

# Rituximab for Anti–Glomerular Basement Membrane Disease



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*Kidney Int Rep* (2019) 4, 614–618; <https://doi.org/10.1016/j.ekir.2018.12.002>

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## INTRODUCTION

Anti-glomerular basement membrane (GBM) disease, characterized by antibodies against the NCI domain of type IV collagen, presents with rapidly progressive glomerulonephritis that advances quickly to end-stage renal disease if not identified and treated in a timely fashion. Pulmonary involvement, caused by autoantibodies targeting the alveolar basement membrane, occurs in 60% to 80% of patients<sup>1</sup> and presents as alveolar hemorrhage. The renal histopathology of anti-GBM glomerulonephritis typically shows a necrotizing and crescentic lesion on light microscopy with linear deposits of IgG along the glomerular basement membrane on immunofluorescence microscopy. The standard treatment for anti-GBM disease consists of corticosteroids, cyclophosphamide, and plasmapheresis until anti-GBM titers become negative. This regimen has been shown to be very effective, particularly if the diagnosis is made early in disease course. In a large retrospective cohort analysis,<sup>2</sup> for patients treated with this regimen who initially presented with a serum creatinine level  $\leq 5.7$  mg/dl, patient survival at 1 year was 100% and renal survival was 95%. Patients with a creatinine level  $>5.7$  mg/dl but not requiring immediate dialysis had patient and renal survival of 83% and 82%, respectively, at 1 year, whereas those who did require dialysis on presentation had patient and renal survival of 65% and 8%, respectively, at 1 year. Typically, after successful treatment, anti-GBM disease is considered a “one and done” disease without relapse, yet one study<sup>3</sup> identified a 3% rate of relapse of disease in patients with anti-GBM disease who were antineutrophil cytoplasmic antibody (ANCA)-negative.

Guidelines and standard-of-care approaches are lacking for treatment of anti-GBM cases that (i) are refractory

to the standard regimen, (ii) exhibit the rare form of relapsing disease, or (iii) in which the standard medication regimen of cyclophosphamide and/or corticosteroids is contraindicated (e.g., due to concerns about effects of cyclophosphamide on fertility in younger patients).

Rituximab is a B-cell depleting agent that has been used with success in a variety of autoimmune diseases. There are now a small number of cases that have been reported in the literature describing the use of rituximab for the treatment of anti-GBM disease, with varying outcomes. In this report, we present a unique case of anti-GBM disease being treated with rituximab due to persistence of disease on standard therapy, and we review the literature on use of rituximab for the treatment of anti-GBM disease.

## CASE PRESENTATION

### Clinical History

At the time of presentation, the patient was a 35-year-old woman with asthma and a diagnosis of systemic juvenile rheumatoid arthritis. Her history included alopecia totalis at the age of 16 that resolved with steroid injections that she had continued to take monthly until the time of presentation. At age 21, she developed daily fevers along with joint pain, malaise, and a rash on the face and chest; these cyclical fevers resolved after 4 years, without further recurrence, while on mycophenolate mofetil treatment. At age 27, the patient developed uveitis in her right eye, which was treated with adalimumab. Since that point, the patient had been healthy and living an active lifestyle. There was no history of autoimmune disease in her family, and no prior history of lung or kidney disease in either the patient or her family.

### Clinical Course

Two weeks before hospital admission, the patient began to experience malaise, fatigue, headache, daily

fevers, nausea and vomiting, and tea-colored urine without a change in amount or frequency of urination. She presented to her primary care physician's office, where her creatinine was found to be 1.46 mg/dl, up from a baseline of 0.80 mg/dl. She was prescribed omeprazole and ondansetron. Two days later, due to continued symptoms, she was admitted to her local hospital where her creatinine on admission was found to have increased to 3.10 mg/dl and then to 5.38 mg/dl by hospital day 3. Urinalysis revealed heavy microscopic hematuria with red blood cell count above the assay detection limit, 10 to 20 white blood cells (WBCs), and approximately 1 g of proteinuria by spot ratio; she also had leukocytosis with WBC >14,000. Test results included negative anti-double stranded DNA, negative antistreptolysin O titers, normal C3 and C4 levels, negative HIV test, negative myeloperoxidase- and PR3-ANCA, and a positive anti-GBM titer of 185 U/ml (measured by multiplex bead array assay). She underwent a renal biopsy that revealed diffuse, severe, necrotizing, crescentic glomerulonephritis with 76% cellular crescents, with immunofluorescence microscopy demonstrating linear IgG staining along the GBM. No pulmonary hemorrhage was present. She was pulsed with 1 g of methylprednisolone for 3 days, dialyzed, and then transferred to our hospital for plasmapheresis.

