Successful eradication of a FVIII inhibitor in a 60-year-old patient with mild haemophilia A using single-agent prednisolone

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Specific eradication of a FVIII inhibitor in a 60-year-old patient with mild haemophilia A using single-agent prednisolone

Keywords
Mild haemophilia A, inhibitor, immunosuppression

Summary
Background: Development of FVIII inhibitors represents a major challenge in patients with mild haemophilia A (HA), because they tend to occur at an older age and classical immune tolerance induction appears to be less effective. Case report: A man (age: 60 years) with mild HA due to the missense mutation, Leu1929Arg, received a single dose of rFVIII at 35 IU/kg prior to routine colonoscopy, totaling 25 lifetime exposure days. Two months later, rFVIII was infused for a traumatic hip haematoma. However, FVIII recovery was inappropriate, and a FVIII inhibitor of 19 BU with type-2 kinetics was detected, resulting in FVIII:C of <1%. Two weeks later, the patient experienced spontaneous iliopsoas bleeding. Parallel to bypassing therapy, we started single-agent immunosuppression with prednisolone at 1.5 mg/kg. FVIII:C “normalized” itself on 10.2% after four weeks. After five months, the inhibitor titre fell to <0.4 BU with sustained remission after one year of follow-up. Conclusion: In mild HA, FVIII inhibitors may share characteristic features with FVIII autoantibodies commonly observed in acquired HA. Therefore, immunosuppressive therapy alone could be successful at least in a subset of patients.

Schlüsselwörter
Milde Hämophilie A, Inhibitor, Immunsuppression

Zusammenfassung

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Patients with mild haemophilia A (HA), defined as HA with residual factor VIII activity (FVIII:C) of 5–40%, generally have a relatively mild bleeding phenotype and rarely experience spontaneous haemorrhages. Standard treatment for minor bleeding or surgery includes the use of

● DDAVP (desmopressin) and

● antifibrinolytic agents.

Replacement therapy with clotting factor concentrate is required for major bleeding or surgery or in case of insufficient response to DDAVP.

These are reasons why patients with mild HA usually do not need regular factor concentrate replacement and why they might have only few lifetime exposure days at an older age (7).

Development of FVIII inhibitors represents a major challenge in these patients, because they tend to occur at an older age (10), at which significant co-morbidities may be present (e.g. atherosclerosis, renal insufficiency, pulmonary emphysema). Such co-existing medical conditions could potentially complicate treatment of acute bleeding events with activated bypassing agents and inhibitor eradication attempts.

Clinical presentation and risk factors for FVIII inhibitors in mild HA haven been summarized in a review by Franchini et al. in 2009 (7). In most patients, the bleeding phenotype changes from mild to severe, because the inhibitor is directed against both exogenous and endogenous (mutated) factor VIII, resulting in FVIII:C of <1%. This may lead to severe spontaneous bleeding into joints and skeletal muscles. In some patients, the bleeding pattern reminds of that observed in acquired haemophilia, i.e. muscle, soft-tissue, gastrointestinal, and urinary tract bleeds (9). Type-2 (non lin-
ear) inhibitor kinetics are observed more often than in patients with severe HA (5).

Only a few patients develop an inhibitor that is exclusively directed against exogenous factor VIII, so their own residual factor VIII activity level remains essentially unchanged (11). For these patients, bleeding treatment and surgery remain a challenge and can only be performed with DDAVP or bypassing agents.

Similar to severe HA, a genetic predisposition such as a positive family history appears to be a major risk factor for inhibitor development in patients with mild HA (1). In the latter, a high incidence for inhibitors was observed associated with specific missense mutations in the A2 domain of the heavy chain and around the C1-C2 junction of the light chain of the factor VIII gene. These mutations may cause conformational changes in the factor VIII molecule with distinct antigenic characteristics compared to wild-type factor VIII. Consequently, infused plasma-derived or recombinant factor VIII may be immunogenic in patients with mild HA and may induce production of inhibitory factor VIII antibodies. Typical mutations have been summarised by Franchini et al. (7) and Hay (9).

Another risk factor for inhibitor development may be the intensity and modality of factor concentrate administration. Especially in patients with mild HA, inhibitors were observed after intensive treatment periods with factor VIII concentrate for surgery or trauma. Continuous infusion seems to be an additional risk factor (13). However, overall inhibitor development seems to be less frequent in mild than in severe HA (9).

A variety of therapeutic options are available for the eradication of inhibitors in mild and moderate HA, including immune tolerance induction (ITI) and immunomodulating agents such as corticosteroids, cyclophosphamide, and the monoclonal CD20 antibody, rituximab. In 1998, Hay reported a series of 9 patients with mild and moderate HA undergoing attempted ITI (10). Of the nine patients, two and five patients achieved complete and partial responses, respectively. No response was observed in two patients. The two patients with a complete response were treated according to the Malmö protocol, which includes immunomodulating strategies, suggesting that immunosuppression may be an important factor for successful inhibitor eradication. There are several single-case studies and series reporting on immunosuppressive strategies with or without high-dose factor VIII. Franchini et al. (6) have summarized published cases, in which rituximab was used. Sixteen cases with mild or moderate HA have been reported with a response rate of 75% using rituximab in different treatment protocols with or without high-dose factor VIII and additional immunomodulating agents like IVIg or corticosteroids. In patients with severe HA, only 12 of 28 (43%) achieved a complete remission with disappearance of the inhibitor (6).

Currently available data, however, are not sufficient to offer evidence-based advice on the optimal treatment of inhibitors in patients with mild HA (3, 5), and management of these patients thus remains a controversial issue.

