Case Report

Rituximab in the treatment of acquired factor VIII inhibitors

Adedayo A. Onitilo[1], Amy Skorupa[2], Asheesh Lal[5], Elizabeth Ronish[3], Richard J. Mercier[6], Rezwan Islam[1], John Lazarchick[4]

[1]Department of Hematology/Oncology, Marshfield Clinic-Weston Center, Weston, Wisconsin, USA; [2]Hematology/Oncology Division, [3]Department of Internal Medicine, and [4]Department of Pathology and Laboratory Medicine, Medical University of South Carolina, Charleston, South Carolina, USA; [5]Hematology/Oncology, Lexington Medical Center, West Columbia, South Carolina, USA; [6]Department of Hematology/Oncology, Marshfield Clinic, Marshfield, Wisconsin, USA

Acquired factor VIII inhibition secondary to antibody development is an uncommon phenomenon occurring at a rate of approximately one person per million each year (1). The exact etiology of this disorder remains unclear. In about half of the cases a precipitating event or condition is unidentifiable. Fifty percent of cases are associated with specific medical conditions (1), such as the postpartum period (2), haematologic and solid malignancies (3), drugs (1, 3), or autoimmune diseases, such as rheumatoid arthritis, autoimmune hemolytic anaemia, Graves disease, multiple sclerosis, or systemic lupus erythematosus (1, 3).

Treatment of factor VIII inhibitors consists of controlling bleeding and eliminating the inhibitor. Elimination of the inhibitor is usually achieved through long-term immunosuppression of antibody formation with steroid (4), cytotoxic agents, such as cyclophosphamide (4), cyclosporine (5), or combination chemotherapy, as well as intravenous immunoglobulin therapy (6). The inhibitor can disappear spontaneously without treatment (7).

Rituximab is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the cytoplasmic membrane of B-cell lymphocytes. Recently, it has been reported to be of therapeutic utility in patients with acquired factor VIII inhibitors, either alone or in combination with cyclophosphamide (8–10). We report our experience with rituximab in six patients with acquired factor VIII inhibitors. One patient had an extremely high factor VIII inhibitor level, 3075 Bethesda units (BU), and remains in durable remission 3 years after therapy with rituximab-based immunosuppression.

Correspondence to:
Dr. Adedayo A. Onitilo
Department of Hematology/Oncology
Marshfield Clinic-Weston Center
3501 Cranberry Boulevard
Weston, WI 54476, USA
Tel.: +1 715 393 1400, Fax: +1 715 393 1399
E-mail: onitilo.adedayo@marshfieldclinic.org

Received 17 May, 2006
Accepted after resubmission 8 June, 2006

Prepublished online June 14, 2006 doi:10.1160/TH-06–03–0183

Thromb Haemost 2006; 96: 84–7

Table 1: Summary of patient data.

Patient	1	2	3	4	5	6
Age/sex	24/F	71/F	75/F	76/M	54/F	73/M
Clinical presentation	Left leg and right arm compartment syndrome Epistaxis Easy bruising	Easy bruising Gastrointestinal bleeding	Upper extremity hematoma Bruising	Gastrointestinal bleeding	Retroperitoneal hematoma	Stoma bleeding
Associated condition	6 weeks postpartum Lupus anticoagulant	None	Bladder cancer Lung mass Lupus anticoagulant	Prostate cancer	None	Laryngeal cancer in remission Lupus anticoagulant
Factor VIII inhibitor titer (Bethesda units)	3075	39	250	112	68	11
Rituximab doses to maximum benefit (375 mg/m^2)	9	3	3	7	4	4
Concurrent or previous immunosuppressive therapy	Azathioprine Vincristine Cyclophosphamide Prednisone	Cyclophosphamide Prednisone	Cyclophosphamide Prednisone	Cyclophosphamide Prednisone	Cyclophosphamide Prednisone	Prednisone Solu-Medrol
Time to complete remission (weeks)	52	36	8	4	2	1
Duration of remission (months)	36	27	4*	21	5	22*

*Patients 3 and 6 both died of sepsis in remission with no detectable inhibitor and with normal factor VIII levels