On admission at our hospital, she was in no acute distress, afebrile, with a blood pressure of 121/73, and breathing comfortably on room air; she had hematuria but no oliguria at this time. Physical examination had no abnormal findings, and notable laboratory tests included a Cr of 8.07 mg/dl. She was continued on hemodialysis 3 times per week and planned for plasmapheresis every other day until her anti-GBM titers became negative. She was also initiated on oral cyclophosphamide 100 mg daily and prednisone 60 mg daily. Rheumatological workup, including anti-SSA, anti-SSB, anti-Jo, anti-Scl70, anti-cardiolipin, b2-glycoprotein, lupus anticoagulant, ANA, and anti-rheumatoid factor, was negative.

The patient was managed on hemodialysis, plasmapheresis, cyclophosphamide, and prednisone for 1 month as an inpatient. During this time, she became oliguric and experienced the redevelopment of uveitis in her right eye, treated again with adalimumab. Her anti-GBM titers were measured throughout the course of her hospitalization. One week after admission to our hospital, the titers were 258 U/ml; 2 weeks later, after 7 sessions of plasmapheresis, the titers were 119 U/ml. After her tenth session of plasmapheresis, her anti-GBM titer remained elevated at 85 U/ml. At this point, cyclophosphamide and plasmapheresis were discontinued, and prednisone taper was initiated. As the patient's anti-GBM titer appeared to reach a nadir

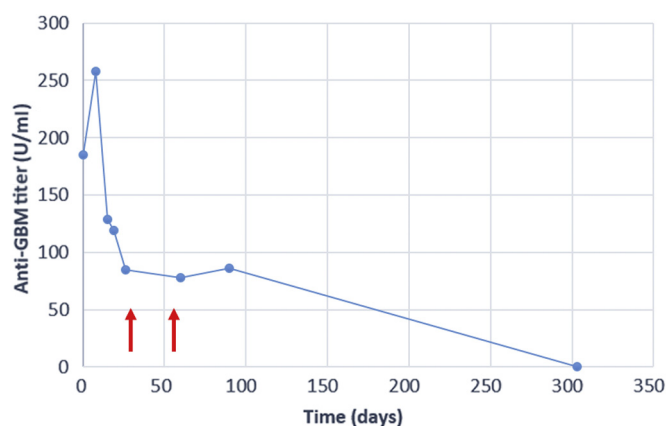
level still well above detection range despite 10 sessions of plasmapheresis and almost 1 month of cyclophosphamide, the decision was made to initiate rituximab treatment with 2 doses of 1000 mg i.v. administered 2 weeks apart (Figure 1) to further decrease anti-GBM antibody levels so the patient could be listed for transplantation. She received no additional doses of rituximab or other alternative immunosuppressive medications.

By follow-up 1 month after the second dose of rituximab, the patient's symptoms of fever, malaise, fatigue, headaches, and nausea and vomiting had resolved. Eight months after her second rituximab dose, the patient's anti-GBM titers were negative, and at follow-up 2 years after her original diagnosis, the patient was still asymptomatic and free of immunosuppressive therapy. She remained on dialysis, however, and was awaiting renal transplantation with no viable living donors. She had not experienced infections, recurrence of disease symptoms, or alveolar hemorrhage after rituximab treatment.

## DISCUSSION

This case adds to the growing literature supporting the efficacy of rituximab in refractory or relapsing anti-GBM disease. A key feature of this case is the patient having a prior history of autoimmune disease, which even if not related to the present diagnosis of anti-GBM disease (rheumatological workup for other autoantibodies was completely negative), may suggest predisposition to a more severe, refractory form of the disease.

