Haemophilia (1999), **5**, (Suppl. 3), 1–9

Management of haemophilia in patients with high-titre inhibitors: focus on the evolution of activated prothrombin complex concentrate AUTOPLEX® T

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Summary. Numerous therapeutic strategies have been applied to the management of patients with inhibitors to factors VIII or IX. Different treatment approaches are analysed including prothrombin complex concentrates (PCCs), activated prothrombin complex concentrates (aPCCs), porcine factor VIII concentrate, inhibitor neutralization, immune tolerance therapy, immunosuppressive regimens and recombinant factor VIIa. Clinical data are reported in the analysis of several treatments. PCCs and aPCCs have gained widespread acceptance as the standard first-line approach for patients with inhibitors. The aPCC AUTOPLEX® T has achieved a high response rate with a low level of thrombotic events. Four case studies are presented in which AUTOPLEX® T has been used successfully. Administration of platelet concentrate or, in elective surgery, waiting for inhibitor levels to decline are useful adjuncts to some treatments. The optimal treatment depends on the patient's inhibitor status – low responder (minimal or no increase in inhibitor levels upon administration of replacement clotting factor) or high responder (replacement clotting factor generates inhibitor production). A suggested algorithm for treating high-responder inhibitor patients is presented.

Keywords: activated prothrombin complex concentrate, AUTOPLEX® T, haemophilia, inhibitors, review, treatment.

Introduction

Prior to the advent of factor VIII bypassing agents – known as prothrombin complex concentrates (PCCs) and activated PCCs (aPCCs) – two decades ago, the management of haemophilia patients with inhibitors to factors VIII or IX was problematic, particularly within the context of serious bleeds or emergency surgery. In particular, the availability of aPCCs has favourably altered the duration and severity of inhibitor-related morbidity and appreciably reduced the near 100% mortality outcome in severe cases. In 1949, recovery from haemarthrosis without replacement therapy required 2–3 weeks; in contrast, recovery from haemarthrosis required 8 h in the majority ($> 80\%$) of patients ($n = 14$) with factor VIII inhibitors treated with an aPCC in one study [1].

Incidence and risk factors

As recently reviewed, inhibitors – circulating antibodies that neutralize factor VIII or IX procoagulant activity – develop in a minimum of 5–15% of patients with haemophilia A [2] and in 1–3% of patients with haemophilia B [3]. However, the prevalence of inhibitors can run much higher in patients with severe haemophilia, with prevalence estimates ranging from 21% to as high as 53% [2,4].

Several risk factors increase the likelihood of a patient developing an inhibitor. These include: haemophilia severity ($< 1\%$ circulating clotting factor levels), age (75% occurrence prior to 30 years of age), genetic predisposition (intron 22 inversion), antigenicity of factor replacement therapy (recombinant factor VIII) and race (increased prevalence among black people) [2,3,5].

Diagnosis of inhibitor status

In clinical situations, patient failure to respond to incrementally increasing doses of factor VIII or IX concentrates suggests the presence of an inhibitor. Diagnosis of an inhibitor status is based on an *in vitro* assay in which the addition of normal plasma or a factor VIII concentrate to inhibitor-containing plasma fails to correct the prolonged activated partial thromboplastin time (aPTT) [2,6]. The level or severity of the inhibitor is measured in Bethesda Units (BU), defined as the amount of inhibitor necessary to produce a 50% loss of factor VIII

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activity from a mixture of inhibitor-containing plasma and an equal volume of normal plasma or concentrate, after 2 h incubation at 37 °C [2,7]. (The inhibitor-containing plasma is diluted to obtain an appropriate factor VIII residual.) Low-level inhibitor status usually is defined as < 10 BU, whereas high-level inhibitor status is > 10 BU [2].

In patients with low-level inhibitors, the administration of replacement clotting factor produces minimal or no increase in inhibitor levels. These patients typically are referred to as low responders. By contrast, the majority ($> 60\%$) of patients with high-level inhibitors are high responders in whom replacement clotting factor generates inhibitor production [2,8]. In the clinical situation, low responders may be treated with increased doses of clotting factor; generally, however, high responders require a treatment approach directed toward bypassing or neutralizing the inhibitor [2]. For example, patients with high inhibitor levels who undergo surgery require a bypassing agent and cannot be managed by plasmapheresis or factor VIII replacement [7].

