Anti-CD20 monoclonal antibody for the treatment of severe, immune-mediated, pure red cell aplasia and hemolytic anemia

Marco Zecca, Piero De Stefano, Bruno Nobili, and Franco Locatelli

Immune-mediated, acquired pure red cell aplasia (PRCA) is a rare disorder frequently associated with other autoimmune phenomena. Conventional immunosuppressive treatment is often unsatisfactory. Rituximab is a monoclonal antibody against the CD20 antigen, highly effective for in vivo B-cell depletion. An 18-month-old girl with both severe PRCA and autoimmune hemolytic anemia, refractory to immunosuppressive treatment, received 2 doses of rituximab, 375 mg/m² per week. The drug was well tolerated. After anti-CD20 therapy, substitution treatment with intravenous immunoglobulin was started. The treatment resulted in marked depletion of B cells; a striking rise in reticulocyte count ensued, with increasing hemoglobin levels, finally leading to transfusion independence. The child is now 5 months off-therapy, with normal hemoglobin and reticulocyte levels. This case suggests a role of anti-CD20 monoclonal antibody for treatment of patients with antibody-mediated hematologic disorders. (Blood. 2001;97:3995-3997)

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Study design

An 18-month-old Caucasian girl was hospitalized due to recent onset of pallor and listlessness. Physical examination at admission was unremarkable, with the exception of pallor and mild jaundice; the patient did not present either spleen or liver enlargement. Full blood count at admission showed normochromic-normocytic anemia (hemoglobin = 5.6 g/dL) with reticulocytopenia (absolute reticulocyte count = 7 × 10⁹/L) and normal white blood cell and platelet counts. Total and unconjugated bilirubin levels were increased (2.31 mg/dL and 1.77 mg/dL, respectively), and serum haptoglobin was undetectable. Tests for hereditary hemolytic anemias, as well as direct and indirect Coombs tests, were negative. Evaluation of the blood film revealed the presence of spherocytes, whereas erythrocyte fragments were not detectable. Serologic tests for parvovirus B19, human cytomegalovirus, and Epstein-Barr virus were negative. Chest x-ray was normal. A blood count performed 6 months earlier had shown normal hemoglobin (12 g/dL).

A bone marrow aspirate performed at admission demonstrated normal representation of myeloid and megakaryocyte precursors, but nearly absent erythroid precursors. In vitro cultures of patient light-density bone marrow cells, performed in triplicate as described previously, demonstrated that, by contrast, growth of the patient’s granulocyte-macrophage progenitors (CFU-GM) was normal. The patient’s plasma profoundly inhibited growth of BFU-E from healthy controls (93 ± 16 and 24 ± 6 without and with patient’s plasma), suggesting the existence of soluble serum factors responsible for both PRCA and hemolysis.

Due to a steadily decreasing hemoglobin level, the child was transfused. Repeated administration of red blood cell concentrates was required in order to maintain hemoglobin above 6 g/dL (Figure 1). In the following weeks, she remained transfusion-dependent, with erythrocyte consumption much higher than that compatible with hyporegenerative anemia (transfusion of 15-20 mL/kg of packed red blood cells every 5-7 days was necessary). In detail, during a period of 10 weeks, 13 erythrocyte transfusions were administered. Serum bilirubin levels remained above normal levels, whereas serum haptoglobin was constantly undetectable. Despite clinical and biochemical signs of continuing hemolysis, the direct antiglobulin test (DAGT), repeatedly performed during this time, remained
showed a striking rise in reticulocyte count, with a maximum value after the first infusion. Because a case of immune-mediated thrombocytopenia successfully treated with anti-CD20 MoAb, has been extensively reported in the literature, we reasoned that selective destruction of B cells producing antibodies in immune hemolytic anemia (AIHA) and autoimmune hemolytic anemia with concomitant antibody-mediated PRCA has been preliminarily reported with variable response.

In our experience, response to anti-CD20 infusion occurred 4 days after the first administration, and it was sustained, allowing discontinuation of all other immunosuppressive therapies. The rapid response and disappearance of B cells from peripheral blood suggested that 2 doses of monoclonal antibody might be sufficient, thus saving costs.

In conclusion, even though a longer follow-up is required to assess the long-term efficacy of this treatment, this case provides a basis for future prospective trials aimed at defining the role of anti-CD20 MoAb for antibody-mediated hematologic disorders.

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Figure 1. Clinical course of the patient and response to treatment. Reticulocyte count and hemoglobin levels are reported in the graph. Black circles represent red blood cell transfusion, tick marks represent immunoglobulin infusions, and rectangles treatment with corticosteroids and cyclosporine-A. Arrows show the 2 infusions of anti-CD20 monoclonal antibody.

References


Results and discussion

Treatment with rituximab resulted in marked depletion of B cells in peripheral blood, as demonstrated by the percentage of CD19⁺ and CD20⁺ cells dropping from the pretreatment values of 12% and 11%, respectively, to values less than 0.5% for both antigens 2 days after the first infusion.

Shortly after the first anti-CD20 MoAb infusion, the patient showed a striking rise in reticulocyte count, with a maximum value of 347 x 10⁶/L achieved 2 weeks after starting the treatment. Progressive increase of hemoglobin level and achievement of transfusion independence (Figure 1) followed the rise in reticulocytes. Bilirubin and haptoglobin levels normalized, as well. The course of the response was as expected and gave further support to a diagnosis of AIHA with concomitant antibody-mediated PRCA.

The child, 5 months after MoAb therapy, is transfusion-independent, with normal hemoglobin and reticulocyte levels. She is no longer receiving immunosuppressive treatment. The percentage of the patient’s B lymphocytes is still below 1%. During the observation period, the child did not develop any significant infectious complication.

As mentioned, so far only one case of immune-mediated thrombocytopenia, successfully treated with anti-CD20 MoAb, has been described to start from 6 to 9 months after the last administration; a normal B-lymphocyte number is usually achieved only 12 months after treatment discontinuation. A significant reduction in immunoglobulin M (IgM) and IgG serum levels is to be expected, with a possible risk of infectious complications, as recently reported. For this reason, we gave replacement therapy with intravenous immunoglobulins.

The outcome of childhood severe, immune-mediated, hematologic cytopenia with conventional immunosuppressive approaches is sometimes unsatisfactory. For this reason, the recent introduction of new immunomodulating agents, such as MoAbs approved for in vivo use, represents an appealing and promising treatment modality for patients with the most severe and/or refractory forms of disease. In refractory or chronic disease, use of rituximab is attractive also because it could reduce or avoid some side effects of prolonged therapy with steroids (eg, fluid retention, severe catabolic damage, hyperglycemia, avascular necrosis of bone, growth impairment) and/or other aspecific immunosuppressive drugs.

In conclusion, even though a longer follow-up is required to assess the long-term efficacy of this treatment, this case provides a basis for future prospective trials aimed at defining the role of anti-CD20 MoAb for antibody-mediated hematologic disorders.


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