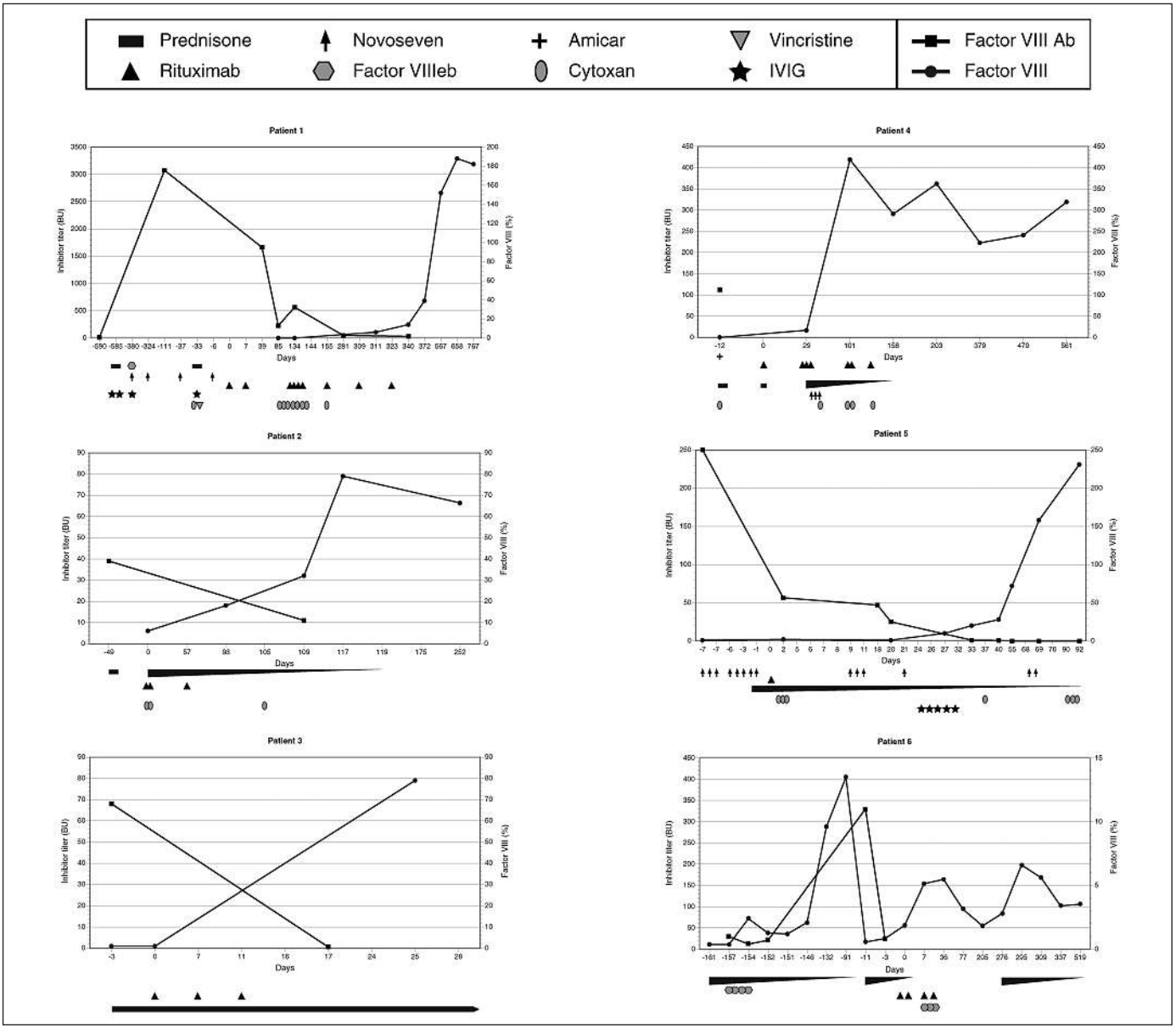

Figure 1: Course of patients 1–6.

