

## CONCISE REPORT

# Treatment of refractory antibody mediated autoimmune disorders with an anti-CD20 monoclonal antibody (rituximab)

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**Background:** Rituximab, a chimeric monoclonal anti-CD20 antibody, has recently been used for the treatment of refractory antibody mediated autoimmune diseases such as immune mediated thrombocytopenia and haemolytic anaemia.

**Patients:** Because of its novel mechanism of action, rituximab was used to treat three patients with refractory systemic antibody mediated autoimmune disorders. The first patient, a 71 year old woman with idiopathic type II mixed essential cryoglobulinaemia, had both dermatological and neurological manifestations with marked renal disease attributed to her cryoglobulinaemia. Patient 2, a 73 year old woman with Goodpasture's syndrome, was refractory to conventional treatment (cyclophosphamide, prednisone, plasmapheresis). She had persistent haemoptysis and haematuria and positive antglomerular basement membrane antibodies. The third patient, a 75 year old man with primary biliary cirrhosis, myelodysplasia, and systemic immune complex vasculitis, had progressive renal insufficiency, a macular erythematous rash, and severe thrombocytopenia.

**Results:** Treatment with rituximab resolved all clinical and laboratory manifestations in the three patients.

**Conclusions:** Rituximab may be an important therapeutic agent for the treatment of patients refractory or intolerant to corticosteroid or cytotoxic treatment, or both.

Treatment of severe antibody mediated autoimmune disorders remains a difficult clinical problem. Treatment usually requires the long term use of corticosteroids alone or combined with cytotoxic agents.<sup>1–3</sup> The combinations of corticosteroids with cytotoxic chemotherapeutic agents, though frequently effective, have broad immunosuppressive effects involving phagocytic cells, T and B lymphocyte function. This lack of specificity, coupled with other systemic effects, may cause considerable toxicity and treatment related morbidity.<sup>3</sup> Patients refractory to standard treatment present an even more complex therapeutic challenge. Therefore, agents that would specifically target B lymphocytes might provide a safer and more effective treatment of the antibody associated autoimmune disorders.

Rituximab (Rituxan, IDEC Pharmaceuticals Corp, San Diego, CA) is a chimeric monoclonal antibody that targets the pan-B lymphocyte antigen CD20.<sup>4</sup> CD20 is a B cell antigen that is present on the pre-B cells, and persists through all stages of B cell differentiation, being present on mature B cells as well as most B cell neoplasms.<sup>5</sup> Rituximab has been remarkably effective in the treatment of relapsed or refractory low grade non-Hodgkin's lymphoma.<sup>6</sup> The mechanisms by which rituximab exerts its lymphotoxic activity include complement dependent cytotoxicity, antibody dependent cellular cytotoxic-

ity, and induction of apoptosis.<sup>7</sup> Rituximab has also been used for the treatment of malignant plasma cell disorders, such as multiple myeloma and Waldenström's macroglobulinaemia, and the treatment of non-malignant plasma cell disorders such as IgM neuropathies, immune thrombocytopenic purpura, autoimmune haemolytic anaemia, and immune mediated pure red cell aplasia.<sup>8–11</sup>

In this report we describe three patients with refractory antibody mediated autoimmune B cell disorders who were treated with rituximab. The clinical and laboratory parameters of all three patients improved. Our report emphasises the potential role of rituximab in the treatment of antibody mediated autoimmune diseases.

## CASE REPORTS

### Case 1

A 71 year old white woman was seen for type II mixed essential cryoglobulinaemia. Six years previously she developed purpuric skin lesions affecting her legs, which were treated with topical drugs without a specific diagnosis. Two years later she developed peripheral sensory neuropathy affecting the arms and legs. In August 2000 she underwent lumbar decompression surgery for disc disease in L4-S1 vertebrae. Her post-operative course was complicated by the development of pancytopenia and acute renal failure (serum creatinine 260 µmol/l; normal <110). Physical examination showed hyperpigmented skin lesions and decreased vibration and pinprick in the legs. Kidney biopsy demonstrated an acute proliferative glomerulonephritis with numerous hyaline thrombi, and immunohistochemistry studies confirmed cryoglobulin induced glomerular injury. Serum cryocrit was measured at 1.7% (normal: undetectable) with cryoglobulin fractionation showing an IgG of 0.210 g/l and IgM of 0.32 g/l. Antinuclear antibody was positive at 8 IU/ml (normal <7.5) with a speckled pattern. Rheumatoid factor was 396 IU/ml (normal < 39), and the erythrocyte sedimentation rate was 13 mm/1st h. Serological studies for hepatitis A, B, and C were negative. Hepatitis C was further excluded by a negative quantitative viral polymerase chain reaction. A lymphoproliferative disorder was excluded by a normal computed tomography and a negative whole body gallium scan.

