CASE REPORT

Anti B cell targeted immunotherapy for treatment of refractory autoimmune haemolytic anaemia in a young infant

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We report the case of an 8 week old infant with fulminant autoimmune haemolytic anaemia refractory to conventional immunomodulating treatment. Massive haemolysis resulted in cardiac decompensation and acute renal failure which necessitated mechanical ventilation and peritoneal dialysis. Rituximab, a chimeric anti-CD20 monoclonal antibody, halted progression of the haemolytic process, but the patient died of acute viral pneumonia and disseminated fungal infection. Earlier introduction of rituximab might have prevented the renal complications. Paediatricians should be aware of this useful therapeutic tool for treatment of refractory autoimmune haemolytic anaemia and balance its use against the risk of potential life threatening infection.

Haemolytic anaemia in early infancy is often a result of blood group incompatibility, hereditary red cell morphological disorders such as congenital spherocytosis and elliptocytosis, and in certain Mediterranean and Asian regions, red cell enzyme abnormalities, including glucose-6-phosphate dehydrogenase deficiency.¹ Autoimmune haemolytic anaemia is an infrequent cause of haemolysis in the first six months of life. This condition is often refractory to conventional immunosuppressive treatment and may run a fulminant course, resulting in severe haemolysis and development of associated life threatening complications.^{2–4} We recently encountered a severe case of idiopathic autoimmune haemolytic anaemia in a young infant who was resistant to high dose corticosteroids and intravenous immunoglobulin (IVIG), and developed acute renal failure secondary to haemoglobinuria after an emergency exchange transfusion. Rituximab, a monoclonal antibody against CD20⁺ B lymphocytes, halted progression of the haemolytic process, but the patient died of acute viral pneumonia and disseminated fungal infection.

CASE REPORT

An 8 week old male infant with uneventful perinatal history and thriving on breast milk was found to have fever and signs compatible with upper respiratory tract infection 48 hours prior to hospital admission. On examination, he was found to be pale, icteric with hepatosplenomegaly, but with no generalised lymphadenopathy. Haemoglobin, reticulocyte count, haptoglobin, and serum bilirubin were 71 g/l, 11%, <0.2 g/l (normal range 0.33–1.71 g/l), and 64 µmol/l, respectively. Direct Coomb's test was positive. Urine microscopy did not reveal red blood cells, but multistix testing was strongly positive for blood, indicating haemoglobinuria.

A diagnosis of idiopathic autoimmune haemolytic anaemia was made, and the patient started on high dose methylprednisolone (5 mg/kg/day) and IVIG (1 g/kg/day for five days).

Despite potent immunosuppression, haemolysis continued and the haemoglobin dropped to 35 g/l within 36 hours of admission. The infant required daily blood transfusion (10–40 ml/kg) to maintain a haemoglobin around 50–70 g/l.

Six days later, the haemolytic process suddenly became accelerated and the haemoglobin fell to 19 g/l. There was acute cardiac decompensation with left ventricular dilatation, and the infant developed adult respiratory distress syndrome requiring positive pressure ventilation and emergency exchange transfusion. Although the latter procedure was carried out slowly over an eight hour period, massive haemolysis continued and resulted in gross haemoglobinuria, acute renal insufficiency with anuria, hyperkalaemia (7.0 mmol/l), and severe metabolic acidosis (pH 6.70, base excess –33.8 mmol/l).

Peritoneal dialysis was commenced immediately after the exchange transfusion and continued for six days. In view of treatment failure and the severity of haemolysis, rituximab (Mabthera, Roche, Basel, Switzerland) was started; two doses (375 mg/m²/dose) were given within a seven day period. The haemolytic process was successfully suppressed, and haemoglobin stabilised at 70–100 g/l. Methylprednisolone was gradually tailed off during the following week. Subsequent flow cytometric analysis failed to detect CD20⁺ lymphocytes, and the requirement for blood transfusion decreased to once per week.

On day 20 of admission, while recovering from the acute episode, the infant developed high fever and respiratory failure, necessitating high frequency oscillatory ventilation (HFOV) and inhaled nitric oxide (iNO; maximum dose 40 ppm) treatment. Chest radiograph showed areas of new infiltrates consistent with pneumonia and two consecutive tracheal aspirate specimens were positive for respiratory syncytial virus (RSV). Endotracheal culture, urine culture, and blood cultures obtained from peripheral vein and indwelling central venous catheters grew *Candida albicans*. Despite maximal cardiorespiratory support and parenteral fluconazole, the patient died of multiorgan failure 28 days after the onset of illness. His parents refused postmortem examination. Figure 1 provides a schematic representation of the sequence of events.