Overview of therapeutic approaches

Numerous therapeutic strategies have been applied to the management of bleeding episodes in patients with inhibitors (Table 1). However, over the past 20 years, the aPCCs, AUTOPLEX® T (Nabi, Boca Raton, FL, USA) and FEIBA® VH (Baxter Healthcare, Glendale, CA, USA), and PCCs, PROPLEX® T (Baxter Healthcare), BEBULIN® (Baxter Healthcare), and KONYNE® 80 (Bayer Biological, West Haven, CT, USA), have gained widespread acceptance as the standard first-line approach to the management of acute bleeding in patients with inhibitors. Porcine factor VIII (HYATE:C®, Speywood, Milford, MA, USA) is more likely to be the treatment of choice in nonhaemophilic patients with acquired inhibitors owing to the expression of autoantibodies although patients also may develop inhibitors to porcine products [2]. A new product actively researched and now approved by the Food and Drug Administration in the United States for treatment of inhibitor patients, recombinant factor VIIa (rFVIIa; NOVOSEVEN®, Novo Nordisk, Bagsvaerd, Denmark), is a useful addition to our therapeutic offering, particularly in patients with factor IX inhibitors, where lack of factor IX in the product eliminates a possible anamnestic response.

Historical perspective: the development of PCCs

The nonactivated PCCs differ from the aPCCs in that they contain less of the active components – factors VIIa, IXa and Xa [9,10]. The efficacy of the PCCs was clearly demonstrated in an early (1978) multicentre, double-blind, randomized, crossover study comparing PROPLEX® T and KONYNE® to an albumin placebo [11,12]. The PCCs proved twice as effective as placebo in the treatment of acute haemarthrosis of the knee, elbow or ankle. Symptomatic improvement was achieved in approximately 50% of episodes in response to a single dose of PCC (75 factor IX units kg^{-1}) within 6 h as compared with placebo, which showed efficacy in 25% of episodes [11,12].

However, several drawbacks limit the use of PCCs. Early in 1980, several investigators observed a decline in the efficacy of PCCs in patients with factor VIII inhibitor due to alterations in the preparation of these agents [1]. Additionally, serious thrombotic complications, such as disseminated intravascular coagulation (DIC) and coronary artery thrombosis, were linked to PCCs, particularly in relation to large doses of KONYNE® [1]. Therefore, although increasing the dose of nonactivated PCC might be a sound rationale for achieving efficacy equivalent to an aPCC [9], it might also increase substantially the risk of a potentially life-threatening thrombotic event.

Table 1. The management of haemophiliac patients with inhibitors: therapeutic approaches

(1) Factor VIII Bypassing Agents
Nonactivated prothrombin complex concentrates (PCCs)
80 factor IX U kg^{-1} at 8-h intervals as needed
–PROPLEX® T
–KONYNE® 80
–BEBULIN®
Activated prothrombin complex concentrates (aPCCs)
80–100 bypassing U kg^{-1} at 4- to 12-h intervals as needed
–AUTOPLEX® T
–FEIBA®
Recombinant factor VIIa
(2) Replacement Therapy
–Human factor VIII (low-level inhibitors–100 U kg^{-1})
–Porcine factor VIII (80 U kg^{-1})
(3) Supportive Procedures/Agents
–Plasmapheresis (2.5 L exchange daily)
–Platelet concentrates (6 Units)
(4) Immune Tolerance Therapy: Factor VIII Dosing Regimens
–The Bonn Method and variations
(5) Immunosuppressive Regimens
–Gamma globulin (intravenous–1 g kg^{-1})
–Cytotoxic agents (cyclophosphamide–150 mg day^{-1})
–The Malmö regimen

The next generation: aPCCs

Activated prothrombin complex: development and mechanism of action

The aPCC, now designated AUTOPLEX® T, was discovered coincidentally as an accidental byproduct of two

lots of PROPLEX (a nonactivated PCC) and was deemed potentially too thrombogenic for clinical use [7]. Intravenous administration of this spontaneously activated PCC to animals confirmed its thrombogenicity, resulting in fatal DIC. However, *in vitro* studies in which this product, first called Auto IX, was added to plasma from patients with factor VIII inhibitors revealed that it corrected the aPTT on a dose–response basis, irrespective of the level of inhibitor [7,13]. In addition, it also corrected plasma containing inhibitor to factor IX to the same extent as plasma containing inhibitor to factor VIII.

