Treatment of Factor VIII Inhibitors with Selective IgG Immunoadsorption – a Single Center Experience in 50 Patients with Acquired Hemophilia*

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Key Words
Acquired hemophilia · FVIII immune tolerance · MBMP protocol · Immunomodulation · Immunoadsorption

Summary
Background: Acquired hemophilia (AH) is a potentially life-threatening disease in which severe bleeding events lead to a mortality of up to 22%. In AH autoantibodies of the IgG subtype inactivate clotting factors. Although the incidence of this disease is low (1–3 per 106), the treatment cost can be immense due to long-term clotting factor substitution. The treatment should aim at a rapid and permanent elimination of autoantibodies and the induction of a new immune tolerance to prevent further bleedings.

Patients and Methods: 50 high-titer (>5 Bethesda Units(BU)/ml) AH patients were treated by the following protocol: i) inhibitor elimination via IgG immunoadsorption, ii) immunosuppression, iii) i.v. immunoglobulin, and iv) high-dose factor VIII substitution. Follow-up time ranged between 12 months and 7 years.

Results: A complete remission was achieved in 46 of 50 patients (92%). Neither bleeding nor therapy-associated mortality occurred after initiation of treatment. The median time to reach undetectable inhibitor levels was 3 days (95% CI 3–6 days), coagulation factors were given at a median of 15 days (95% CI 12–18 days). The median treatment duration was 17 days (95% CI, 14–20 days). Conclusions: IgG immunoadsorption allows for a fast and permanent inhibitor elimination, being the basis of the high immunomodulatory potency of our protocol which results in long lasting complete remissions in 92% of our patients.

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Schlüsselwörter
Erworbene Hemmkörperhämophilie · FVIII-Immuntoleranz · MBMP-Protokoll · Immunmodulation · Immunadsorption

Zusammenfassung


* Dedicated to Prof. Dr. Peter Hanfland, Bonn, on the occasion of his 65th birthday.
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Introduction

Acquired hemophilia (AH) is characterized by an acute onset of severe bleeding in nonhemophilic patients. With an incidence of 1–3 per million it is a rare condition [1]. In almost half of the patients the medical condition causing AH cannot be identified [1]. Bleeding events are induced by spontaneously occurring IgG autoantibodies (inhibitors) predominantly targeting factor VIII (FVIII). An approximately biphasic age distribution was found for the emergence of these inhibitors, with peaks in young adults (20–30 years) and in the elderly (60–80 years). In vitro FVIII inhibitors have complex type II pharmacokinetics showing a rapid and nonlinear inactivation of FVIII. Such kinetics makes it extremely difficult to achieve an inhibitor saturation by antigen addition. Therefore, FVIII substitution therapy is ineffective in the presence of high-titer inhibitors [2, 3].

A recently published meta-analysis by Delgado et al. [4] including 245 AH patients and focusing on various treatment regimens clearly demonstrated that patients with persistent inhibitors showed an increase of the mortality rate by up to 42%. Complications constitute the main problem in the treatment of AH. They are the result of extended bleeding, bleeding treatment such as surgery in cases of compartment syndrome, and transfusion-related reactions. Furthermore, infections due to prolonged chemotherapy occur, particularly in patients over 65 years [5, 6].

Various immunosuppressant agents (corticosteroids, azathioprine, cyclophosphamide) have been the treatment of choice in AH over the last 30 years [4], but those may require several months to act [7–9]. They are beneficial in low-titer patients (<5 Bethesda Units (BU)/ml), but commonly fail in high-titer AH (>5 BU/ml).

An optimal therapy of AH should primarily eliminate the inhibitor to protect patients from bleeding events and secondarily induce immune tolerance to regain normal hemostasis. The rapid elimination of the inhibitor will also prevent complications associated with long-term immunosuppression.

Immunoadsorption (IA) is an extracorporeal treatment with an antihuman IgG adsorber especially suitable for the rapid elimination of the inhibitor. It removes autoantibodies of all IgG subclasses, without affecting other plasma proteins. It is thus more selective than plasmapheresis and allows long-term intensive plasma treatment [10].

The present report is an update of our experience in treating severe cases of AH with IA.

