Successful long-time treatment with mycophenolate-mofetil in a child with acquired factor VIII inhibitor

C. Wermes1; C. Niekrens2; K.-W. Sykora1
1Department of Paediatric Haematology and Oncology, Medical School Hannover, Germany; 2Klinik für Kinder- und Jugendmedizin, Klinikum Delmenhorst, Germany

Case report

Successful long-time treatment with mycophenolate-mofetil in a child with acquired factor VIII inhibitor

E-mail: wermes.cornelia@mh-hannover.de

Summary

Here, we report about a boy (age: 18 years) who developed an acquired factor VIII inhibitor at the age of 9 years. He presented with bleeding in his right ankle, multiple haematomas and a high-titer factor VIII type II inhibitor (400 BU). Therapy: He received treatment with MMF (CellCept®), dexamethasone-immunglobulin pulses, and rituximab together with high dose FVIII (Hannover protocol). His inhibitor titer decreased rapidly, and half-life and recovery normalized. Inhibitor titres increased after reduction of the factor VIII dose, and increased further after MMF was stopped. A second treatment course with MMF again resulted in reduction of the titre, improvement in half life and recovery, and no more bleedings. Inhibitor reappeared with MMF dose reduction, again accompanied by severe bleeding. Additional rituximab stopped the bleedings, and treatment with MMF has been continued since. Conclusion: Although the laboratory parameters showed no complete remission, severe bleedings and expensive factor replacement could be avoided by long-term treatment with MMF.

Schlüsselwörter

Erworbene Hämophilie, Faktor-VIII-Inhibitor, Mycophenolat-mofetil, Immunsuppression

Zusammenfassung


Acquired haemophilia is a rare but potentially life-threatening disorder with an estimated incidence of 0.2–1.0 cases per one million persons per year (12).

Excluding postpartum inhibitors, acquired haemophilia is a disorder of middle and older age and occurs equally in both sexes (1).

The bleeding pattern is quite different from that observed in congenital haemophilia and in general the family and personal history are negative for bleeding symptoms. Major bleeding occurs in most of the patients (65.5%) and is either spontaneous or secondary to trauma or surgery (1, 2). The mortality rate has been estimated to be in the range of 7.9% to 22% (4, 7, 9, 13, 14, 16, 19, 22). The typical bleeding patterns include bleedings of

● the skin,
● the soft tissues,
● the muscles, and
● mucous membranes (e.g. epistaxis, haematuria, and gastrointestinal bleeding).

Also, postpartum haemorrhage can occur. In contrast to congenital haemophilia joint bleeding has been described in only a minority (3,9).

The disease is caused by an autoantibody directed against factor VIII, frequently due to an underlying autoimmune condition, malignant disorder, certain drugs, or pregnancy, leading to a reduction of factor VIII levels (1, 6). In about 50% idiopathic factor VIII inhibitors have been described (12). In contrast to inherited haemophilia these patients typically have type II inhibitors characterized by non-linear inactivation. Factor VIII baseline levels are often higher than 1% even in the presence of high titre inhibitory antibodies (17).
The occurrence of acquired factor VIII inhibitors in children is very rare (12, 18). Lupus antibodies should be taken into account in the differential diagnosis because they also show a prolonged aPTT and reduced factor VIII levels, typical laboratory parameters for acquired haemophilia (17).

Treatment includes the first, the haemostatic management of bleeding and second, inhibitor eradication. Underlying immune disorder should be treated in addition.

Bleeding episodes can be treated by bypassing agents as recombinant factor VIIa (NovoSeven®) and/or a factor eight inhibitor bypassing activity (FEIBA®). Both agents have been shown to be efficacious in acquired haemophilia (5). Whereas in adults, immunosuppressive treatment, including steroids alone or in combination with cyclophosphamide (10), high-dose immunoglobulins, cyclosporine, and/or rituximab is established (8, 11), no standard treatment schedules are available in the paediatric patient group. Mycophenolate-mofetil (MMF, CellCept®) is an immunosuppressive drug of interest in inhibitor treatment because of its T- and B-cell inhibitory action. It was successfully used in a patient with acquired haemophilia in combination of plasma exchange, corticosteroids, and cyclophosphamide (20). In addition, experience with MMF exists in the Hannover protocol which is used to treat children with refractory inhibitors in congenital haemophilia B (15, 21).