For many years, the precise mechanism for the bypassing activity of this product was unknown and was attributed to the presence of active forms of multiple coagulation factors, including factors VII, IX, X and XI, with the dominant factor, initially believed to be factor Xa, unconfirmed [14]. A recent study, utilizing Colorimetric Active Site-Specific Immunoassay (CASSIA) technology, has shown that the high concentrations of factors VIIa and IXa most likely account for the therapeutic efficacy of AUTOPLEX® T and its precursor [10].

Clinical data

AUTOPLEX® was initially used clinically in the context of emergency surgery and life-threatening acute bleeds unresponsive to other therapeutic approaches. In 1972, Fekete and colleagues first reported the successful use of AUTOPLEX® to control bleeding in several haemophilic patients with inhibitors [15]. My first use of AUTOPLEX® was in a 58-year-old woman with an idiopathic inhibitor of 70 BU, in order to facilitate emergency tracheotomy for the removal of a massive, strangulating haematoma from the posterior pharynx [7].

Subsequently, in 1974, Kurczynski and Penner administered AUTOPLEX® to eight patients (six of whom had failed to respond to large doses of factor VIII), representing 60 bleeding episodes [14]. No thrombotic complications were observed. AUTOPLEX® effectively decreased aPTT and prothrombin times (PT) and increased factor X 200–300% and factor VII 2000% [14].

In several instances in which AUTOPLEX® was unavailable, the parent product PROPLEX® T was substituted, permitting comparison between the two compounds [6]. PROPLEX® T (50–100 U kg^{-1}, 2–3 bottles per kg) achieved a 20% first-dose response, whereas AUTOPLEX® (50–80 U kg^{-1}) achieved a 75% first-dose response [6].

In a later cohort of 14 patients, Abildgaard *et al*. found that AUTOPLEX® achieved an 84% response rate in minor bleeding episodes, including joint, soft tissue and mucus membrane [1]. AUTOPLEX® also demonstrated efficacy in eight additional major bleeding episodes. The minor side-effects observed included: transient headache (three patients), transient chest discomfort (one child) due to rapid 100 U kg^{-1} dose administration (< 15 min) and an erythematous pruritic eruption (one patient) responsive to intravenous diphenhydramine. Although no serious complications were noted, two children developed reversible hypofibrinogenaemia immediately following infusion [1]. Therefore, Abildgaard concluded that antifibrinolytics should not be used in conjunction with AUTOPLEX® to minimize the remote possibility of a thrombotic event [1], although it has been used safely and effectively by other haemophilia treaters [16]. However, it has been hypothesized that the small amounts of heparin in AUTOPLEX® may provide protection against thrombosis [7].

In a 1987 study of 60 patients representing 120 bleeding episodes, Kantrowitz and co-workers further confirmed that AUTOPLEX® T achieved good to excellent responses in 87% of bleeds [17]. The efficacy was greater than 92% for open wound bleeds and 85% for closed bleeds [17]. Open bleeding treated with higher doses (> 50 FEU kg^{-1}) was associated with a better outcome ($P < 0.01$) than open bleeding treated with lower doses ($\leqslant 50$ FECU kg^{-1}).

Clinical experience with AUTOPLEX® supports a pronounced dose–response effect, particularly within the context of severe bleeding episodes including surgery. In 17 cases, dose levels > 50 U kg^{-1} achieved good or excellent results, defined as control of bleeding with one or two treatments within a 24-h period, while good responses of less than 50% were observed in 10 cases in which a lower dose < 50 U kg^{-1} was used [7].

The appropriate dose for surgical candidates or patients with severe bleeds, in my experience, is dictated by the patient's inhibitor level. For example, a high responder's inhibitor level should be reduced prior to surgery, if possible. The AUTOPLEX® T treatment regimen recommended for surgical candidates and severe bleeds is outlined in Table 2 [7]. In general, surgical candidates

Table 2. Suggested AUTOPLEX® T treatment regimens for high responders by severity and inhibitor level*

Spontaneous, mild-to-moderate bleeds	Low-dose AUTOPLEX® T (30–50 U kg^{-1}) every 8 h
Surgical candidates or patients with severe bleeds and high inhibitor levels	High-dose AUTOPLEX® T (75–100 U kg^{-1}) every 4–8 h
Surgical candidates or patients with severe bleeds and low inhibitor levels	Plasmapheresis followed by factor VIII for 6 days, then AUTOPLEX® T (80 U kg^{-1}) every 8–12 h 6 days

*Personal experience, Dr John Penner.

with high inhibitor levels > 10 BUs require an aPCC regimen, whereas those with low inhibitor levels usually can be managed with a combination regimen that includes pheresis followed by factor VIII or IX replacement and an aPCC [7].

