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Successful use of rituximab in Evans syndrome and refractory immune thrombocytopenic purpura

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Case Report

Successful use of Rituximab in Evans syndrome and refractory immune thrombocytopenic purpura

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Abstract

Immune cytopenias are mediated by auto-antibodies produced by B-lymphocytes. Conventional treatment of immune-mediated haematological disorders includes immunosuppression with steroids and other immune modulating therapies and in some refractory cases, splenectomy. Response rates to conventional and second-line agents are variable and a proportion of patients require lifelong immunosuppression to maintain the disease in remission. Rituximab, an anti- CD 20 monoclonal antibody has gained widespread acceptance in the management of B-cell malignancies. Additionally, it has been used to treat the disorders associated with autoantibody production. We report herein the successful use of Rituximab in the treatment of two patients with autoimmune cytopenias one had Evan's syndrome and other had refractory immune thrombocytopenic purpura. Both of these patients are still in remission at 16 and 25 months following treatment.

Introduction

Autoantibodies directed against blood cells give rise to various haematological disorders. Immune thrombocytopenic purpura (ITP) is mediated by auto-antibodies against platelets leading to thrombocytopenia and mucocutaneous bleeding[1] while Evans syndrome is a rare disorder characterized by thrombocytopenia and auto-immune haemolytic anaemia (AIHA).[2] Commonly employed therapies for autoimmune cytopenias are usually corticosteroids and/or intravenous immunoglobulin. Other options like azathioprine, cyclosporine, vincristine, danazol or combinations of these agents are frequently used as second-line agents while splenectomy is indicated in relapsed or refractory cases.[3] However, current treatment regimens tend to be relatively non-selective in their mechanism of action and aim for generalized immunosuppression and may be associated with systemic toxicities.[2] Rituximab is a monoclonal antibody directed against CD-20 antigen present on B-lymphocytes. Although, Rituximab has been approved for various B-cell lymphoproliferative diseases, there has been growing experience in its use in other autoimmune diseases.[4] In this report, we describe, cases of Evans syndrome and refractory immune thrombocytopenic purpura successfully treated with Rituximab.

Case 1:

A 14-year-old girl presented with history of fever and menorrhagia. Physical examination revealed mild jaundice and petechial rash on lower extremities. Past history was significant for acute ITP six-months back that remitted after a course of steroids. At presentation, her blood count showed haemoglobin of 9.1 g/dL, platelets 25 x 10^9/L, and white cells 4.5 x 10^9/L. The peripheral blood film showed polychromasia, nucleated red cells and marked spherocytosis. The polyspecific direct anti globulin test was strongly positive and monospecific DAT was positive for IgG. Clinical chemistry revealed a raised indirect bilirubin 4.2 mg/dl, elevated lactate dehydrogenase 2880 IU/L and a raised positive titer of anti ds-DNA 14.8 IU/ml. The results of ANA (antinuclear antibody) were indeterminate. However, the diagnosis of SLE (systemic lupus erythematosus) was excluded on the basis of absence of systemic disease as well as a negative panel of extractable nuclear antibodies that includes anti-Ro, anti-RNP, anti-La and anti-Sm. There was no evidence of lymphoproliferative disorder either on CT scanning or on bone marrow biopsy. She

was diagnosed as Evans Syndrome and therapy was commenced with oral prednisolone at a dose of 1 mg/kg/day. After two weeks, the patient attained a partial response with platelet count of 58,000, however, a significant rise in haemoglobin was not seen. Subsequently, gradually tapering doses of steroids dropped her platelet counts and haemoglobin. No significant improvement was seen after the addition of second line agent, azathioprine. She persistently remained thrombocytopenic with platelet counts fluctuating between 5-10 x 10^9/L and she also required pack red cell transfusion on multiple occasions for correction of anaemia. Considering the refractory nature of the disease, she was given Rituximab at a dose of 375 mg/m^2 weekly for six consecutive weeks. After the first dose of rituximab, her haemoglobin and platelet count improved significantly from the baseline (haemoglobin 10.3 g/dL and platelets 79 x 10^9/L) and LDH and bilirubin also returned towards normalization enabling both cessation of transfusion support and weaning of the prednisolone dosage. After completion of sixth dose of Rituximab she attained haemoglobin of 11.1 g/dl and platelets of 132 x 10^9/L. Her prednisolone and azathioprine were tapered and stopped within 3 months. Currently at 16-months follow-up, her haemoglobin is 11.9 g/L and platelets 201 x 10^9/L with otherwise, normal bilirubin, LDH, reticulocyte count and a negative DAT

Case 2:

A 21-year-old girl presented with complaints of gum bleeding and petechial rashes. General physical and systemic examination was unremarkable except for purpuric rashes on the upper and lower limbs. She was a known case of chronic refractory ITP and was diagnosed in 2000. She has received multiple drugs in the past which included oral and intravenous steroids, azathioprine, intravenous immune globulin and cyclophosphamide. Splenectomy was done in 2001 considering the refractory nature of the disease. This time at presentation her platelet count was 3 x 10^9/L; other CBC parameters were within normal limits. Her direct antiglobulin test and ANA profile was negative. Considering her past history, she was offered a trial of Rituximab, and was started on weekly Rituximab at a dose of 375mg/m^2 for four consecutive weeks. Upon, completion of 4th dose of weekly Rituximab, her platelet count normalized to 235 x 10^9/L. Currently on 25-months follow-up she is maintaining a normal platelet count.

Discussion

The use of Rituximab is currently limited in autoimmune haematological disorders, partly because it is not an approved indication for the usage and also because of the cost as well. However, based on the encouraging results from various recent studies Rituximab has been successfully used in an off-label setting in a wide range of clinical disorders.[2]

Previous studies have reported a variable response to the use of Rituximab in Evans syndrome, as some have reported a success[5] while others have noted no appreciable response.[6] The complete remission rate with the use of Rituximab in Evans syndrome and ITP has been reported around 40% and 75% respectively, with no difference of responses seen between splenectomized and non-splenectomized patients.[7,8] The patients who responded to Rituximab and achieved complete remission have shown a median duration of remission of about 73 weeks.[9,10]

In this report, both patients met the criteria for a response as defined by the normalization of a rise in haemoglobin of at least 1.5 g/L from baseline and an absolute haemoglobin level above 10 gm/dL and platelet count >50 x10^9/L at least 1 month after completion of therapy.[7] The cases reported here add to the relatively sparse data on the use of Rituximab in Evans syndrome and immune thrombocytopenic purpura and based on the growing literature and experience with Rituximab, it should now be considered as an option in refractory auto-immune cytopenias.

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