Response of refractory ITP in a patient with common variable immunodeficiency (CVID) to treatment with rituximab

T M El-Shanawany, P E Williams, S Jolles
Department of Immunology, University Hospital of Wales, Cardiff. CF14 4XW.

Abstract

CVID is the commonest serious antibody deficiency in adults. There are a number of associated complications including autoimmunity, of which immune thrombocytopenic purpura (ITP) is a relatively common example. ITP usually responds to treatment with corticosteroids, other immunosuppression, splenectomy or high dose intravenous immunologlobulin (IVIG). The management of ITP refractory to these treatments remains challenging. We report a patient with CVID who developed ITP and remained platelet transfusion dependent despite high dose IVIG and splenectomy. Treatment with rituximab resulted in normalisation of the platelet count and the patient remains transfusion independent at one year following rituximab therapy.

Take Home Messages

Autoimmune diseases, ITP in particular, often complicate CVID.
Rituximab can successfully treat ITP in the setting of CVID where other treatment modalities have failed.
There may be recurrence of ITP following successful treatment with rituximab, after a variable period of time from months to years.
Whether re-treatment with rituximab at this stage is effective needs evaluating.

Case Report

A 65 year old woman was referred following the discovery of pan-hypogammaglobulinaemia on investigation for recurrent sinus and chest infections (IgG 0.6g/l; IgA 0.16g/l; IgM 0.44 g/l). Other causes of immunodeficiency were excluded and a diagnosis of CVID made. IVIG was commenced and the sinus and chest symptoms markedly improved. Eleven months after the diagnosis she presented with a purpuric rash affecting her legs and blood blisters in her mouth. Examination was otherwise unremarkable and a full blood count (FBC) demonstrated severe thrombocytopenia (platelets 4×10^9/l; haemoglobin (Hb) 13.1g/l; white cell count (WCC) 5.0×10^9/l; neutrophils 1.15×10^9/l). Bone marrow examination revealed a slightly hypocellular marrow felt to be consistent with her age but with slightly increased numbers of megakaryocytes. A diagnosis of ITP was made. She received a platelet transfusion and was treated with high dose IVIG (Octagam 30g daily for five days). Her platelet count improved and a month later was 93×10^9/l. Shortly afterwards, a second episode of thrombocytopenia again responded to high dose IVIG. There was no corresponding

improvement of her neutropenia, but she remained clinically well on replacement dose IVIG and prophylactic amoxicillin.

Her thrombocytopenia recurred three years later (platelets 3×10^9/l). She also remained neutropenic (0.8×10^9/l). Steroids were not tried at any point in the treatment of her ITP as the patient refused to take steroids due to her fears of side effects. On this occasion high dose IVIG failed to provide a lasting improvement to her platelet count and she remained on 30g of Octagam twice weekly and required frequent platelet transfusions. She was referred for splenectomy and this was performed 3 months later. In the lead up to the splenectomy she received granulocyte colony stimulating factor (GCSF) which successfully reversed her neutropenia during the peri-operative period. The operation was performed without complication and she made a good recovery. However, no improvement in platelet count occurred following splenectomy and she remained platelet transfusion dependent, despite continued 30g Octagam twice weekly.

High levels of platelet bound immunoglobulin were demonstrated by direct platelet immunofluorescence using flow cytometry (PIFT-FC). The presence of platelet autoantibodies was therefore likely, though the target antigen was not delineated as her serum was negative when assayed against GP IIb/IIIa and GP Ia. Granulocyte specific IgG was also present in the patient's serum against three out of three donor panel cells.

She received a course of rituximab (375mg/m^2 once weekly for four weeks) which was tolerated without any ill effects. Within a month of completion of the rituximab course she was transfusion independent and had a platelet count of 170×10^9/l. The frequency of IVIG was gradually decreased to 30g every 3 weeks and a year later her platelet count currently runs around 200×10^9/l. The neutrophil count initially fell following rituximab therapy, and then rose back to a similar level as pre-rituximab. The most recent neutrophil count is 0.76×10^9/l. Repeat platelet immunology is now normal though granulocyte specific IgG persists. Figure 1 summarises the platelet and neutrophil counts over a 6 year period.

Discussion

Common variable immunodeficiency is a diagnosis of exclusion and describes patients with hypogammaglobulinaemia in whom secondary immunodeficiencies and primary immunodeficiencies have been excluded [1]. In addition to the increase in infections due to the immunodeficiency, there are a number of associated complications including autoimmune diseases of which ITP is one of the commonest. In one study of 248 patients with CVID, 56 patients were found to have autoimmune disease. Of these, 22 had ITP and 2 had autoimmune neutropenia [2].

ITP results from accelerated platelet destruction due to the presence of autoantibodies against platelet glycoproteins. Treatments for ITP include corticosteroids, and immunosuppressive agents such as azathioprine. High dose IVIG first established itself as an immunomodulatory agent in the treatment of ITP, though its use is usually limited to patients in whom corticosteroids have failed or who have clinical features of haemorrhage [3]. Splenectomy is often effective and results in a "cure" in up to 75% of patients [4].