In anti-GBM disease, anti-GBM autoantibodies bind chiefly to the  $\alpha 3$  chain of the NCI domain of type IV collagen in the glomerular basement membrane, ultimately leading to glomerular capillary wall destruction and crescent formation.<sup>4</sup> Both animal and clinical patient studies have demonstrated the pathogenicity of



**Figure 1.** Patient's anti-glomerular basement membrane (anti-GBM) antibody titers over disease course. Red arrows indicate rituximab administration.

these autoantibodies,<sup>5,6</sup> and their removal has been shown to be associated with renal recovery.<sup>6</sup> These findings reinforce the importance of the role of B cells, which generate antibodies, in the pathogenesis of anti-GBM disease; therefore, rituximab, a monoclonal antibody that targets CD20-positive B cells, in theory should be a viable treatment option for this disease.

Rituximab, initially approved for treatment of non-Hodgkin lymphoma, removes CD-20 positive B cells from the circulation by direct induction of apoptosis and antibody-, and complement-mediated cytotoxicity.<sup>7</sup> Studies have demonstrated that rituximab effectively depletes autoantibodies and induces remission in a variety of glomerular diseases, including ANCA-associated glomerulonephritis,<sup>8</sup> glomerulonephritis associated with systemic lupus erythematosus, and membranous nephropathy.<sup>9</sup> In all of these cases, rituximab was shown to be noninferior to the standard treatment regimen. In IgA nephropathy, however, rituximab depleted circulating B cells, but failed to effect improvements in proteinuria or estimated glomerular filtration rate.<sup>10</sup>

Rituximab also may prove to be effective in treating anti-GBM disease. To date, the medical literature has published a total of 22 cases (including our case) of anti-GBM disease, without other concurrent kidney disease (e.g., ANCA-associated vasculitis), that were

treated with rituximab (Table 1). Of the 22 cases, rituximab was initiated in 15 for disease-refractory to standard treatment or relapsed disease. In all but 1 of these cases, rituximab treatment resulted in undetectable, or near-undetectable, anti-GBM antibody titers posttreatment, with resolution of disease symptoms. The one exception to this was a case published by Sauter *et al.*,<sup>11</sup> in which a patient who had received a deceased donor renal transplant 3 years after initial diagnosis of Goodpasture's disease was found 18 months after transplantation to have recurrent disease. The patient was treated with rituximab after the standard regimen failed to result in remission, but anti-GBM titers never became undetectable, renal function continued to decrease, and the patient was ultimately placed on renal replacement therapy.<sup>11</sup> In these 15 cases, even when anti-GBM titers became negative, rituximab treatment was not able to reverse dialysis dependency.

In the other 7 cases, rituximab was used as part of the initial treatment regimen instead of cyclophosphamide. Out of these, 6 completely cleared anti-GBM antibodies in less than 4 weeks; the seventh case had an initial drop in anti-GBM titer from >680 U/ml to 44 U/ml in 3 weeks, and then gradually became undetectable over a couple of months. Four of the 7 patients progressed to end-stage renal disease, with the patient ending up on dialysis or with a transplant, but 1