Clinical experience: case studies

The following four cases reflect the types of clinical situations in which I have successfully used AUTOPLEX® T or its precursor to manage bleeding episodes in haemophilia patients with inhibitors.

Case 1: surgical use in a patient with a haematoma

The initial case described in our first article on anti-inhibitor bypassing activity was a 58-year-old white female who was admitted to the University of Michigan hospital after having developed a haemorrhagic condition manifested by multiple ecchymosis over the trunk and extremities and by the presence of a large haematoma obstructing the posterior pharynx. The patient's condition was life-threatening, not only from the active haemorrhage but more dramatically from the respiratory obstructive event – a result of the haematoma. The need to maintain an airway was vital; however, the surgeons were reluctant to proceed in view of the inability to control haemostasis. Laboratory assessment revealed a remarkably prolonged aPTT, which could not be corrected with normal pooled plasma and which demonstrated a lack of factor VIII (antihaemophilic factor) activity. The patient's condition was diagnosed as a haemorrhagic disorder resulting from an acquired inhibitor to factor VIII. The laboratory assessment was similar to what we had found previously in patients with haemophilia who had developed inhibitors to replacement factor VIII. The patient had been in good general health but was obese and of small stature. Administration of AUTOPLEX® controlled bleeding from the tracheostomy. An additional dose of the product was infused on three occasions and allowed for gradual regression of the haematoma without additional bleeding. The response to the product was identified by a sharp decline in the aPTT immediately after the infusion and lasting for approximately 1 h and the shortening of the PT lasting for a number of hours. In addition, it was possible to measure a marked elevation in factor VII, X and prothrombin. The patient recovered completely without complications.

Comment

The response to the product was monitored by means of the aPTT and PT, both of which declined immediately after the infusion. It was apparent from the management of this case that product effectiveness might last as long as 8 h but perhaps would be reinforced most effectively by a 4- to 6-h dosing schedule.

Case 2: hip replacement surgery in a patient with haemophilia B

The patient, a 34-year-old faculty member at one of our state universities, had a lifelong history of haemophilia B and had developed resistance to factor IX therapy, as indicated by failure of the standard PCCs (containing factor IX) to correct the aPTT. Additional studies noted that a high level of inhibitor had developed (84 BU). The patient was admitted with a traumatic fracture of the right femoral head. After several months in traction, healing at the fracture site was not evident, and it was proposed that the patient be committed to a permanent brace. He was unwilling to accept this handicap and argued for surgical replacement with a prosthetic device. The procedure progressed once it was found that the inhibitor level had declined to less than 2 BU as a result of 3–4 months without treatment and thus lack of antigen stimulus. He received the standard PCC, containing factor IX activity, at $50\,U\,kg^{-1}$ prior to the surgery and at $25\,U\,kg^{-1}$ every 12 h immediately after. On postoperative day 5, it was found that the corrective effect of the PCC had diminished and that it was not possible to recover factor IX activity in the patient's plasma. Resistance had recurred to the extent that the inhibitor level had risen to 185 BU. Treatment with an aPCC (AUTOPLEX®) was then instituted at $80\,U\,kg^{-1}$ every 6 h. Bleeding complications did not occur, and the patient recovered fully.

Comment

In this case, the inhibitor level was allowed to decline to the point that the patient would again respond to concentrates containing factor IX. This management strategy was successful for approximately 5 days, at which time the anamnestic response to the factor IX antigen resulted in a rapid increase in circulating antibody. When the aPCC was substituted, the PT decreased to a value less than normal, while the aPTT corrected partially, thus achieving haemostasis.

