Induction of tolerance after combined immunosuppression and -adsorption in two patients with acquired haemophilia after severe haemorrhages controlled by sequential administration of rFVIIa and FEIBA

Marcus Stockschläder¹; Leilani Ruf²; Anne Linderer³; Thomas Schroeder²; Wolfram T. Knoefel³; Rainer Haas³; Günther Giers¹; Andrea Gerhardz¹; Christoph Sucker¹; Rainer B. Zott¹; Rüdiger E. Scharf⁴

¹Department of Haemostasis and Transfusion Medicine, Heinrich Heine University Medical Center, Düsseldorf, Germany; ²Department of Haematology, Oncology, and Clinical Immunology, Heinrich Heine University Medical Center, Düsseldorf, Germany; ³Department of General Surgery, Heinrich Heine University Medical Center, Düsseldorf, Germany

A cquired haemophilia is a rare, clinically significant haemostatic disorder caused by spontaneous development of autoantibody antibodies (inhibitors) against factor VIII coagulant protein (FVIII:C) (1). There is a recognized association between development of acquired antibodies to factor VIII:C and a number of diseases, especially those with an autoimmune basis. Other risk factors include malignancy, certain drugs, pregnancy and the postpartum period (2–4). In about half of the cases, however, the inhibitor is idiopathic (5).

Circulating inhibitors to factor VIII:C may lead to an acquired haemostatic state and life-threatening bleeding complications. Fatality is high, reaching 22% in some series depending on age, inhibitor titer levels, and response to treatment (6–8). Patients in whom the inhibitor cannot be eliminated may have a mortality rate as high as 42% (8). Since the inhibitors have complex type 2 kinetics with a nonlinear inactivation of factor VIII:C making it difficult to saturate the inhibitor by adding antigen (2, 9), factor VIII:C substitution therapy is unsuccessful in the presence of high-titer inhibitors unless very high-dose factor VIII:C is given (10). Control of bleeding is usually achieved with FVIII bypassing activity such as activated prothrombin complex concentrates (aPCC; e.g. FEIBA) or recombinant factor VIIa (rFVIIa; e.g. NovoSeven). The primary objective for treating patients should be the safe and rapid elimination of the inhibitor and the development of long-term immune tolerance.

Here, we report two factor VIII inhibitor patients who presented with life-threatening bleeding complications and failed initial high-dose haemostatic treatment with NovoSeven. New bleeding complications were controlled by addition of FEIBA. After successfully reducing high-titer inhibitors by immunoadsorption, immunotolerance to endogenous factor VIII:C was achieved by combined immunosuppressive treatment with corticosteroids, cytotoxic drugs, and rituximab. Without administration of exogenous plasmic or recombinant factor VIII, the inhibitor disappeared and factor VIII:C activity returned to normal levels.