Serological titres for influenza A and B, parainfluenza type 1–3, hepatitis B and C, Epstein-Barr virus, parvovirus, adenovirus, cytomegalovirus, RSV (titre on admission), and mycoplasma were not raised (<10). The infant showed positive direct Coombs test for polyspecific antihuman globulin (+++), anti-IgG (+++), and anti-C3d (+). The cold agglutinin titres for adult (1) cells, cord (1) cells, and patient's cells were 32, 16, and 64 (normal range 1–32), respectively.

Abbreviations: iNO, inhaled nitric oxide; IVIG, intravenous immunoglobulin; HFOV, high frequency oscillatory ventilation; RSV, respiratory syncytial virus

Figure 1 Schematic representation of the sequence of events of the patient following hospital admission. D, died; EX, exchange transfusion; H, heart failure; I, intravenous immunoglobulin treatment; P, RSV pneumonia; R, rituximab treatment; Re, renal failure; S, fungal septicaemia; T, blood transfusion.

Maternal blood was marginally positive for antinuclear antibody (80 (normal titre <40)), but negative for anti-DNA, anti-Ro, and anti-La antibodies. Serological tests for syphilis were also non-reactive.

DISCUSSION

Rituximab, a chimeric anti-CD20 monoclonal antibody, has been shown to be highly effective *in vitro* in destroying B lymphocytes using either human complement or antibody dependent cell mediated cytotoxicity. The drug action has also been reported to be equally efficient *in vivo*, as B lymphocytes became undetectable in peripheral blood after a single dose of drug.³ In view of its unique pharmacological property and highly selective action on CD20⁺ cells, rituximab has been chosen for treatment of various types of B lymphocyte mediated immune diseases, including non-Hodgkin lymphoma,⁶ myasthenia gravis,⁷ IgM related polyneuropathies,⁸ systemic lupus erythematosus,⁹ immune thrombocytopenia,^{10,11} and cold agglutinin disease.¹² Recently, anti-B cell targeted immunotherapy has been tried on patients with refractory autoimmune haemolytic anaemia with various degree of success.²⁻⁴ However, its use in newborn infants has not been reported. This case report describes our experience of using this new medication in a 2 month old infant with severe autoimmune haemolytic anaemia.

Despite the fulminant haemolytic process that was refractory to conventional immunosuppressive and immunomodulating agents in this infant, the response to rituximab was prompt and effective. Tolerance of drug treatment was good and there was no incidence of infusion associated adverse effects. The requirement for blood transfusion was dramatically reduced, and circulating CD20⁺ cells were no longer detectable in the circulation after two doses of drug. We suspected that the need for continuing infrequent blood transfusion was related to routine and frequent blood sampling in a small baby. Clinical signs suggestive of haemolysis, such as haemoglobinuria, hyperbilirubinaemia, and hyperkalaemia began to subside within 48 hours of starting

the drug. The effectiveness and rapidity of response to rituximab in this infant closely corresponded with those observed in older children and adults.²⁻⁴ It is possible that the earlier use of monoclonal antibody treatment in our patient might have prevented the massive haemolytic episode, acute cardiac decompensation, renal complications, and the need for peritoneal dialysis. Furthermore, this specific anti-B cell targeted immunotherapy might in future replace or shorten the duration of conventional immunosuppressive treatment, and thus minimise the side effects of these drugs. Although many reports did not indicate an overt increase in the incidence of infectious complications,^{2-4,13} our patient developed fulminant RSV pneumonia requiring HFOV and iNO, and disseminated fungal infection despite IVIG protection. It is possible that the use of high dose corticosteroids during the early phase of the disease and the depletion of circulating B lymphocytes contributed to increasing the risk of life threatening viral and opportunistic infections. Serious hepatitis B, parvovirus, and varicella zoster infections have been previously associated with patients receiving rituximab.¹⁴⁻¹⁶ The risks of prolonged B lymphocyte depletion and potential serious infection need to be balanced against the potential benefits of this new treatment.

Our experience supports the growing evidence that rituximab is capable of stopping red cell haemolysis in refractory autoimmune haemolytic anaemia. Tolerance of drug treatment appears to be good and the response is rapid and effective. Although rituximab induced immunosuppression is considered to be less severe than the cocktail of immunosuppressants, corticosteroids, and cytotoxic agents commonly used for treatment of this condition, the potential for life threatening viral and opportunistic infections is a major concern. As with any new treatment modality, the benefit of therapy must be balanced against the potential risk of serious adverse effects. Paediatricians should be aware of this new therapeutic tool for treating severe autoimmune haemolytic anaemia, but until there are more data on the safety of rituximab, anti-B cell targeted immunotherapy should be considered experimental. The exact role of rituximab in the

treatment of B cell mediated autoimmune diseases, the optimal dose, and the duration of drug treatment require to be properly defined by further clinical trials.

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