Study design

Six patients from three institutions in the United States (Marshfield Clinic, Wisconsin, Medical University of South Carolina, and Lexington Medical Center, South Carolina) were diagnosed with acquired factor VIII inhibitors and treated with weekly infusion of rituximab 375mg/m^2. All patients received a brief course of other immunosuppressive drugs, including cyclophosphamide and prednisone, while one patient also received vincristine and azathioprine. Supportive therapy with recombinant factor VIIa and packed red blood cells were given to arrest acute bleeding. Factor VIII inhibitors were titered by the Bethesda assay. The dilute Russell's viper venom time test was used for lupus anticoagulant detection.

Results

Six patients, two males and four females, ranging in ages 24 through 76 years are presented. Major presenting symptoms included haematoma and mucosal bleeding. Peak inhibitor titer ranged between 11–3075 BU. The duration of inhibitor after rituximab administration ranged from 1 week to 12 months. Associated medical conditions included parturition, bladder cancer, lung mass, metastatic prostate cancer, and two spontaneous occurrences. Therapies given prior to or concomitant with rituximab included cyclophosphamide and prednisone, as well as vincristine and azathioprine in one patient. Three patients had concomitant lupus anticoagulant detected with factor VIII inhibitors. The response rate was 100% with duration of response between 21–36 months with no relapse to date. Two patients in remission died of unrelated causes (sepsis). No deaths were at-

tributed to inhibitor-related bleeding complications. There were two cases of thrombosis (patients 3 and 4). Patient 3 developed an upper extremity deep vein thrombosis following factor VIIa administration in anticipation for cystoscopy, when her factor VIII level was 158%. Patient 4, whose factor VIII was 419%, developed a deep vein thrombosis and subsequently a pulmonary embolus during hospitalization. In both instances the inhibitor titers were below detectable levels. The cases are summarized in Table 1 and Figure 1.

Discussion

We report our experience with six patients with acquired factor VIII inhibitors. Our results contribute to the body of emerging literature supporting the role of rituximab in the treatment of these inhibitors.

In our series of six patients, antibody titers dropped rapidly after initial treatment with rituximab-based therapy with very little requirement for costly replacement therapy of recombinant factor VIIa. The rate of reduction in the inhibitor titer, as well as the duration of inhibitor detection, revealed a dose-response relationship. An inverse pattern was seen between the peak inhibitor titer and the rate of resolution of inhibitor and between the duration of inhibitor detection after rituximab therapy.

Similar to other published reports, we noted a rapid reduction in the inhibitor titer with rituximab without any need for long-term maintenance immunosuppressive therapy (8, 11). Patient 1 from our series whose peak antibody level was 3075 received various strategies including plasmapheresis, immunosuppression with intravenous gamma globulin, steroid, azathioprine, and combination chemotherapy with cyclophosphamide, vincristine, and prednisone, and failed to induce antibody remission over 19 months. This patient ultimately achieved a durable complete remission with multiple doses of rituximab. Antibody was undetectable at 12 months from the initiation of the first rituximab dose. She has remained in remission at 36 months follow-up. Patient 2, contrary to previous reports, took 6 months to achieve an undetectable antibody level in spite of a more modest inhibitor titer (8, 11, 12).

Patient 6 initially responded to prednisone therapy alone, but the inhibitor reappeared 9 months later. He had a remarkable response to rituximab with disappearance of antibody within 1 week and remained in remission with an undetectable inhibitor titer until he died 22 months later of sepsis.

Uniquely, none of our patients have relapsed with a follow-up of over 36 months, including a patient with an extremely high antibody titer of 3075 before therapy with rituximab. Complete disappearance of antibodies and normalization of factor VIII were found in the two patients who died in remission of non-inhibitor related causes at 2 and 22 months, respectively. Of note, all our patients were treated with a short course of other immunosuppressive therapy. Stasi et al. (9) reported that complete response without relapse occurred in patients with an inhibitor titer >100 BU and three patients with inhibitor titers >100 BU had a transient partial response. All had complete and sustained response to combination therapy with rituximab plus intravenous cyclophosphamide.