Rituximab is an anti-CD20 humanised monoclonal antibody which causes temporary B cell depletion [5]. The mechanisms of action include complement activation, antibody

dependant cell mediated cytotoxicity and direct effects on B cells mediated via CD20 binding [6]. Rituximab is licensed for the treatment of B cell non-Hodgkin's lymphoma where it is used at a dose of 375mg/m^2 weekly for four consecutive weeks. Increasing interest is being shown in the use of rituximab for the treatment of autoimmune diseases where B cells/autoantibodies are suspected to play a role in the pathogenesis [7].

With regards to ITP, a number of studies have investigated the potential benefit of rituximab. The largest study of 57 adults achieved a response in 31 patients (18 patients had a complete response defined as a platelet count $>150 \times 10^9$/l and 13 had a partial response). Of those who had a complete response, most maintained the response at one year, but only two of the 13 who had a partial response maintained their response [8]. The duration of response over a longer term was assessed in a study of 24 paediatric patients with chronic ITP. Fifteen patients had a complete response, 6 of whom relapsed at time points varying from 3 to 18 months. The other 9 patients still had ongoing complete responses (6 had responses lasting more than 1 year, 2 had continued responses at 24 and 30 months) [9]. A case report of two patients with autoimmune thrombocytopenia and neutropenia who were treated with rituximab demonstrated sustained remission of thrombocytopenia in both patients but only one patient had resolution of neutropenia [10].

There are two case reports of rituximab being used to treat ITP associated with CVID. In the first, rituximab resulted in only a partial response and a rise in platelet count to around 40×10^9/l [11]. The second patient had both ITP and neutropenia in association with CVID. Following rituximab the platelet count rose to 130×10^9/l and the neutrophil count normalised. However, the patient remained on steroids at a reduced dose of 10mg/day [12].

This case report describes the successful use of rituximab to treat ITP in a patient with CVID. The platelet count remains at $>150 \times 10^9$/l one year following treatment though the neutropenia has persisted with neutrophil counts of around 0.8×10^9/l. The anti-platelet autoantibodies resolved but granulocyte specific IgG persisted. Why rituximab therapy led to the clearance of anti-platelet but not anti-granulocyte antibodies is not clear. Neutropenia has been associated with rituximab therapy [13], but in this case our patient's neutropenia predated rituximab therapy by some years and anti-granulocyte antibodies were present.

It is becoming increasingly apparent that rituximab has a place in the treatment of ITP, including when it is present in association with other conditions. The exact position of rituximab in treatment protocols it still to be determined but for now it is likely to be used when other treatment options have failed. Monoclonal antibodies are expensive and while rituximab is no exception, this has to be balanced against the cost of regular platelet transfusions and the health and fiscal costs which result from the long term use of steroids. A number of other questions remain such as whether the full dose of 375mg/m^2 used to treat B cell non-Hodgkin's lymphoma is also required for ITP, or whether a lower dose would still provide the same clinical benefit. The literature suggests that recurrence of ITP treated with rituximab should be expected, though after a variable time period lasting months to years. Whether re-treatment with rituximab at this stage is effective requires evaluation.

References

(1) Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). *Clin Immunol.* 1999;**93**:190-7.

(2) Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol.* 1999;**92**:34-48.

(3) Jolles S, Sewell WAC, Misbah SA. Clinical uses of intravenous immunoglobulin. *Clin Exp Immunol.* 2005;**142**:1-11.

(4) Kumar S, Diehn FE, Gertz MA, Tefferi A. Splenectomy for immune thrombocytopenic purpura: long-term results and treatment of postsplenectomy relapses. *Ann Hematol.* 2002;**81**:312-9.

(5) Reff ME, Carner K, Chambers KS, *et al*. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. *Blood.* 1994;**83**:435-45.

(6) Leget GA, Czuczman MS. Use of rituximab, the new FDA-approved antibody. *Curr Opin Oncol.* 1998;**10**:548-51.

(7) Kazkaz H, Isenberg D. Anti B cell therapy (rituximab) in the treatment of autoimmune diseases. *Curr Opin Pharmacol.* 2004;**4**:398-402.

(8) Cooper N, Stasi R, Cunningham-Rundles S, *et al*. The efficacy and safety of B-cell depletion with anti-CD20 monoclonal antibody in adults with chronic immune thrombocytopenic purpura. *Br J Haematol.* 2004;**125**:232-9.

(9) Wang J, Wiley JM, Luddy R, *et al*. Chronic immune thrombocytopenic purpura in children: assessment of rituximab treatment. *J Pediatr.* 2005;**146**:217-21.

(10) Faurschou M, Hasselbalch HC, Nielsen OJ. Sustained remission of platelet counts following monoclonal anti-CD20 antibody therapy in two cases of idiopathic autoimmune thrombocytopenia and neutropenia. *Eur J Haematol.* 2001;**66**:408-11.

(11) Carbone J, Escudero A, Mayayo M, *et al*. Partial response to anti-CD20 monoclonal antibody treatment of severe immune thrombocytopenic purpura in a patient with common variable immunodeficiency. *Ann N Y Acad Sci*. 2005;**1051**:666-71

(12) Mahevas M, Le Page L, Salle V, Cevallos R, Smail A, Duhaut P, et al. Efficiency of rituximab in the treatment of autoimmune thrombocytopenic purpura associated with common variable immunodeficiency. *Am J Hematol.* 2006;**81**:645-6.

(13) Chaiwatanatorn K, Lee N, Grigg A, *et al*. Delayed-onset neutropenia associated with rituximab therapy. *Br J Haematol*. 2003;**121**:913-8.