Initial treatment consisted of four months of high dose prednisone (60 mg/day), resulting in minimal clinical improvement. Because of the patient's debilitated state and the failure to wean her off corticosteroids, a trial of rituximab treatment (375 mg/m<sup>2</sup>) was started. After three weekly treatments with rituximab, prednisone was stopped. After the sixth week of rituximab treatment the patient's skin lesions and peripheral neuropathy had improved considerably. Her serum creatinine had fallen to 120 µmol/l. Repeat cryoglobulins were negative (table 1). After rituximab treatment serum quantitative immunoglobulins demonstrated hypogammaglobulinaemia with IgG 6.58 g/l (normal 7.68–16.32), IgA 0.98

**Table 1** Patient characteristics and treatment summary

Case No and diagnosis	Rituximab doses	Marker pretreatment	Marker post-treatment
1. Mixed essential cryoglobulinaemia type II	6	Cryocrit: 1.7% (fractionation: IgG 0.21 g/l, IgM 0.320 g/l) Lymphocyte Ct: 2218 ×10 <sup>6</sup> /l	Cryoglobulins: negative Lymphocyte Ct: 1938 ×10 <sup>6</sup> /l
2. Goodpasture's syndrome	6	Anti-GM: 51 U/ml Lymphocyte Ct: 495 ×10 <sup>6</sup> /l	Anti-GM: none Lymphocyte Ct: 836 ×10 <sup>6</sup> /l
3. Immune complex vasculitis	8	C1q: 69 µg (normal <4 µg) Raji cell: 275 µg Eq/ml (normal <12 µg Eq/ml) Lymphocyte Ct: 816 ×10 <sup>6</sup> /l	C1q: <4 µg Raji cell: 7.3 µg Eq/ml Lymphocyte Ct: 1491 ×10 <sup>6</sup> /l

Anti-GM, antiglomerular basement membrane antibodies.

g/l (normal 0.68–3.78), and IgM 0.29 g/l (normal 0.60–2.63). Eight months after the rituximab treatment the patient remains in remission.

### Case 2

A 73 year old woman presented with fever, cough, hypoxia, and haemoptysis. Her past medical history was significant for hypertension, hyperlipidaemia, coronary heart disease, and degenerative joint disease. On admission, the patient was intubated and required respiratory support. The lung biopsy was diagnostic of Goodpasture's syndrome. Antiglomerular basement membrane antibodies were raised at 108 U/ml (normal <3).

Initial treatment consisted of a plasmapheresis, cyclophosphamide, and prednisone, resulting in a remission that lasted a year. The patient relapsed with haemoptysis and haematuria, and re-treatment with steroids and plasmapheresis was begun, followed by oral cyclophosphamide and prednisone maintenance treatment. However, the patient continued to be symptomatic with intermittent haemoptysis, haematuria, and persistent increases of antiglomerular basement membrane antibodies. Treatment with rituximab (375 mg/m<sup>2</sup>) was started with the patient receiving a total of six weekly doses. After the second infusion the patient's symptoms improved markedly; by the fourth cycle of rituximab, cyclophosphamide and prednisone were stopped. After the sixth cycle, her symptoms had resolved completely. Anti-GM antibodies were undetectable when tests were repeated (table 1). Serum quantitative immunoglobulins were as follows: IgG 4.48 g/l, IgA 1.47 g/l, and IgM 0.70 g/l. Maintenance treatment with daily azathioprine was started. Ten months after completion of the rituximab treatment, she remains in remission.