Case I
A 60-year-old male patient developed spontaneous macrohematuria. Since imaging of the abdomen revealed a polycystic mass in the left renal pelvis, he underwent laparotomy. Postoperative bleeding complications necessitated two surgical revisions. A subsequent thorough coagulation screen showed a significantly prolonged aPTT (92 seconds [sec]; normal range 29–37 sec) which was due to factor VIII:C activity of less than 1%. After obtaining a positive plasma mixing, quantitation of the factor VIII:C inhibitor revealed a titer of 36 Bethesda units (BU). For immediate control of bleeding, the patient was treated with NovoSeven (90 µg/kg body weight). Despite shortening of the administration intervals of rFVIIa (7.2 mg) to every three hours, the patient developed epistaxis and haematothorax necessitating the transfusion of altogether 20 units of packed red blood cells. While maintaining the rFVIIa dose, FEIBA (5,000 IE four times a day) was added (Fig. 1B). Bleeding complications subsided and the dose of rFVIIa was slowly tapered. Daily physical examination and laboratory investigations evaluating the platelet count, fibrinogen, and D-dimers did not reveal any signs of thromboembolic complications or disseminated intravascular coagulation. Concurrent immunosuppressive therapy consisted of prednisone (2 mg/kg body weight per day), cyclophosphamide (2 mg/kg body weight per day), and four weekly doses of rituximab (375 mg/m² BSA). Daily immunoadsorption (Ig-Thera-isorb, Miltenyi Biotec, Teterow, Germany; Sepharose CL-4B coupled with polyclonal sheep antibodies to human immunoglobulins; 25 sessions; processed plasma volume of approx. 7,000 ml) was performed to accelerate inhibitor elimination. Factor VIII:C activity increased steadily and remained within the normal range after discontinuation of immunosuppressive therapy (Fig. 1A).
Figure 1: Case 1. A) Time course of FVIII activity (%) and Bethesda units (BU) in patient 1. The time period during which immunoadsorption was performed is indicated as black bar with arrows. B) Type and amount (total daily dose in mg for rFVIIa and in IE for FEIBA) of FVIII bypassing agents.
Figure 2: Case 2. A) Time course of FVIII activity (%) and Bethesda units (BU) in patient 2. The time period during which immunoadsorption was performed is indicated as black bar with arrows. B) Type and amount (total daily dose in mg for rFVIIa and in IE for FEIBA) of FVIII bypassing agents.
Case 2
Two weeks after stopping interferon therapy (INF-β) for multiple sclerosis, a 60-year-old white male developed persistent pain in the right arm which was assumed to be caused by a thrombotic event and treated with low-molecular-weight heparin (LMWH). Because of worsening pain and additional haematomas, magnetic resonance tomography of the arm was performed which showed a deep haematoma causing the patient’s discomfort. A detailed analysis of coagulation parameters showed a prolonged aPTT of 86 sec due to a factor VIII:C activity of less than 1%. Determination of the factor VIII:C inhibitor activity revealed a titer of 30 BU (Fig. 2A). For immediate control of haemorrhage, the patient was treated with NovoSeven (90 µg/kg body weight). After initial bleeding control, the patient developed new haematomas and rectal bleeding resulting in a significant drop in haemoglobin levels necessitating transfusion of altogether 16 units of packed red blood cells. Despite shortening of the dosing interval of rFVIIa (7.2 mg) to every three hours, FEIBA (initially 5,000 IE four times a day) had to be added to control bleeding (Fig. 2B). Subsequently, the dose of rFVIIa was slowly tapered.

No thromboembolic complications occurred. Concurrent immunosuppressive therapy consisted of prednisone (2 mg/kg body weight per day), cyclophosphamide (2 mg/kg body weight per day), and four weekly doses of rituximab (375 mg/m² body weight). For immediate control of haemorrhage, the patient was treated with NovoSeven (90 µg/kg body weight). Determination of the factor VIII:C inhibitor activity revealed a titer of 30 BU (Fig. 2A). For immediate control of haemorrhage, the patient was treated with NovoSeven (90 µg/kg body weight). After initial bleeding control, the patient developed new haematomas and rectal bleeding resulting in a significant drop in haemoglobin levels necessitating transfusion of altogether 16 units of packed red blood cells. Despite shortening of the dosing interval of rFVIIa (7.2 mg) to every three hours, FEIBA (initially 5,000 IE four times a day) had to be added to control bleeding (Fig. 2B). Subsequently, the dose of rFVIIa was slowly tapered.

No thromboembolic complications occurred. Concurrent immunosuppressive therapy consisted of prednisone (2 mg/kg body weight per day), cyclophosphamide (2 mg/kg body weight per day), and four weekly doses of rituximab (375 mg/m² BSA). Immunoadsorption (Ig-Therasorb; 25 sessions, processed plasma volume of 7,000 ml) was started. Factor VIII:C activity increased steadily and remained within the normal range after discontinuation of immunosuppression (Fig. 2A).

Discussion
Three treatment aspects of acquired haemophilia are of utmost importance: haemostatic control of acute bleeding episodes, immunosuppression to stop production of inhibitory antibodies, and induction of immunotolerance to endogenous FVIII:C. Treatment of bleeding complications in inhibitor patients requires the use of agents which can bypass the need for FVIII:C to generate thrombin. Currently, two such agents are available. FEIBA VH (Baxter, Glendale, CA, USA), an activated prothrombin complex concentrate (aPCC) has been used in patients with high-responding inhibitors for decades (11). In a recent retrospective survey of 34 patients with acquired haemophilia, an overall complete response rate of 86% with a typical dosage regime of 75 IU/kg FEIBA given every 8–12 hours (h) has been reported (12). A dose of 200 IU/kg within a 24-h period should not be exceeded, however, to avoid thromboembolic complications. The incidence of adverse events in 4.05 per 10^5 applications over a 10-year period indicates that thrombotic complications associated with FEIBA use are rare (13). Recombinant factor VIIa (NovoSeven, Bagsvaerd, Denmark) is also highly effective in controlling bleeding with a reported efficacy rate of 80% – 90% (14, 15). There are published case reports of arterial thrombosis associated with the use of rFVIIa (16, 17). Between 1996 and 2002 more than 600,000 doses (90 µg/kg) of rFVIIa have been given while only 21 thrombotic events occurred (18). The recently published FEBIA NovoSeven Comparative Study (FENOC) (19) demonstrated that FEIBA and NovoSeven appeared to have similar effects on joint bleeds evaluated 6 h after treatment for 96 bleeding episodes in inhibitor patients with congenital haemophilia. Patients with acquired haemophilia may develop bleeding refractory to monotherapy with either rFVIIa or FEIBA. The different mechanisms of action provide a theoretic foundation for interindividual as well as intraindividual variation in the clinical efficacy between the two agents (20, 21). Laboratory evidence of additive effects of FEIBA and rFVIIa has been published (22). However, treatment with a combination of these agents is not widely practiced due to concerns for the development of thromboembolic complications (23–25).