Case 3: surgical management of a pelvic haematoma with AUTOPLEX® T and platelets

A large pelvic haematoma occurred in a 24-year-old haemophilic patient in the form of a pseudotumour. The mass in the pelvis continued to enlarge in this patient, who had developed an inhibitor to factor VIII that reached a level of 96 BU. Following factor VIII replacement, it was apparent that the pseudotumour was not responding to treatment and continued to exert its effect on the bony structure of the pelvis, with almost complete

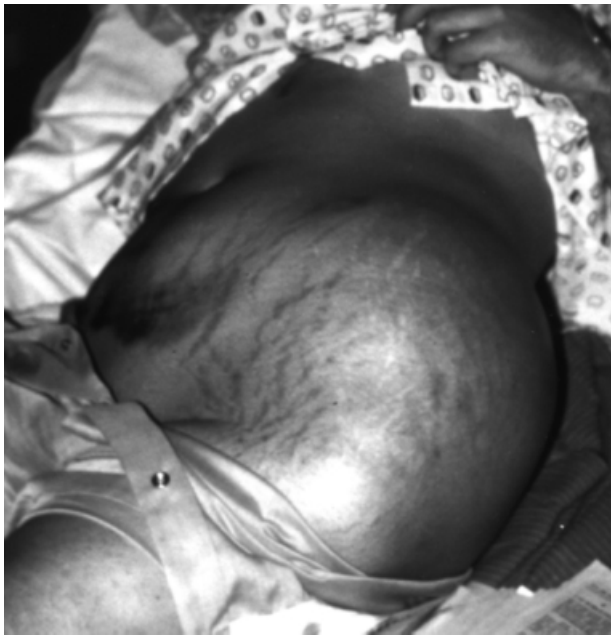

Fig. 1. Case 3: surgical management of a pelvic haematoma with AUTOPLEX® T and platelets.

erosion of the wing of the ileum. The patient was not treated with factor VIII for 3 months, at which time his inhibitor level had declined to 4 BU. In anticipation of surgery, plasmapheresis was initiated with the exchange of 2.5 L of plasma on two occasions, reducing the inhibitor level to < 1 BU. Surgery proceeded with continuous factor VIII infusion during the 8-h operation and following until postoperative day 5, at which time the aPTT values again became prolonged, indicating the disappearance of factor VIII activity and the rapid increase of inhibitor activity. AUTOPLEX® T was then administered at 80 U kg^{-1} every 6 h. Despite the fact that the PT and aPTT values improved, a small amount of bleeding persisted at the wound site. Platelet concentrates (6 units) were administered in conjunction with AUTOPLEX® T at 6-h intervals for three doses. Bleeding was controlled. Dosing was then extended to 12-h intervals with the patient subsequently recovering and returning home after 4 weeks in the hospital.

Comment

In this situation, the very extensive procedure – which removed the pseudotumour capsule by dissecting it from both sides of the destroyed ileum – required effective haemostasis. Once the inhibitor levels increased, bleeding occurred again. Since it was noted that platelet values had declined to 110 000, probably due to increased utilization, support with platelet concentrates was offered. This approach also may have provided an additional haemostatic benefit beyond that of the aPCC, recognizing that the platelets' phospholipid binding could protect the active clotting factors from acquired and natural inhibitors. The patient required 12 units of packed red blood cells during the procedure and 6 units during the remainder of his hospitalization. Although the use of platelet concentrates alone to control bleeding in patients with inhibitors has met with inconsistent responses [2], I have had many successes when platelets have been employed as an adjunct to AUTOPLEX® T.

Case 4: management of subdural haematoma

A 23-year-old haemophilic male with a factor VIII inhibitor level of 34 BU developed a subdural haematoma following a minor head injury. The patient complained of headache with progressive symptoms of nausea, vomiting and weakness. He was brought to the emergency room, where he received 80 units kg^{-1} of AUTOPLEX® T immediately. Subsequently, a subdural haematoma was revealed on a CT scan. AUTOPLEX® T was administered at 6-h intervals for the next 24 h, during which time the patient improved. Dosing was then reduced to 12-h intervals until the patient was discharged 5 days later.

Comment

The patient was a known haemophiliac with high-responding factor VIII inhibitors. He had been receiving the aPCC FEIBA® at home on a regular basis for treatment of acute bleeding episodes, but his inhibitor levels did not decline, most likely due to the continued antibody stimulation by small amounts of factor VIII in the product. The administration of AUTOPLEX® T was effective in preventing further progression of the haemorrhage. It was not necessary to resect the haematoma, and regression occurred over a 4-week period.

In my experience, in cases of elective surgery, it is worthwhile to wait for inhibitor levels to decline to < 20 BU, then institute plasmapheresis to reduce the inhibitor level to < 5 BU. At this point, factor VIII replacement is practical, generally requiring 10 000 units to overcome any residual antibody. Haemostasis can then be achieved and an adequate factor VIII level maintained by constant infusion, as it is in haemophiliacs without an inhibitor. Anamnesis, however, generally will present itself by day 5, although on several occasions it has developed on day 7 and, on one occasion, on day 13. Careful monitoring of the aPTT will demonstrate increasing inhibitor activity.