### Case 3

A 75 year old white man, previously known to our institution, presented with a new onset pruritic macular erythematous rash, progressive renal failure, and severe thrombocytopenia. His past medical history included myelodysplasia with a macrocytic anaemia, primary biliary cirrhosis, and a T cell rich B cell lymphoma, affecting the right cervical node and the anterior mediastinum. His lymphoma was successfully treated in 1998 with four cycles of rituximab and half doses of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). He had remained in complete remission up to the time of his presentation.

A physical examination on presentation showed extensive purpuric, macular, erythematous lesions across his chest and both of his legs extending to the ankles. His laboratory findings included an antinuclear antibody of 200 IU/ml in a centromeric pattern, a C1q immune complex assay of 69 µg (normal <4), and Raji cell assay for immune complexes of 275 µg Eq/ml (normal < 12 µg). No cryoglobulins were detected.

Platelet count was 39×10<sup>9</sup>/l (normal 150–450×10<sup>9</sup>/l), and serum creatinine was raised at 160 µmol/l. A diagnosis of immune complex vasculitis was made. Treatment with corticosteroids was started, but stopped after only one week owing to severe steroid psychosis. Because of his underlying bone marrow and hepatic disorders, the patient was treated with single agent rituximab (375 mg/m<sup>2</sup>) for eight weekly cycles. After rituximab treatment the skin pigmentation resolved and the platelet count rose to 76×10<sup>9</sup>/l. Serum creatinine decreased to 124 µmol/l. Both C1q and Raji cell laboratory values returned to normal (table 1). Currently, seven months after rituximab treatment, he remains in complete remission.

### DISCUSSION

Patients with antibody mediated autoimmune disorders usually respond to treatment with glucocorticoids or cytotoxic treatment, or both.<sup>1–3</sup> Patients who are refractory or intolerant to the initial therapeutic regimens have a poor prognosis. Rituximab can effectively deplete CD20 positive B lymphocytes for 6–9 months<sup>4</sup>, and consequently offers a novel therapeutic approach to a variety of autoimmune diseases. Moreover, rituximab is well tolerated and has a toxicity profile limited to relatively rare allergic reactions.<sup>6</sup>

B Lymphocytes have been shown to react with many self antigens. There is also evidence that some autoantibodies may drive their own production. It has been suggested in studies of rheumatoid arthritis that a subset of rheumatoid factors may stimulate the survival of B lymphocytes producing the same autoantibodies.<sup>12</sup> Agents that exclusively target B cells might therefore disrupt autoantibody production. However, despite effective elimination of nearly all peripheral CD20 positive B lymphocytes by rituximab, the total levels of serum IgG and IgA immunoglobulins remain unchanged for prolonged periods, with only moderate and early declines in IgM.<sup>13</sup> Therefore, the exact mechanism by which rituximab interferes with the full spectrum of B cell autoimmunity is still not known.

In this report we describe the therapeutic effects of rituximab in three patients with different antibody mediated autoimmune diseases. To our knowledge, similar cases have not previously been reported. Zaja *et al* successfully used rituximab in a patient with HCV induced type II mixed cryoglobulinaemia.<sup>14</sup> Rituximab has also been combined with chemotherapy for the treatment of rheumatoid arthritis.<sup>15</sup>

In this report the clinical and laboratory parameters of all three patients remitted completely. The first patient with cryoglobulinaemia and the third patient with immune complex vasculitis probably shared an IgM mediated pathological process. The apparent success of rituximab treatment might have resulted from the depletion of IgM producing B cells. However, the patient with the Goodpasture's disease, had an IgG mediated autoimmune process. The mechanism of response in this instance is less clear and we cannot exclude

the possibility that her previous treatment contributed to the induction of her remission.

The duration of remission induced with rituximab treatment is unknown. Rituximab depletes the B lymphocytes for only 6–9 months.<sup>4</sup> Therefore, repeated or maintenance rituximab treatment with or without other cytotoxic agents may be required in some patients for a sustained remission. However, without a clear understanding of the mechanisms responsible for the therapeutic efficacy of rituximab, it is not possible to predict fully the duration of our patients' remissions.

In conclusion, this report indicates that rituximab may be an important therapeutic agent in certain autoimmune diseases. We suggest that the precise role of rituximab should be further defined in properly designed clinical trials for de novo as well as refractory antibody mediated autoimmune disorders.

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