Similar to other reports (8) lupus anticoagulant was detected concomitantly with factor VIII inhibitor in 50% of our patients (patients 1, 3 and 6). This may pose both a diagnostic and management dilemma. As in patient 1, who had bilateral limb amputation due to compartment syndrome, the coexistence of lupus anticoagulant and acquired factor VIII inhibitor is important to recognize. Treating the patient with anticoagulation may increase bleeding due to acquired factor VIII inhibitor, worsening compartment syndrome and limb jeopardy. Stasi et al. (9) reported three of 10 patients (30%) to have concomitant lupus anticoagulant. Two of these patients also tested positive for antinuclear antibodies with speckled pattern. Lupus anticoagulant and antinuclear antibodies were not detected 8 weeks after the last rituximab infusion.

Our case series showed rebound elevation in factor VIII level following therapy with rituximab. As in patient 4, this elevation can be extreme and quite protracted. Elevation of factor VIII has been associated with increased risk of venous thrombosis (13). In three of our patients factor VIII level peaked at 231%, 419%, and 405%. Two patients developed venous thrombosis during hospitalization for other unrelated medical conditions when their inhibitor levels were undetectable. Periodic monitoring of factor VIII levels post-rituximab therapy in patients with acquired factor VIII inhibitor in remission is very important. Appropriate prophylaxis for anticoagulation in thrombosis-prone patients should be considered during hospitalization.

Conclusion

We conclude that rituximab has both therapeutic and financial implications in the treatment of acquired factor VIII inhibitors. We would like to caution, however, that rebound elevation in factor VIII can occur months after the disappearance of the inhibitor at which point a greater risk of thrombosis rather than bleeding exists. Further studies need to be completed to define the effectiveness, safety, and cost benefits of rituximab treatment in acquired factor VIII inhibitors. The possible role of rituximab-induced immunosuppression leading to sepsis is an important consideration with this management approach.

Acknowledgements

The authors wish to thank Marshfield Clinic Research Foundation for its support through the assistance of Linda Weis and Alice Stargardt in the preparation of this manuscript.

References

1. Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, et al. Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. Br J Haematol 2003; 121: 21–35.

2. Michiels JJ. Acquired hemophilia A in women postpartum: clinical manifestations, diagnosis, and treatment. Clin Appl Thromb Hemost 2000; 6: 82–6.

3. Green D, Lechner K. A survey of 215 non-hemophilic patients with inhibitors to Factor VIII. Thromb Haemost 1981; 45: 200–3.

4. Green D, Rademaker AW, Briet E. A prospective, randomized trial of prednisone and cyclophosphamide in the treatment of patients with factor VIII autoantibodies. Thromb Haemost 1993; 70: 753–7.

5. Schulman S, Langevitz P, Livneh A, et al. Cyclosporine therapy for acquired factor VIII inhibitor in a patient with systemic lupus erythematosus. Thromb Haemost 1996; 76: 344–6.

6. Sultan Y, Kazatchkine MD, Maisonneuve P, et al. Anti-idiotypic suppression of autoantibodies to factor

VIII (antihaemophilic factor) by high-dose intravenous gammaglobulin. Lancet 1984; 2: 765–8.
7. Lottenberg R, Kentro TB, Kitchens CS. Acquired hemophilia. A natural history study of 16 patients with factor VIII inhibitors receiving little or no therapy. Arch Intern Med 1987; 147: 1077–81.
8. Wiestner A, Cho HJ, Asch AS, et al. Rituximab in the treatment of acquired factor VIII inhibitors. Blood 2002; 100: 3426–8.
9. Stasi R, Brunetti M, Stipa E, et al. Selective B-cell depletion with rituximab for the treatment of patients with acquired hemophilia. Blood 2004; 103: 4424–8.
10. Kain S, Copeland TS, Leahy MF. Treatment of refractory autoimmune (acquired) haemophilia with anti-CD20 (rituximab). Br J Haematol 2002; 119: 578.
11. Mathias M, Khair K, Hann I, et al. Rituximab in the treatment of alloimmune factor VIII and IX antibodies in two children with severe haemophilia. Br J Haematol 2004; 125: 366–8.
12. Aggarwal A, Grewal R, Green RJ, et al. Rituximab for autoimmune haemophilia: a proposed treatment algorithm. Haemophilia 2005; 11: 13–9.
13. Rosendaal FR. High levels of factor VIII and venous thrombosis. Thromb Haemost 2000; 83: 1–2.