Additionally, assay for factor VIII activity usually will note a sudden decline in activity, despite any attempt to increase the infusion dose. AUTOPLEX® T can then be administered at 6- to 8-h intervals for several days and then extended to 12-h intervals to allow for an additional 5 days of healing. On the other hand, when presented with a

patient who is actively bleeding, has an inhibitor level above 5 BU and is thus nonresponsive to replacement by factor VIII, initial administration of 100 U kg^{-1}, repeated at 4- to 6-h intervals as necessary to control haemostasis, can be effective. Furthermore, in situations where the bleeding is not entirely controlled, I have found that adding 6 units of platelet concentrate immediately following, or in conjunction with, AUTOPLEX® T has been most effective in sealing bleeding sites. It is important to note that PCCs retain little, if any, active forms of clotting factors (e.g. protease) and, in my opinion, have little, if any, effect on severe or serious bleeding events.

FEIBA®: clinical study data

Used extensively in Europe, FEIBA® effectively controlled > 80% of bleeding episodes in clinical trials [18–20]. Though AUTOPLEX® T and FEIBA® are generally considered equivalent in efficacy, unlike AUTOPLEX® T, FEIBA® has been associated with a significant incidence of anamnesis and rare reports of thrombotic events, including one lethal myocardial infarction [21]. In addition, the assay for product potency differs; FEIBA® units determined in inhibitor-containing plasma and AUTOPLEX® T with factor VIII-deficient plasma. The AUTOPLEX® T unit has been considered by some investigators to indicate a greater potency, perhaps 20%.

In 1981, Sjamsoedin and colleagues reported that FEIBA® (88 U kg^{-1}, FEIBA® units) improved joint mobility in 64% of patients as compared with 52% treated with a PCC (48 U kg^{-1}, factor IX units) at 6 h [18]. Fifteen patients, representing 150 mucocutaneous, joint and muscle bleeding episodes, were enrolled in this double-blind, randomized trial in which a PCC served as the control. At 24 h, both groups had improved markedly, with 90% of FEIBA®-treated patients and 78% of PCC-treated patients demonstrating improved joint mobility.

In a 1983 multicentre trial, Hilgartner *et al*. evaluated FEIBA® (50 U kg^{-1}) in a study of 49 patients, representing 165 bleeding episodes (155 occurred in joints, muscles or mucus membranes and 10 involved serious emergencies including three central nervous system episodes and four surgical procedures) [19]. Although 93% of bleeding episodes were ultimately controlled, it took 25 h or more to control 56% of bleeding episodes and, at 12 h, only 36% of bleeding episodes were under control.

A 1997 French multicentre study evaluated the thrombotic potential of FEIBA® in 60 patients, representing 433 bleeding episodes including 30 surgical cases [20]. Although FEIBA® effectively controlled 81% of bleeding episodes, it was associated with a relatively high incidence (32%) of anamnesis, defined as an increase in inhibitor level to > 50% of the preinfusion level [20]. As seen with AUTOPLEX® T, however, an increase in inhibitor titre does not necessarily negate the efficacy of treatment. In 98.8% of bleeding episodes, FEIBA® was well tolerated; however, in three cases, biological signs suggestive of DIC occurred within days of treatment initiation but proved reversible with interruption of treatment [20].

In 1988, Chavin *et al*. reported a lethal case of acute myocardial infarction occurring in a 15-year-old boy following 5 days' treatment with FEIBA® (300 U kg^{-1} day^{-1}) [21].

Porcine factor VIII concentrate

Porcine factor VIII concentrate introduced in the 1950s has been used since the 1980s to provide effective second- or third-line therapy for patients with inhibitors who fail factor VIII and PCC therapy [22]. However, it is often used as first-line therapy in nonhaemophilic patients with acquired factor VIII inhibitors.