**Case report**

In January of 2011, a 60-year-old patient with mild HA due to the missense mutation, Leu1929Arg, received a single dose of recombinant human full-length FVIII (rFVIII) at a dose of 35 IU/kg of body weight in preparation for a routine colonoscopy, totalling 25 lifetime exposure days. At that time, FVIII:C and FVIII inhibitor were 9.5% and 0.5 Bethesda units (BU), respectively.

Two months later, the patient suffered a traumatic soft-tissue hip haematoma, for which he received immediate rFVIII replacement therapy with 35 IU/kg of body weight. However, FVIII recovery was inappropriate, and a FVIII inhibitor of 19 BU with type-2 kinetics was detected, resulting in FVIII:C of <1% (Fig. 1). Two weeks later, the patient was admitted due to spontaneous right iliopsoas bleeding (Fig. 2). Initial bypassing therapy with recombinant human FVIIa was switched to activated prothrombin complex concentrate (APCC), resulting in significant clinical improvement.

In parallel, we started single-agent immunosuppressive therapy with prednisolone at a dose of 1.5 mg/kg of body weight. FVIII:C increased to 4.1% after ten days and “normalized” at 10.2% after four weeks with an inhibitor of 3.6 BU still detectable (Fig. 1). However, after four months of treatment, the inhibitor titre fell to <0.5 BU. Stepwise reduction of the prednisolone dose was started after FVIII:C had risen to the patient’s former residual level.

**Fig. 1** Time course of factor VIII activity and inhibitor before, during, and after immunosuppressive therapy with single-agent prednisolone. The corticosteroid was started on February 24, 2011, at a dose of 100 mg. The dose was reduced to 50 mg at week 5 and subsequently tapered every week over the following two months. Follow-up was 11.5 months after the start of treatment.
(at week 5), and immunosuppressive treatment was eventually stopped at week 13 (Fig. 1). Apart from slight weight gain, ankle oedema, muscle cramps, and moderate dysthymia, no serious adverse events occurred. So far, after one year of follow-up after inhibitor detection and seven months after achieving a negative inhibitor titre, the patient has experienced no further bleeding complications and has not been re-exposed to exogenous FVIII.

Discussion

Overall, inhibitor development seems to be rare in patients with mild HA. However, for those patients whose bleeding phenotype changes from mild to severe, it can be a serious, sometimes life-threatening complication of factor VIII replacement therapy, which may prompt physicians to attempt inhibitor eradication. In this case, the advanced age of most patients and possible cardiovascular or other co-morbidities need to be carefully considered, because they may confer a higher risk of treatment-related adverse events.

Scarc data and no controlled clinical trials addressing this topic are available in the literature. Therefore, the treatment decision has to be based on the patient’s individual case history with specific attention to the current bleeding pattern and existing co-morbidities.

In patients with mild HA, FVIII inhibitors may share characteristic features with FVIII autoantibodies commonly observed in acquired haemophilia (10). Therefore, immunosuppressive therapy alone (i.e. without concomitant ITI using high-dose factor VIII) could be a promising treatment approach at least in a subset of patients. Shortly after inhibitor occurrence, our patient developed spontaneous iliopsoas haemorrhage (Fig. 2), which may be regarded as a typical bleeding complication in patients with acquired HA. In addition, we detected a factor VIII inhibitor with type-2 kinetics that neutralized both substituted, exogenous and the patient’s own, mutated factor VIII, thus showing striking similarities with an acquired factor VIII autoantibody.

The factor VIII missense mutation, Leu1929Arg, found in our patient has not been previously shown to confer a particularly high risk of inhibitor development (7, 9). Furthermore, no typical risk factors, such as intensive treatment periods, infections, or a positive family history, could be identified. Taken together, the pathophysiology of inhibitor development in our patient appeared to be characteristic of a “true” autoimmune disease, which made us consider initiating upfront immunosuppressive therapy.

In this regard, few cases have been published using rituximab or cyclophosphamide mostly in combination with corticosteroids and/or IVlg (4, 6, 8, 12, 14). To our knowledge, this is the first case report suggesting that single-agent prednisolone may be an efficacious and well-tolerated treatment option in some patients with mild HA and a positive factor VIII inhibitor.

Data on patients with acquired HA indicate that in about half of cases, the high mortality rate of up to 20% is due to infectious complications associated with intensive immunosuppressive therapy (2). As a result of clotting factor replacement during the 1970s our patient had positive tests for both hepatitis B and hepatitis C, but no evidence of active disease. Hepatitis B may be reactivated under intensive immunosuppressive therapy, especially, when rituximab is included in the regimen. This is why we started with single-agent prednisolone with the option to escalate immunosuppression by cyclophosphamide and/or rituximab with concomitant antiviral treatment in case of an insufficient response. However, with regard to the rapid increase of FVIII:C after 10 days and its “normalisation” at the patient’s former level after four weeks (Fig. 1), intensification of immunosuppression did not seem to be necessary. There were no serious treatment side effects. In particular, the patient did not experience any infectious complications. Until now there have been no further bleeding episodes, and the patient has not been re-exposed factor VIII.

Whether administration of plasma-derived or recombinant factor VIII will be safe again in our patient, or whether it will induce an anamnestic immune response with rapid reappearance of the inhibitor, remains speculative at the moment.

Conclusion

Inhibitors in mild haemophilia A are rare, and there is currently no standard treatment available. Since randomised clinical trials are difficult to conduct due to the heterogeneity of affected patients, treatment decisions have to be based on published single-case studies and smaller patient series.

In this regard, our report may provide valuable additional information to haemophilia healthcare providers. However, prospective registries or observational
studies are urgently needed to eventually derive stronger treatment recommendations for patients with mild haemophilia A and factor VIII inhibitors.

Conflict of interest
The authors stated that they had no interests that might be perceived as posing a conflict or bias.

References