**Table 1.** Previously published cases of rituximab use in anti-GBM disease without other concurrent glomerular disease

Reference	Age	Sex	Lung Involvement	Creat pre-Tx (mg/dl)	Creat Post-Tx (mg/dl)	Anti-GBM pre-Tx (U/ml or titer)	Anti-GBM post-Tx (U/ml or titer)	Rituximab dose and duration	F/U length (mo)	Outcome
Arzoo <i>et al.</i> (2002) <sup>22,a</sup>	73	F	Y	NR	NR	108	Undetectable	375 mg/m <sup>2</sup> , 6 weekly doses	10	Remission
Wechsler <i>et al.</i> (2008) <sup>17</sup>	55	M	N	3.5	1.2	8.6	Undetectable	375 mg/m <sup>2</sup> , 4 weekly doses	16	Remission
Sauter <i>et al.</i> (2009) <sup>11</sup>	29	M	N	1.6	Dialysis	43	< 20	375 mg/m <sup>2</sup> , 3 weekly doses	3	Loss of graft, HD
Schless <i>et al.</i> (2009) <sup>15</sup>	18	F	Y	2.3	Dialysis	57	Undetectable	1000 mg, 1 dose	2.5	Remission, HD
Schless <i>et al.</i> (2009) <sup>15</sup>	20	M	N	7.4	3.39	94	Undetectable	1000 mg, 1 dose	3	Remission
Mutsaers <i>et al.</i> (2010) <sup>23,a</sup>	20	F	N	7.06	2.10	270	Undetectable	375 mg/m <sup>2</sup> , 2 doses, 2 wks apart	2	Remission
Shah <i>et al.</i> (2012) <sup>24,a</sup>	54	M	Y	Dialysis	Dialysis	>680	Undetectable	375 mg/m <sup>2</sup> , 4 weekly doses	49	Remission, HD
Shah <i>et al.</i> (2012) <sup>24,a</sup>	17	M	Y	3.1	1.1	131	Undetectable	375 mg/m <sup>2</sup> , 2 weekly doses	33	Remission
Narayanan <i>et al.</i> (2014) <sup>25,a</sup>	21	M	Y	12.8	Dialysis	191	3	2 doses (unknown), 2 wks apart	4	Remission, HD
Touzot <i>et al.</i> (2015) <sup>26,a</sup>	21	F	N	2.41	1.92	Undetectable	Undetectable	375 mg/m <sup>2</sup> , 4 weekly doses	3	Remission
Touzot <i>et al.</i> (2015) <sup>26,a</sup>	46	F	N	Dialysis	Dialysis	1:200 (IIF)	Undetectable	375 mg/m <sup>2</sup> , 4 weekly doses	12	Remission, HD
Touzot <i>et al.</i> (2015) <sup>26,a</sup>	16	F	N	0.92	0.93	Undetectable	Undetectable	375 mg/m <sup>2</sup> , 4 weekly doses	10	Remission
Touzot <i>et al.</i> (2015) <sup>26,a</sup>	65	M	N	3.81	2.73	1:40 (IIF)	Undetectable	375 mg/m <sup>2</sup> , 4 weekly doses	56	Remission
Touzot <i>et al.</i> (2015) <sup>26,a</sup>	19	F	N	2.30	0.82	25	Undetectable	375 mg/m <sup>2</sup> , 4 weekly doses	39	Remission
Touzot <i>et al.</i> (2015) <sup>26,a</sup>	22	M	Y	0.96	1.10	19	Undetectable	375 mg/m <sup>2</sup> , 4 weekly doses	12	Remission
Touzot <i>et al.</i> (2015) <sup>26,a</sup>	21	F	N	1.52	1.00	40	Undetectable	375 mg/m <sup>2</sup> , 4 weekly doses	93	Remission
Touzot <i>et al.</i> (2015) <sup>26,a</sup>	17	F	Y	1.39	Dialysis	8	Undetectable	375 mg/m <sup>2</sup> , 4 weekly doses	6	Remission, HD
Lemahieu <i>et al.</i> (2018) <sup>27,a</sup>	29	M	N	20	2.4	>680	1.7	1000 mg, 2 weekly doses	6	Remission
Heitz <i>et al.</i> (2018) <sup>16</sup>	NR	NR	N	7.99	Dialysis	1:10 (IIF)	Undetectable	375 mg/m <sup>2</sup> , 4 weekly doses	39	Remission, transplant
Heitz <i>et al.</i> (2018) <sup>16</sup>	NR	NR	N	3.09	Dialysis	1:640 (IIF)	Undetectable	375 mg/m <sup>2</sup> , 4 weekly doses	9	Remission, PD
Heitz <i>et al.</i> (2018) <sup>16</sup>	NR	NR	Y	6.84	Dialysis	1:200 (IIF)	Undetectable	375 mg/m <sup>2</sup> , 4 weekly doses	14	Remission, transplant

Creat, serum creatinine; F, female; F/U, follow-up period; GBM, glomerular basement membrane; HD, hemodialysis; IIF, indirect immunofluorescence; M, male; N, no; NR, not reported; PD, peritoneal dialysis; Tx, treatment; Y, yes.