High-titer factor VIII autoantibodies have been efficiently eliminated by intensive large-volume immunoadsorption (26, 27). Currently, two columns are available: Immunosorba (sepharose-bound staphylococcal protein A) and Ig-Therasorb (sepharose-bound polyclonal sheep antibodies to human immunoglobulin). Immunoadsorption removes anti-factor VIII:C antibodies with high efficacy (inhibitor titer reduction of 70 – 90%) (26, 28, 29). The procedure is generally well tolerated. Mild side effects were reported in less than 1% of treated patients (28, 30, 31). Since specialized equipment and expert technical knowledge are required to perform immunoabsorption, the method is restricted to specialized centres. In most cases, immunoadsorption has been used as part of multimodal immunomodulating therapeutic concepts for long-term inhibitor eradication, such as the Bonn-Malmö Protocol which also includes factor VIII:C substitution, administration of intravenous immunoglobulin, and immunosuppression (28). As in the presented cases, immunoabsorption has also been used as part of salvage therapy of otherwise refractory bleeding due to acquired haemophilia. In this setting, immunoabsorption was reported to lead to a rapid and significant decrease of inhibitor titres, improved levels, recovery and half-life of factor VIII:C, and cessation of bleeding. Thus, immunoabsorption should be considered for treatment of acquired haemophilia, particularly when a fast inhibitor titer reduction is necessary (32). It should be remembered, however, that unsatisfactory responses to immunoabsorption have also been reported in patients with acquired haemophilia (33).

In contrast to the recently published series of 35 patients treated according to the modified Bonn-Malmö protocol (28), our patients were not substituted with FVIII:C concentrates. We reasoned that since immunoabsorption leads to elimination of anti-FVIII:C autoantibodies and a fast increase in factor VIII:C activity, recovering endogenous factor VIII:C might trigger the elimination of autoreactive cell clones by mechanisms such as Fas mediated cytotoxicity (34) and induced biosynthesis of anti-idiotypic antibodies (35). Autoreactive cell clones stimulated by FVIII:C are likely to have a faster cell cycle and to become more sensitive to immunosuppressive drugs. Apart from the usual treatment with corticosteroids combined with cytotoxic agents, case reports have indicated that off-label use of rituximab may offer an additional option for managing otherwise unresponsive cases of acquired haemophilia (36). Rituximab, a chimeric monoclonal antibody targeting the CD20 antigen on B cells, eliminates autoreactive B-cell clones by inducing apoptosis primarily in pre-B-cell clones (37–40). The use of rituximab has been considered in cases where patients prove resistant to first line therapy or in patients in whom steroids and/or cytotoxic drugs are contraindicated. Cases of fatal progressive multifocal leukoencephalopathy have been reported following off-label use of rituximab for the treatment of certain autoimmune diseases, however.
These two case reports are remarkable in many respects: (i) They demonstrate that although both patients were immediately treated with increasing doses of rFVIIa to control bleeding, breakthrough bleedings necessitating transfusion of packed red blood cells occurred. (ii) In such severe cases, addition of activated prothrombin complex concentrate (FEIBA) may lead to prompt haemostatic control. (iii) Despite the combined use of two activated FVIII bypassing agents, thrombocytoblastic events do not necessarily occur. (iv) Immunoadsorption led to rapid and efficient decrease of inhibitor levels. (v) Tolerance to endogenous FVIII:C was induced by immunomodulation (corticosteroids, cyclophosphamide, and rituximab) resulting in rapid recovery and sustained levels of FVIII:C activity. (vi) Exogenous plasmic or recombinant FVIII:C might not be necessary to induce tolerance.

References


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