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Use of prothrombin complex concentrates and activated prothrombin complex concentrates as prophylactic therapy in haemophilia patients with inhibitors

C. A. LEISSINGER

Associate Professor of Medicine & Pathology, Tulane University School of Medicine, Section of Hematology/Medical Oncology, 1430 Tulane Avenue SL78, New Orleans, LA 70122, USA

Summary. Haemophilia patients with inhibitors are treated for acute bleeding with prothrombin complex concentrates (PCCs) or activated prothrombin complex concentrates (aPCCs). Despite this therapy, patients with high-level inhibitors are at increased risk of developing devastating joint disease. This paper examines available information that supports the study of PCCs and/or aPCCs as prophylactic therapy for haemophilia patients with inhibitors. This strategy would require that PCCs or aPCCs be administered repetitively in a dose that is sufficient to prevent haemarthrosis without causing thrombogenic events, or causing anamnestic response in inhibitor titre. PCC doses ranging from 30 to 50 U kg^{-1} every other day for up to 8 months have resulted in subjective improvement both in bleeding associated with target joints and in the management of chronic joint inflammation. aPCC doses as low as 50–100 U kg^{-1} every other day have been useful in postsurgical prophylaxis. The risk of developing a myocardial infarction or clinically relevant disseminated intravascular coagulation is linked to total dosages of either PCCs or aPCCs greater than 200 U kg^{-1} day^{-1}. It is uncertain what anamnestic response would result from prophylaxis, but with typical therapy the aPCCs cause such a response in only a small percentage of patients. Based on these findings, a clinical trial of these products used in doses of 50–100 U kg^{-1} every other day would appear to be warranted in patients who have permanent inhibitors and frequent joint bleeding.

Keywords: activated prothrombin complex concentrates, antibody, AUTOPLEX® T, haemophilia A, inhibitors, prophylaxis.

Introduction

As many as 30–35% of patients with severe haemophilia A and 5–10% of patients with mild or moderate haemophilia A will develop antibodies (or inhibitors) following exposure to factor VIII replacement therapy [1]. The majority of these inhibitors will be of sufficiently high titre to neutralize the effectiveness of factor VIII concentrates, even when used in very large doses. Most patients who develop high-titre inhibitors will experience the onset of these inhibitors early in life after only limited exposure to factor VIII replacement therapy [2].

The development of inhibitors to factor VIII presents a serious management problem. For those patients whose inhibitor titres exceed 5 Bethesda Units (BU), replacement therapy with factor VIII concentrates is generally ineffective. Following early reports that prothrombin complex concentrates (PCCs) were clinically effective in the management of bleeds in patients with high-titre inhibitors, these products and the later activated prothrombin complex concentrates (aPCCs) became the mainstay of treatment for such patients [3–5]. It is universally accepted that neither PCCs (e.g. PROPLEX® T, Baxter Healthcare, Glendale, CA, USA; KONYNE® 80, Bayer Biological, West Haven, CT, USA; PROFILNINE®, Alpha Therapeutic, Los Angeles, CA, USA; BEBULIN®, Baxter Healthcare, Glendale, CA, USA) nor aPCCs (AUTOPLEX® T, Nabi, Boca Raton, FL, USA; FEIBA® VH, Baxter Healthcare, Glendale, CA, USA) are as effective in inhibitor patients as factor VIII is in noninhibitor patients or in patients with low-titre, low-responding inhibitors who can receive large enough doses of factor VIII to overcome their inhibitor and produce measurable circulating levels of factor VIII [4,6,7]. For this reason, an attempt at eradicating high-responding

Correspondence: Cindy A. Leissinger, MD, Associate Professor of Medicine & Pathology, Tulane University School of Medicine, Section of Hematology/Medical Oncology, 1430 Tulane Avenue SL78, New Orleans, LA 70122, USA. Tel.: +1 504 588 5482; fax: +1 504 588 5483.

inhibitors by immune tolerance therapy is nearly always indicated in patients with high-responding inhibitors of recent onset. While immune tolerance therapy is successful in many inhibitor patients, a significant portion of patients (perhaps as many as 30–40%) will be resistant to therapy and will have a persistent inhibitor [8].

For the vast majority of chronic inhibitor patients, PCCs and/or aPCCs are first-line therapy and are given as 'on-demand' treatment for acute bleeding. Early comparative controlled trials demonstrated the efficacy of PCCs and aPCCs in the management of acute bleeding episodes [9–12]. Initially, two different PCC products were compared to placebo in a randomized, double-blind, crossover study, which showed that both PCC products were superior to placebo (but similar to each other) in both subjective and objective improvement in haemarthrosis [9]. In a follow-up study that compared an aPCC to one of the PCCs used in the initial trial, there was essentially no difference in clinical efficacy of either product when follow-up evaluations were performed at 6 h [11]. However, in a separate study comparing an aPCC to a control, nonactivated PCC, there was significant improvement in both subjective and objective criteria associated with aPCC use when follow-up evaluation was performed at 24 h [12]. The relative efficacy of PCCs versus aPCCs in the treatment of bleeds remains unanswered. Without a clear consensus as to one product's superiority over the other, both PCCs and aPCCs are currently used, often interchangeably, to manage inhibitor patients [12,13].