Patients and Methods

Patients

Between 1998 and 2005, a series of 50 patients (20 males, 30 females) with AH and high-titer inhibitor to FVIII (>5 BU/ml) [11] were treated. Upon admission, all patients exhibited life-threatening bleeding that required blood transfusions. The FVIII level at initial diagnosis and at the beginning of the treatment was <1% of normal (70–140%). The types of bleeding observed included muscle bleeding (n = 45), which was associated with compartment syndrome (n = 4), retroperitoneal bleeding (n = 12), retropharyngeal bleeding requiring artificial respiration (n = 4), and hematuria (n = 3).

The mean age (±SD) of the patients was 63 ± 16.7 years (median age 68 years, range 28–81 years). Underlying diseases were detected in 15 patients. In 4 women the inhibitor was diagnosed peripartally (i.e. within 3 months of childbirth). Four patients suffered from another autoimmune disease (mixed connective tissue disease n = 2, psoriasis n = 4, polymyalgia rheumatica n = 1, Sjögren’s syndrome n = 1), and in 3 patients the inhibitor occurred as paraneoplastic syndrome (lung cancer n = 1, paraproteinemia n = 2, lymphoma n = 1).

Three patients who were diagnosed before 1998 initially received diverse conventional treatments and were subsequently treated by our protocol. Of the 50 patients that received the MBMP, 48 completed the treatment. In 2 patients, our protocol was interrupted in the 3rd or 12th treatment cycle due to co-morbidities (epileptic seizure, obesity). The novel treatment protocol was approved by the Ethical Committee of the Medical Faculty at the University of Bonn. All patients gave informed written consent.

Methods

The inhibitor analysis was performed using the Nijmegen modification of the Bethesda assay [12]. Differential diagnosis in relation to the lupus erythematosus-associated inhibitor was established with the dilute Russell viper venom test, lupus-activated partial thromboplastin time, the plasma dilution test, and determinations of FII, FV, FVII, FIX, FX and FXI. The FVIII levels were determined by two methods: the one-stage clotting assay and the chromogenic FVIII assay. Recombinant FVIIa (rFVIIa) was substituted in 10 patients to achieve an immediate reduction in bleeding diathesis during the patient’s transfer to our hospital.

Complete remission (CR) was defined as normal FVIII activity (70–140%) without factor substitution and undetectable inhibitor titer levels during a minimum follow-up period of 12 months. Partial remission (PR) was defined as attaining FVIII recovery by up to 30% and/or a reduction of the inhibitor titer to less than 5 BU/ml.

The treatment protocol was as follows:

i) large-volume IA (2.5–3 x total plasma volume on days 1–5),

ii) IV substitution (0.3 g/kg body weight (BW)/day, on days 5–7),

iii) immunosuppressive therapy with cyclophosphamide (1–2 mg/kg BW/day) and prednisolone (1 mg/kg BW/day) from day 1 until remission (dose reduction),

iv) administration of FVIII (100 U/kg BW or, in one exceptional case (BMI > 40), up to 200 U/kg BW) every 6 h.

The treatment was repeated several times, depending on the clinical response and on coagulation factor activity.

Our protocol incorporates elements of the previously reported Bonn Protocol [11], which emphasizes on immune tolerance induction, and the Malmo Protocol, which focuses on IA and immunosuppression [13], and was thus called the modified Bonn-Malmo Protocol (MBMP). Extracorporeal treatment was performed as described in detail elsewhere [10]. The target of processing was 2.5 times the plasma volume, and apheresis was continued for 5 days in each treatment cycle. A median plasma volume of 5,320 ml (range 3,500–9,500 ml) was used. After apheresis, either plasma-derived or human rFVIIa was administered. The FVIII dosage could be optionally reduced by 20% throughout the treatment cycle in cases with satisfactory clinical response (50–80% FVIII residual activity after 4–6 h). Treatment-related side effects due to concomitant chemotherapy were scaled as follows: 0 = no side effects, 1 = mild side effects (nausea, hair loss, loss of appetite), 2 = severe side effects (fever, infection, alopecia, neutropenia, thrombopenia), and 3 = sepsis. In the latter case MBMP was immediately halted.