<sup>a</sup>See [Supplementary References](#) for references 22–27.

patient who presented with 100% crescents and dialysis dependency was able to come off dialysis. On this basis, it could be suggested that rituximab, when used as part of the primary regimen instead of cyclophosphamide, appears to facilitate rapid anti-GBM antibody clearance, but it does not necessarily preserve renal function in patients with severe disease. Literature on ANCA-associated glomerulonephritis had described the use of a combination of rituximab and cyclophosphamide as a primary treatment regimen for that disease; this combination was found to achieve high rates of disease remission, lower rates of disease relapse than with rituximab alone, and acceptable safety signals.<sup>12,13</sup> This combination approach of cyclophosphamide plus rituximab may be an intriguing avenue of further study in anti-GBM disease as well.

In the 22 anti-GBM cases reported in the literature, pulmonary hemorrhage resolved after rituximab treatment in all patients who presented with this feature. Doses of rituximab varied across cases, with some patients receiving weekly doses of 375 mg/m<sup>2</sup> for 2 to 6 weeks, and others being treated with 1 or 2 doses of 1000 mg. With respect to timing of rituximab administration in patients also receiving plasmapheresis, approximately 65% of administered rituximab can be removed by plasma exchange; therefore, rituximab should be administered post-plasma exchange and may require a delay (e.g., 48 hours) before subsequent plasma exchange.<sup>14</sup> The only reported complications of rituximab treatment for anti-GBM disease were seizures and leukoencephalopathy that developed 6 weeks posttreatment and subsequently resolved,<sup>15</sup> esophageal candidiasis,<sup>16,17</sup> and temporary thrombocytopenia.<sup>16</sup>

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines specify no recommendations for treatment of refractory anti-GBM disease,<sup>18</sup> but the Kidney Disease Outcomes Quality Initiative recommendations suggest azathioprine treatment if anti-GBM antibodies persist in spite of treatment with cyclophosphamide.<sup>19</sup> There have also been case reports of treatment of refractory anti-GBM disease with a regimen that includes mycophenolate mofetil.<sup>20,21</sup> No controlled trials have been performed to study the efficacy of these therapies for the treatment of refractory anti-GBM disease. Given the rarity and severity of refractory or relapsing anti-GBM disease, randomized clinical trials comparing cyclophosphamide to rituximab or other alternative treatment methods are unlikely to be performed in the foreseeable future. Thus, case reports are expected to comprise the entirety of the literature on which medical decisions will be made with regard to this subject (Table 2).

Although a controlled clinical trial against placebo and perhaps against the standard treatment regimen with cyclophosphamide would be ideal, and necessary, to draw

**Table 2.** Teaching points of case report

Standard treatment for anti-glomerular basement membrane (anti-GBM) disease consists of steroids, cyclophosphamide, and plasmapheresis
Approximately 3% of patients with anti-GBM disease are refractory to standard treatment
A number of case reports, including the case presented here, suggest that rituximab, a B-cell depleting agent with efficacy in other autoimmune glomerular diseases, may be a viable treatment option for anti-GBM disease that does not respond to cyclophosphamide
Rituximab may rapidly reduce autoantibody titers in patients with anti-GBM disease, but the drug has not been shown to consistently reverse dialysis dependency
There are not currently enough data to support use of rituximab as a first-line agent for anti-GBM disease

definitive conclusions, the growing literature on the use of rituximab for treatment of anti-GBM disease continues to demonstrate its efficacy. On the basis of the current literature, we suggest using rituximab for cases refractory to the standard treatment regimen with persistence of anti-GBM antibodies and failure to achieve symptomatic improvement within 4 weeks of treatment initiation. In addition, for young patients with anti-GBM disease in whom avoidance of cyclophosphamide is desired to preserve fertility, use of rituximab might be considered despite the limited amount of supportive data for this strategy.

## DISCLOSURE

All the authors declared no competing interests.

