Rituximab for Anti–Glomerular Basement Membrane Disease

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INTRODUCTION

Anti–glomerular basement membrane (GBM) disease, characterized by antibodies against the NC1 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 patients¹ 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,² for patients treated with this regimen who initially presented with a serum creatinine level ≤ 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 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 study³ 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 s, 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 ζ3 chain of the NC1 domain of type IV collagen in the glomerular basement membrane, ultimately leading to glomerular capillary wall destruction and crescent formation. Both animal and clinical patient studies have demonstrated the pathogenicity of...
these autoantibodies, and their removal has been shown to be associated with renal recovery. 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 CD20 positive B cells from the circulation by direct induction of apoptosis and antibody-, and complement-mediated cytotoxicity. Studies have demonstrated that rituximab effectively depletes autoantibodies and induces remission in a variety of glomerular diseases, including ANCA-associated glomerulonephritis, glomerulonephritis associated with systemic lupus erythematosus, and membranous nephropathy. 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.

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., 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. 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 et al. (2002)           | 73  | F   | Y                | NR                  | 108                  | Undetectable                 | 375 mg/m²                      | 6 weekly doses               | 10              | Remission |
| Wechsler et al. (2008)        | 55  | M   | N                | 3.5                 | 1.2                  | 8.6                          | Undetectable                 | 375 mg/m²                      | 4 weekly doses               | 16              | Remission |
| Sauter et al. (2009)          | 29  | M   | N                | 1.6                 | Dialysis             | 43                            | < 20                          | 375 mg/m²                      | 3 weekly doses               | 3               | Loss of graft, HD |
| Schless et al. (2009)         | 18  | F   | Y                | 2.3                 | Dialysis             | 57                            | Undetectable                 | 1000 mg, 1 dose               | 2.5             | Remission |
| Mutsaers et al. (2010)        | 20  | M   | N                | 7.4                 | 3.39                 | 94                            | Undetectable                 | 1000 mg, 1 dose               | 3               | Remission |
| Shah et al. (2012)            | 54  | M   | Dialysis         | 7.06                | 2.10                 | 270                           | Undetectable                 | 375 mg/m², 2 doses, 2 wks apart | 2               | Remission |
| Shah et al. (2012)            | 17  | M   | Y                | 3.1                 | 1.1                  | 131                           | Undetectable                 | 375 mg/m², 2 weekly doses     | 33              | Remission |
| Narayanan et al. (2014)       | 21  | M   | Y                | 12.8                | Dialysis             | 191                           | 3                             | 2 doses (unknown), 2 wks apart | 4               | Remission, HD |
| Touzot et al. (2015)          | 21  | F   | N                | 2.41                | 1.92                 | Undetectable                 | 375 mg/m²                      | 4 weekly doses               | 3               | Remission |
| Touzot et al. (2015)          | 46  | F   | N                | Dialysis           | 1:200 (IIF)          | Undetectable                 | 375 mg/m²                      | 4 weekly doses               | 12              | Remission, HD |
| Touzot et al. (2015)          | 18  | F   | N                | 0.92                | 0.93                 | Undetectable                 | 375 mg/m²                      | 4 weekly doses               | 10              | Remission |
| Touzot et al. (2015)          | 65  | M   | N                | 3.81                | 2.73                 | 1:40 (IIF)                    | Undetectable                 | 375 mg/m²                      | 4 weekly doses               | 56              | Remission |
| Touzot et al. (2015)          | 19  | F   | N                | 2.30                | 0.82                 | 25                            | Undetectable                 | 375 mg/m²                      | 4 weekly doses               | 39              | Remission |
| Touzot et al. (2015)          | 22  | M   | Y                | 0.96                | 1.10                 | 19                            | Undetectable                 | 375 mg/m²                      | 4 weekly doses               | 12              | Remission |
| Touzot et al. (2015)          | 21  | F   | N                | 1.52                | 1.00                 | 40                            | Undetectable                 | 375 mg/m²                      | 4 weekly doses               | 93              | Remission |
| Touzot et al. (2015)          | 17  | F   | Y                | 1.39                | Dialysis             | 8                             | Undetectable                 | 375 mg/m²                      | 4 weekly doses               | 6               | Remission, HD |
| Lemahieu et al. (2018)        | 29  | M   | N                | 20                  | 2.4                  | >80                           | 1.7                           | 1000 mg, 2 weekly doses       | 6               | Remission, transplant |
| Helle et al. (2018)           | NR  | NR  | N                | 7.99                | Dialysis             | 1:10 (IIF)                    | Undetectable                 | 375 mg/m²                      | 4 weekly doses               | 39              | Remission, transplant |
| Helle et al. (2018)           | NR  | NR  | N                | 3.09                | Dialysis             | 1:840 (IIF)                   | Undetectable                 | 375 mg/m²                      | 4 weekly doses               | 9               | Remission, PD |
| Helle et al. (2018)           | NR  | NR  | Y                | 6.84                | Dialysis             | 1:200 (IIF)                   | Undetectable                 | 375 mg/m²                      | 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.

*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.12,13 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/m² 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.14 The only reported complications of rituximab treatment for anti-GBM disease were seizures and leukoencephalopathy that developed 6 weeks posttreatment and subsequently resolved,15 esophageal candidiasis,16,17 and temporary thrombocytopenia.16

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines specify no recommendations for treatment of refractory anti-GBM disease,18 but the Kidney Disease Outcomes Quality Initiative recommendations suggest azathioprine treatment if anti-GBM antibodies persist in spite of treatment with cyclophosphamide.19 There have also been case reports of treatment of refractory anti-GBM disease with a regimen that includes mycophenolate mofetil.20,21 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 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.

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