Follow-up time ranged between 12 months and 7 years.
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Data Analysis
All statistical analyses were performed using SPSS, version 11.0 (SPSS, Inc., Chicago, IL, USA). Nonparametric statistics, the Spearman rank correlation (r(s)) and the Mann-Whitney U test were done. The primary study endpoints were the time of apheresis at which i) activity of the inhibitor was first undetectable, ii) the factor substitution was discontinued upon relevant normal FVIII activity levels for 24–48 h after a single 30 IU/kg BW FVIII dose, and iii) the MBMP treatment was terminated without the requirement for further apheresis. Kaplan-Meier analysis was performed to evaluate the time at which these endpoints were reached. The median time to reach these endpoints was calculated on the basis of the respective 95% confidence intervals (95% CI).

Results

Immunoadsorption
A total of 1,008 IA procedures (apheresis) were carried out with an average of 20 (range 3–62) apheresis sessions per patient. The extracorporeal treatment was well tolerated. Mild side effects such as hypotension, hypesthesia due to citrate anticoagulation (citric reactions) and allergic reactions occurred in less than 1% of all apheresis sessions and did not require an interruption of treatment. An average inhibitor reduction of up to 75% was achieved.

In patients without paraneoplastic syndrome, the number of apheresis sessions correlated with the inhibitor level (r(s) = 1, p = 0.0046).

Factor Substitution
The average amount of FVIII that had to be substituted during the MBMP to achieve CR in patients was 0.254 ± 0.5 × 10⁶ IU (median 0.152 × 10⁶ IU, range 0.013–1.87 × 10⁶ IU). Patients with PR received an average of 0.39 × 10⁶ ± 0.26 × 10⁶ IU (median 0.41 IU × 10⁶, range 0.1–0.7 × 10⁶ IU) FVIII concentrate. The FVIII substitution therapy correlated with the inhibitor titer and with the patient’s plasma volume (r(s) = 1, p = 0.002; r(s) = 1, p = 0.03). Ten of the MBMP patients required supplementary therapy with rFVIIa. A mean of 12 × 10³ ± 10.1 × 10³ kIU rFVIIa (median 10.50 × 10³ kIU, range 2.2–30.0 × 10³ kIU) was administered for a median duration of 4 days (range 2–7 days).

The time course of the development of the FVIII activity and the administered dosages of FVIII for one representative patient are shown in figure 1. This 64-year-old patient had a pre-treatment FVIII inhibitor titer of 374 BU/ml, and the inhibitor was eliminated before the third treatment cycle.

Clinical Outcome, Treatment Efficiency and Side Effects
Figure 2 indicates the time points at which undetectable inhibitor levels were achieved (fig. 2a), coagulation factor concentrates could be discontinued (fig. 2b), and a stable inhibitor elimination was achieved (fig. 2c). Three days (95% CI, 3–6 days), 15 days (95% CI, 12–18 days) or 17 days (95% CI, 14–20 days) were required to reach these endpoints. In 4 patients the MBMP induced PR with a median increase of the inhibitor levels to 2.3 BU/ml (range 1–4.5 BU/ml), resulting in a median FVIII recovery of 30% (range 27–35%). In 2 of these patients the treatment was interrupted as consequence of other concomitant diseases. One of these patients experienced remission 6 months later.

In 3 patients a malignant disorder with a poor prognosis was diagnosed during the course of the treatment. The improvement of blood clotting due to our protocol permitted these patients to undergo diagnostic steps for tumor staging, including pleurodesis, lymph node biopsy or mediastinoscopy without bleeding events.

The overall rate of CR was 92% (46/50 patients). When patients with underlying cancer were excluded, the CR rate was 97% (49/50 patients).
In all 50 patients the acute bleeding episodes were rapidly controlled within the first 2–3 apheresis procedures, and no subsequent episodes were encountered. Of the 50 patients, 42 tolerated the MBMP treatment very well, with only 1 patient experiencing moderate side effects such as nausea and slight hair loss. Five patients exhibited severe side effects (infection n = 6, neutropenia n = 1, mucositis n = 1) which were successfully managed by antibiotics.