## SUPPLEMENTARY MATERIAL

### Supplementary References.

Supplementary material is linked to the online version of the paper at [www.kireports.org](http://www.kireports.org).

## REFERENCES

1. Shiferaw B, Miro V, Smith C, et al. Goodpasture's disease: an uncommon disease with an atypical clinical course. *J Clin Med Res.* 2016;8:52–55.
2. Levy JB, Turner AN, Rees AJ, Pusey CD. Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression. *Ann Intern Med.* 2001;134:1033–1042.
3. Glassock RJ. Atypical anti-glomerular basement membrane disease: lessons learned. *Clin Kidney J.* 2016;9:653–656.
4. Syeda UA, Singer NG, Magrey M. Anti-glomerular basement membrane antibody disease treated with rituximab: a case-based review. *Semin Arthritis Rheum.* 2013;42:567–572.
5. Lerner RA, Glassock RJ, Dixon FJ. The role of anti-glomerular basement membrane antibody in the pathogenesis of human glomerulonephritis. *J Exp Med.* 1967;126:989–1004.
6. McAdoo SP, Pusey CD. Anti-glomerular basement membrane disease. *Clin J Am Soc Nephrol.* 2017;12:1162–1172.
7. Randall KL. Rituximab in autoimmune diseases. *Aust Prescr.* 2016;39:131–134.
8. Pendergraft WF, Falk RJ. Understanding the role of rituximab in ANCA GN: regressing toward the mean. *J Am Soc Nephrol.* 2015;26:771–774.



9. Fiorentino M, Tondolo F, Bruno F, et al. Treatment with rituximab in idiopathic membranous nephropathy. *Clin Kidney J.* 2016;9:788–793.
10. Lafayette RA, Canetta PA, Rovin BH, et al. A randomized, controlled trial of rituximab in IgA nephropathy with proteinuria and renal dysfunction. *J Am Soc Nephrol.* 2017;28:1306–1313.
11. Sauter M, Schmid H, Anders HJ, et al. Loss of a renal graft due to recurrence of anti-GBM disease despite rituximab therapy. *Clin Transplant.* 2009;23:132–136.
12. Cortazar FB, Muhsin SA, Pendergraft WF 3rd, et al. Combination therapy with rituximab and cyclophosphamide for remission induction in ANCA vasculitis. *Kidney Int Rep.* 2018;3:394–402.
13. McGregor JG, Hogan SL, Kotzen ES, et al. Rituximab as an immunosuppressant in antineutrophil cytoplasmic antibody-associated vasculitis. *Nephrol Dial Transplant.* 2015;30(Suppl 1):i123–i131.
14. Hildebrand AM, Huang SH, Clark WF. Plasma exchange for kidney disease: what is the best evidence? *Adv Chronic Kidney Dis.* 2014;21:217–227.
15. Schless B, Yildirim S, Beha D, et al. Rituximab in two cases of Goodpasture's syndrome. *NDT Plus.* 2009;2:225–227.
16. Heitz M, Carron PL, Clavarino G, et al. Use of rituximab as an induction therapy in anti-glomerular basement-membrane disease. *BMC Nephrol.* 2018;19:241.
17. Wechsler E, Yang T, Jordan SC, et al. Anti-glomerular basement membrane disease in an HIV-infected patient. *Nat Clin Pract Nephrol.* 2008;4:167–171.
18. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. Abstract. *Kidney Int Suppl.* 2012;2:142.
19. Beck L, Bomback AS, Choi MJ, et al. KDOQI US Commentary on the 2012 KDIGO Clinical Practice Guideline for Glomerulonephritis. *Am J Kidney Dis.* 2013;62:403–441.
20. Kiykim AA, Horoz M, Gok E. Successful treatment of resistant antglomerular basement membrane antibody positivity with mycophenolic acid. *Intern Med.* 2010;49:577–580.
21. Mori M, Nwaogwugwu U, Akers GR, McGill RL. Anti-glomerular basement membrane disease treated with mycophenolate mofetil, corticosteroids, and plasmapheresis. *Clin Nephrol.* 2013;80:67–71.