**Case report**

The boy (age: 18 years) developed an acquired factor VIII inhibitor at the age of 9 years presenting with a bleeding in his right ankle and multiple hematomas. He was found to have a high-titer factor VIII inhibitor (400 BU). The relapse of a preexisting treatment-resistant nephrotic syndrome was diagnosed at the same time. In addition, he suffered from asthma, atopic dermatitis, adipositas, and psychomental retardation. Congenital haemophilia A has been excluded by molecular genetic analysis. His personal and family history has been negative for bleedings. Because of psychosocial problems, treatment with immuno-adsorption was not performed. Due to his adipositas, prednisone has not been given, too. To avoid post-treatment infertility and to reduce the risk for second malignancies, cyclophosphamid was also not chosen in his first-line therapy.

**Therapy**

He received an alternative immune tolerance therapy (ITT; Hannover protocol) which has been described to be effective in haemophilia B patients with inhibitors. The ITT ([Fig. 1](#)) includes MMF (CellCept) and dexamethasone-immunoglobuline pulses followed by rituximab. High dose FVIII was continued during the whole treatment period. During the first days, the type II inhibitor decreased rapidly, and half life and recovery normalised. This success was only short-lived, possibly due to a reduction of the factor VIII dose. After MMF treatment has been stopped the inhibitor titre increased steadily, although the nephrotic syndrome disappeared. The therapy has been complicated by psychotic episodes, especially during the treatment with dexamethasone. Adipositas increased further and immunosuppressive therapy led to persistent localized skin infection (panaritium). Finally, due to septic complications this treatment was stopped.

**Fig. 1** Hannover protocol: treatment and results

---

Hämostaseologie 4a/2012 © Schattauer 2012
Further treatments including cyclosporin A, Campath-1H (alemtuzumab), additional rituximab, and the change of the factor VIII concentrate (plasmatic factor concentrate instead of recombinant FVIII) were not successful.

Finally, a further treatment trial with MMF (initially with additional factor VIII concentrate) was performed and was well tolerated (Fig. 2a). Although the inhibitor did not disappear completely, the titre decreased, half life and recovery of the substituted factor VIII normalised and no more bleedings occurred. Unfortunately, inhibitor reappeared when the dose of MMF was reduced (Fig. 2b). The relapse was accompanied by recurrent joint bleedings which was treated successfully with recombinant FVIII. An additional treatment with rituximab has been required to reach remission again (Fig. 2). One month after rituximab had been administered, CMV-reactivation occurred, but disappeared without treatment.

Three and a half years later the patient had stopped the treatment by himself. Again, a relapse occurred (Fig. 2) and he suffered from a severe bleeding into his left kidney. Recombinant factor VIIa as well as a FEIBA treatment failed. Additional immunosuppressive treatment with rituximab was necessary to stop the severe bleeding.

During the following immunosuppressive period the patient developed transient agranulocytosis and developed pneumonia which was treated with antibiotics. A bone marrow aspirate showed toxic changes. Treatment with MMF was paused for a few days and continued after recovery of granulocytes. Although the inhibitor titre was negative (Fig. 2b), laboratory parameters showed no complete remission. The factor VIII-levels were < 50% (Fig. 2a). However, clinically the patient had no bleeding.

Conclusion

In this patient, MMF was the most effective treatment of his acquired factor VIII inhibitor. The patient reached a partial laboratory and complete clinical response. The use of several other immunosuppressive agents – excluding rituximab – was less effective and accompanied by severe side effects. Efforts to taper MMF treatment resulted in relapses of the disease. Clinically, the patient suffered from multiple allergic or immune disorders that included allergic asthma, atopic dermatitis, and transient relapsing nephrotic syndrome. These conditions also responded to this treatment.

The combined T- and B-cell immunosuppressive effect and low toxicity of MMF may make it especially suitable for the treatment of antibody-mediated disease like acquired haemophilia.
Severe bleedings and expensive factor replacement could be avoided in this patient by using long-term treatment with MMF.

Conflict of interest
The authors declare, that they have no conflict of interest.

References