During a long-term follow-up (median 54 months, range 12–86 months), there was no evidence of any inhibitor relapse in 48 patients. Two patients experienced a period in which FVIII declined to 10–50%, without any bleeding events 10 and 12 months after the initial MBMP treatment. Both patients had received a conventional therapy prior to our protocol treatment. These relapses were managed by apheresis for 5–6 days and by immunosuppressive therapy. The interventions succeeded in restoring normal FVIII levels, and the clinical condition of the patients remained stable over a follow-up period of 7 years. None of the patients died as a direct consequence of bleeding events. Seven patients died during long-term follow-up due to concomitant diseases that were not associated with AH.

Fig. 2. Treatment endpoints were rapidly reached in the MBMP group. Kaplan-Meier plots of a median time to reduce inhibitor to undetectable levels = 3 days (95% CI 3-6 days), b median time of factor substitution = 15 days (95% CI 12-18 days) and c median time of treatment = 17 days (95% CI 14-20 days). The abscissa shows time in apheresis days. Numbers above the Kaplan-Meier curves represent patients concluding the protocol within the corresponding time period. Vertical excursions of the curves signify the occurrence of events.
Discussion

The treatment of patients with coagulation inhibitors is still difficult, especially in the case of serious bleeding or if surgery is required [14]. In contrast to normal plasmapheresis, IA allows a selective IgG depletion from patients’ plasma and thus a highly efficient removal of inhibitors without further loss of plasma proteins and especially of coagulation factors which might be fatal in acute bleeding [15]. To our opinion the rapid inhibitor elimination allows a FVIII recovery (above 2–3 times of normal) which, along with the FVIII substitution, a magnitude to re-induce immune tolerance in vivo. In AH threshold concentrations of partly denaturated FVIII in the patients’ plasma perpetuate the autoimmune reaction. For successful re-induction of immune tolerance intact FVIII must be presented to autoreactive B and T cells in high concentrations. Thus, high-dose FVIII substitution just after IA is an important part to ensure treatment success.

Recently rituximab, a CD20 antibody which selectively depletes pre-B cells, has been reported to induce inhibitor elimination within 3–12 weeks, especially in low-titer patients [16, 17]. However, critical bleeding events were managed by additional plasmapheresis in combination with clotting factor substitutions. High-titer patients required repeated administrations of rituximab and additional cyclophosphamide treatment to attain inhibitor elimination [15]. However, long-term follow-up studies of this treatment are still missing [17].

With 17 days (95% CI 14–20 days), the median treatment duration of our protocol was shorter than that of the rituximab plus cyclophosphamide treatment and substantially shorter than those of conventional regimens which are reported to require 21 weeks to 16 months [18–20]. Therefore, the initial high costs of the FVIII and IA treatment are recovered in general by the rapid inhibitor elimination and the diminution of the disease duration. Furthermore, a shorter immunosuppressive treatment reduces the rate of infections, thereby increasing the survival rate especially of elderly AH patients [4].

In tumor patients inhibitors often occur as a paraneoplastic syndrome. Especially elderly patients with AH should therefore be screened for tumor diseases. In our study, 3 patients were diagnosed to have paraneoplastic syndromes. In these patients our treatment achieved only a PR. The FVIII recovery was sufficiently high to allow tumor diagnostics, but CRs may only be achieved in case of a successful tumor treatment. We therefore suggest to categorize AH with underlying tumor disease as a separate entity of AH.

So far 50 high-titer AH patients suffering from life-threatening bleeding have been treated uniformly and successfully with our treatment protocol. Bleeding could be controlled immediately, and there was no bleeding or therapy-associated mortality in any of our patients. The long-term follow-up lasting up to 7 years clearly demonstrates the induction of a long-term immune tolerance. Our detailed information on important clinical parameters (severity, number of bleeding events, the use of clotting factors, days of hospitalization) enables a cost-benefit analysis to compare our therapy with actual and future treatment strategies.

In summary, the immune tolerance induction regimen presented here can successfully and rapidly eradicate the autoantibodies causing AH. Therefore, this approach has already been judged as the emerging first-line therapy in severe AH [1, 21].

References