In a study by Kessler and Ludlam, 21 nonhaemophilic patients with acquired factor VIII inhibitors who received porcine factor VIII as initial therapy experienced clinical responses ranging from fair to excellent, with some anamnesis and no thrombocytopenia [23]. However, the incidence of side-effects to porcine factor VIII usually is lower in acquired haemophilia than in congenital haemophilia [23]. The major limitations of porcine factor VIII in congenital haemophilia are cross-reactivity, anamnesis and thrombocytopenia. In a multicentre retrospective study, Hay and co-workers observed that the median level of inhibitor cross-reactivity was 15% and that cross-reactivity was present in 73% of patients [22]. The specific anamnestic response observed in 52 available patients was brisk (7.5%), intermediate (54%) and absent (38%) [22]. Thrombocytopenia, a dose-related phenomenon, occurs only in the context of intensive replacement therapy for severe bleeding or surgery, as opposed to regular replacement therapy [22]. Apart from its major limitations, the side-effects of porcine factor VIII are generally mild, dose-related, transient and idiosyncratic [22].

Inhibitor neutralization

Plasmapheresis, followed by factor VIII replacement, is used to reduce inhibitor levels temporarily in severe bleeding episodes (e.g. in the context of surgery) [2]. Recently, a computer-aided system was developed to remove factor VIII inhibitors from plasma collected through plasmapheresis in order to reduce inhibitor levels below 10 BU, the level at which standard factor VIII replacement is once again effective [2]. The limitations of plasmapheresis include cost, time and the special equipment required [2].

Immune tolerance therapy: factor VIII dosing regimens

High-dose induction with factor VIII through the 'Bonn Method' may induce long-term immune tolerance in high responders [2]. Time-consuming and expensive, this approach takes 1–3 years and involves a two-to four-step process [2,24].

The original two-step process involves giving patients factor VIII ($100\,U\,kg^{-1}$) and FEIBA® ($50\,U\,kg^{-1}$) twice daily until the inhibitor level reaches $< 1\,BU\,mL^{-1}$. During this high-dose induction, FEIBA® is used to prevent bleeding. The patient then receives high-dose factor VIII ($150\,U\,kg^{-1}$) without supportive FEIBA®, until the inhibitor disappears completely and the half-life of factor VIII returns to normal. Other patients have simply received $150\,U\,kg^{-1}$ of factor VIII twice daily until the inhibitor is no longer present and the half-life of administered factor VIII is normal. Once normal half-life is achieved, some treaters use additional steps. The final patient can receive a standard 'as-needed' regimen of factor VIII [2]. In addition, some haemophilia treaters follow successful immune tolerance therapy with standard daily prophylactic regimens of factor VIII administration. Doses of $50\,U\,kg^{-1}$ of factor VIII daily or every other day can suppress inhibitor activity within 6 months. The latter programmes are much less costly and often are effective in young patients with recent inhibitor development.

Immunosuppressive regimens: the Malmö regimen

Immunosuppressive regimens attempt to suppress IgG_4 antibodies against factor VIII or factor IX without inhibiting coagulation [2]. Although a variety of immunosuppressive drugs have been used over the years, the most successful approach to the treatment of patients with moderate and high levels of inhibitors involves the use of a cyclophosphamide strategy known as the Malmö regimen.

This regimen first involves plasmapheresis to reduce the inhibitor levels of high responders to manageable levels, then intravenous cyclophosphamide ($12–15\,mg\,kg^{-1}$) for 2 days, followed by oral cyclophosphamide ($2–3\,mg\,kg^{-1}$) for 8–10 days. Next, the patient receives factor VIII or IX for 3 weeks in induction doses high enough to neutralize the inhibitor, followed by daily maintenance doses targeted toward stabilizing factor activity levels at $40–100\,U\,dL^{-1}$ plasma. Beginning on day 4 of treatment, intravenous immunoglobulin ($0.4\,g\,kg^{-1}\,day^{-1}$) is given for 5 days. Once the inhibitor has been eradicated or considerably reduced in level, factor VIII or factor IX is administered prophylactically 2–3 times per week [2]. Although this regimen is effective, it is complicated and costly.

Investigational therapies

Approved in Europe, recombinant factor VIIa (rFVIIa) is now approved by the United States Food and Drug Administration and available in the United States. In a multicentre European study, the efficacy of rFVIIa ranged from 80 to 92%, when administered via continuous infusion in the surgical setting [25,26].

Several problems have been associated with rFVIIa. First, its half-life is the shortest of any coagulation factor concentrate, necessitating frequent bolus doses in the surgical setting and, therefore, additional treatment costs [25]. Second, the optimum dose has not yet been defined [25]. Third, the potential for consumption coagulopathy and fibrinolysis has raised concerns about thrombotic and coronary events. In a multicentre study, one case of DIC and one of myocardial infarction were reported [25], and there have been other similar reports, including one in treating acquired haemophilia [26–28].

