Case report

Rituximab in anti-glomerular basement membrane disease

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Introduction

The role of rituximab has expanded beyond the treatment of non-Hodgkins lymphoma,1 to include successful management of rheumatoid arthritis,2 systemic lupus erythematosus,3 anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis4 and primary glomerulonephritis.5 Decrease incidence of side-effects or toxicity, coupled with clinical effectiveness, suggests that B-cell depleting agents may convey an advantage over traditional immunosuppressive agents.

Rituximab therapy has previously been reported in anti-glomerular basement membrane (GBM) disease.6,7 Because of side-effects such as sterility and the risk of infection in the febrile patient with conventional therapy, we have used rituximab in anti-GBM disease to suppress antibody production.

We report three cases of anti-GBM disease treated with rituximab along with steroids and plasma exchange.

Case 1

A 54-year-old man with a history of hypertension and multiple sclerosis presented with severe renal failure (serum creatinine 1874 μmol/l) and anuria. His GBM antibodies were >680 U/ml. He was dialysis dependent from the outset and treated with i.v. pulsed methylprednisolone (PMP) 1 g daily for four days, i.v. cyclophosphamide and plasma exchange. He developed overt pulmonary haemorrhage on Day 5, along with thrombocytopenia and leucopenia. Because of fears of infection and signs of marrow suppression, we switched cyclophosphamide (only one dose given) to rituximab (375 mg/m² four times weekly doses). He received 50 sessions of plasma exchange to reduce his antibody levels. He remained dialysis dependent. He is now on the national renal transplant waiting list and no complications of rituximab have been noted, since its use 49 months ago. GBM antibodies remain undetectable.

Case 2

A 64-year-old man presented with 1 year history of intermittent nasal obstruction, nasal discharge, anorexia, nausea and weight loss. On admission his serum creatinine was 536 μmol/l, C-reactive protein (CRP) 230 mg/l. Urine dipstick revealed 3+ blood and protein. His serum was positive for GBM antibodies (49 U/ml) and p-ANCA (myeloperoxidase [MPO] = 369 U/ml). His renal biopsy showed 75% crescents, acute tubular necrosis and some chronic interstitial changes. Immunofluorescence showed linear deposition of immunoglobulin G (IgG) along the GBM. He was initially dialysis dependent. He received high-dose steroids and oral cyclophosphamide (50 mg/day), converting to rituximab (375 mg/m² four times weekly i.v. doses) 7 days later because of thrombocytopenia and very high CRP. One week after the fourth dose of rituximab, he became dialysis independent and his GBM antibodies levels dropped to <6 U/ml 6 weeks later. His maintenance prednisolone was stopped after 16 months. Thirty seven months after presentation, his serum creatinine is 260 μmol/l, with undetectable p-ANCA (MPO) and GBM antibodies. Characteristic findings on...
kidney biopsy with no relapse episode suggest anti-GBM disease as a primary diagnosis.

**Case 3**

A 17-year-old male, admitted with 5 days history of nausea, vomiting, lethargy, breathlessness with haemoptysis and weight loss. His haemoglobin (HB) on admission was 5.9 g/dl, reticulocyte count of 4.5%, mean corpuscular volume (MCV) 77 fl, bilirubin 41 µmol/l, normal transaminases and alkaline phosphatase. His kidney function was normal (serum creatinine 80 µmol/l). chest X-ray (CXR) showed right mid-zone consolidation and some interstitial shadowing on the left side. He was treated for atypical pneumonia with erythromycin. Mycoplasma antibodies were detected by agglutination test (serology negative later). He was transfused, endoscopy and follow-up was arranged as an outpatient. He was re-admitted 5 days later from clinic, with a continuation of his symptoms. Renal impairment was apparent (serum creatinine 272 µmol/l, HB 7 g/dl, urine dipstick 3+ blood and 3+ protein. Computed tomography (CT)-chest showed bilateral ground glass appearance suggestive of haemorrhage. GBM antibodies were positive at 131 U (normal <3). Kidney biopsy confirmed anti-GBM disease with 80% of glomeruli involved by cellular crescents. Cyclophosphamide therapy was declined because of concerns regarding fertility. He received PMP 1 g i.v. for four days along with 2 doses of rituximab 375 mg/m², one week apart and 17 plasma exchanges. GBM antibodies reduced to <3 U/ml 20 days after rituximab was commenced. Maintenance treatment included oral prednisolone, 30 mg daily, slowly tapered and stopped in 1 year. His serum creatinine after 33 months is 100 µmol/l and creatinine clearance of 60 ml/min. GBM antibodies remain undetectable.

**Discussion**

Anti-GBM disease is a rare auto-immune disorder characterized by rapidly progressive glomerulonephritis with crescentic changes in glomeruli and characteristic linear IgG deposition along the GBM on renal biopsy; when accompanied by pulmonary haemorrhage, the condition is known as Goodpasture syndrome. The disease is associated with pathogenic antibodies against the non-collagenous domain (NC1) of the α-3 chain of type 4 collagen. Historically, untreated patients have poor renal survival and high mortality, particularly from pulmonary haemorrhage. Use of plasma exchange in combination with prednisolone and cyclophosphamide dramatically improves outcomes.

There is a strong association between anti-GBM disease and HLA class 2 alleles, such as DRB*1501 suggesting a role for T lymphocytes in the initial breaking of tolerance in this auto-immune disease. Nevertheless, GBM antibodies were shown to be pathogenic following adaptive transfer experiments and their depletion and removal is associated with clinical recovery, supporting a pivotal role for B cells.

Rituximab is a murine/human chimeric anti-CD20 monoclonal antibody that depletes B cells and was licensed in 1997 for the treatment of non-Hodgkins lymphoma. Two case reports of the use of rituximab in anti-GBM disease have previously been published. We used rituximab in three patients with anti-GBM disease. Cases 1 and 3 received steroids and plasma exchange along with rituximab. Case 2 did not receive plasma exchange as vasculitis was initially suspected as the primary problem before the biopsy and he made excellent progress without it. Case 1 had severe renal impairment with exceptionally high levels of GBM antibodies. He did not recover renal function but his pulmonary haemorrhage and GBM antibodies resolved with the rituximab-based regimen. Case 2 recovers renal function having been dialysis dependent. This might be explained by tubular necrosis on the renal histology, the presence of ANCA or possibly the beneficial effects of rituximab therapy. Our third case, presenting with mild to moderate renal impairment had impressive recovery of renal function. Renal function at diagnosis is said to be the best predictor of renal survival.

Due to the rarity of this disease, it is difficult to perform randomized control studies. Our experience suggests that rituximab is effective in anti-GBM disease and its use may avoid side-effects associated with cyclophosphamide and limit steroid use and toxicity.

**Conflict of interest:** None declared.

**References**


