://doi.org/10.1016/j.ekir.2020.06.008>

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Focal segmental glomerulosclerosis (FSGS) is one of the most common causes of nephrotic syndrome in adults, and the incidence of this diagnosis is increasing.^{1–4} This histological diagnosis can result from many conditions such as reflux nephropathy, significant obesity, or genetic mutations affecting

structural elements of the glomerular filtration barrier. The idiopathic form of this disease is due to a circulating factor(s) that disrupt the glomerular filtration barrier, resulting in widespread podocyte foot process effacement (FPE) and proteinuria.^{5–7} Reported recurrence rates following the first kidney transplantation