Despite these drawbacks, the product appears effective and will be particularly beneficial in factor IX inhibitor patients as mentioned, for its inability to produce anamnesis.

A suggested algorithm for treating high responder inhibitor patients is shown in Fig. 2.

Conclusion

Over the past 20 years, the factor VIII bypassing agents – the PCCs (PROPLEX® T and KONYNE®) and the aPCCs (AUTOPLEX® T and FEIBA®) – have been widely used to manage acute bleeding in patients with inhibitors, thereby greatly reducing the morbidity and mortality associated with serious bleeds and surgery. In comparison with placebo, the PCCs achieve 50% response rates in acute episodes of haemarthrosis. However, serious thrombotic events, such as DIC, have been associated with these agents.

By contrast, the aPCC AUTOPLEX® T achieves $> 80\%$ response rates and has remained virtually unassociated with thrombotic events in clinical trials and experience to date. FEIBA®, though often as effective as AUTOPLEX® T, has been linked to a significant incidence of anamnesis and, in rare instances, thrombotic events.

The complexity of administration that adds time to response and variable efficacy of alternative inhibitor therapies, such as plasmapheresis, immune tolerance therapy and immunosuppressive agents, limits these approaches, while porcine factor VIII requires appropriate testing to establish lack of cross-reactivity. This applies particularly to those patients with haemophilia who can be expected to respond to treatment with a factor VIII bypassing agent. In this respect, clinical trials suggest $> 80\%$ efficacy with the newly approved rFVIIa. Further evaluation will be needed in clinical settings to determine

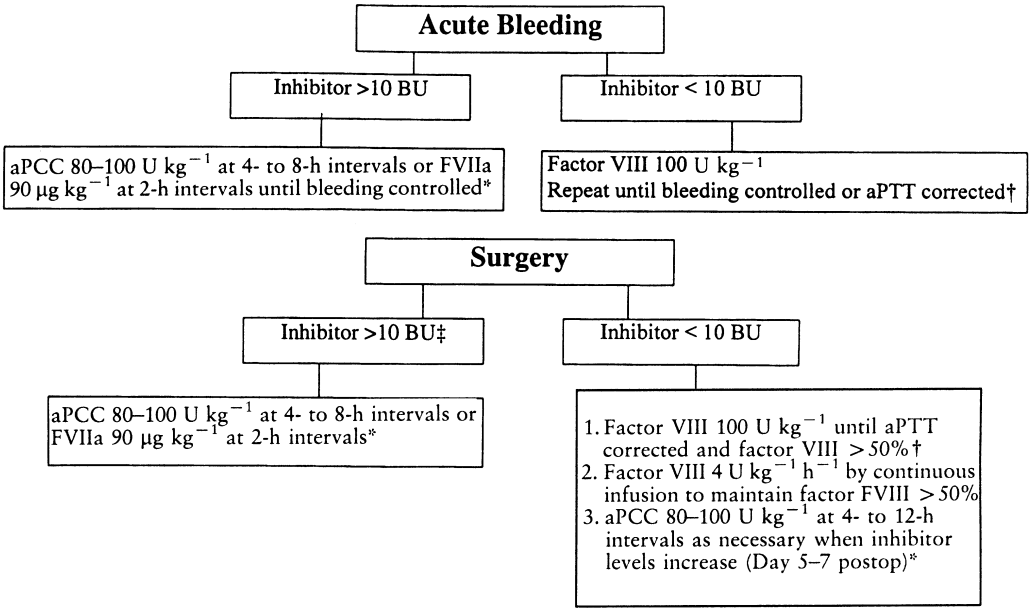

Fig. 2. Algorithm for treating high-responder inhibitor patients. Note: mild acute reactions to aPCCs (fever, joint pain) are not uncommon during administration. Pretreatment with steroids (SOLU-CORTEF®, Pharmacia & Upjohn, Kalamazoo, MI, USA) and antihistamines (BENADRYL®, Warner-Lambert, Morris Plains, NJ, USA) usually will avoid this situation. BU = Bethesda Units. *Platelet concentrates may be beneficial. †Plasmapheresis may be necessary. ‡Surgery should be delayed, if possible, until inhibitors have declined to < 10 BU.

cost benefits and risks for complications. Nonhaemophilia patients, however, who develop factor VIII inhibitors spontaneously or in association with various disorders are more apt to benefit from alternative measures, such as porcine factor VIII and immunosuppression.

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