Despite their clinical benefit as demonstrated in the above trials, neither PCCs nor aPCCs can predictably effect haemostasis in the manner that replacement of a deficient factor can. For this reason, patients with high-level inhibitors are at increased risk of developing devastating joint disease. These poor joint outcomes are reflected in the high percentage of inhibitor patients with end-stage arthropathies. Progressive arthropathies often lead to a lifetime of joint disease, and many such patients will permanently require assistive devices such as wheelchairs and crutches for mobility. Unfortunately, owing to the inherent risks of haemorrhage and the difficulty in reliably providing haemostasis, there is a natural reluctance to perform elective orthopaedic surgery on high-responder inhibitor patients, which might otherwise lessen some of the chronic debilities of joint disease [5,14]. Thus, surgery in this patient population is usually reserved only for life-threatening or emergency situations.

Primary and secondary prophylaxis in current haemophilia treatment

In patients with severe haemophilia A without inhibitors, and particularly in children, prophylaxis using replacement factor concentrates on a regular basis is often undertaken to prevent bleeding and consequent joint damage. Usually, amounts of factor VIII are given three times weekly or often enough to maintain the trough factor VIII level above 1–2%. Long-term follow-up studies of patients maintained on prophylactic factor VIII since early childhood suggest significantly reduced prevalence of joint abnormalities compared with those treated with factor VIII on demand [15,16].

For inhibitor patients whose likelihood of developing severe joint disease is even greater than in patients without inhibitors and whose bleeding is harder to control once it starts, the question arises whether prophylaxis with PCCs or aPCCs would prove beneficial in the prevention of joint bleeding. PCCs and aPCCs have been given little consideration as prophylactic therapy in inhibitor patients because of concerns over safety and the duration of efficacy. Among the disadvantages of these bypassing agents are their unpredictable effects on haemostasis, the uncertain duration of their haemostatic effects, the inability to verify or monitor therapeutic effectiveness by laboratory testing, and the increased risk of thrombosis associated with large, repeated doses.

Nevertheless, both PCCs and aPCCs have been used successfully for surgical and dental prophylaxis as well as postsurgical prophylaxis for durations of several weeks to months [7,17–21]. In addition, there are anecdotal reports in the literature of successful prevention of bleeds using PCCs as routine prophylaxis. For example, doses of PCCs ranging from 20 to 50 U kg^{-1} every other day for up to 6 months have resulted in subjective improvement in the number of joint bleeds and in the management of chronic joint inflammation in small numbers of patients [3,18,22,23].

It is the purpose of this paper to examine information available to support the study of PCCs/aPCCs as prophylactic therapy in this group of patients who have the greatest likelihood of developing permanent and irreversible joint damage. Is there evidence that PCCs or aPCCs can be administered repetitively in a dose that is sufficient to prevent haemarthrosis without causing untoward thrombogenic events? To answer this, it is necessary to review the data available in an attempt to answer two basic questions: (1) what is the minimum effective dose and dosing frequency of PCCs/aPCCs needed to prevent bleeds? and (2) what is the maximum safe dose and dosing frequency to avoid untoward, thrombogenic complications?

Minimum effective dose and frequency of PCCs/aPCCs to prevent bleeding

Although there are no controlled clinical trials designed to study the ability of PCCs/aPCCs to prevent bleeding in inhibitor patients, there are numerous published reports

of clinical efficacy and safety when these products are used prophylactically. The majority of these reports are concerned with postsurgical prophylaxis. Prevention of surgical and postsurgical bleeding has been accomplished with both aPCC products at a broad range of doses and frequency. Table 1 summarizes the available literature on major surgeries in inhibitor patients in which PCCs/aPCCs were the only factor concentrates administered during surgery and then continued for at least 2 days postoperatively [7,17–21]. While total doses per day ranged from 50 to 400 U kg^{-1} in divided doses given every 6–12 h, postsurgical dosing tended to cluster around 150 U kg^{-1} day^{-1} given as either 50 U kg^{-1} every 8 h or 75 U kg^{-1} every 12 h. As might be expected with published cases, outcomes were good, with excess bleeding reported during prophylactic treatment in only four of the 13 patients. In addition to these cases where doses and details of follow-up were given, there are at least five other successful major surgeries reported with AUTOPLEX® T coverage in which the amounts and duration of therapy were not given [7] and 11 minor surgical and endoscopic orthopaedic procedures in which FEIBA® was used with excellent operative and postoperative haemostasis for up to 6 days after surgery [21]. Interestingly, several patients were reported to have surgical site bleeding only after cessation of prophylaxis, a fact strongly suggesting that prophylaxis was indeed associated with control of bleeding. No complications were noted in association with any of the reported surgical cases.

In considering prophylaxis for the prevention of joint bleeding, one may assume that less haemostatic capability is needed than for prevention of postsurgical bleeding, a conclusion that follows current patterns of factor concentrate usage in these very different situations. Prophylaxis of joint bleeding is effective when maintaining factor VIII trough levels above 1% in noninhibitor haemophilia patients, while postsurgical prophylaxis requires trough levels above 30–50% during the initial period of healing, with decreasing factor VIII requirements in later stages of healing. While required factor VIII levels can clearly not be translated into usefulness when dealing with PCC/aPCC use in similar clinical situations, they nonetheless describe a haemostatic system in factor-deficient patients that has a continuous range of sensitivity and effectiveness.

As an example of this, patients with low-titre, high-responding inhibitors who had surgery performed under factor VIII coverage for the initial postoperative period (until the anamnestic rise of their inhibitor titre) have been successfully managed with subsequent use of relatively low doses of aPCCs for the later stages of postsurgical prophylaxis, compared with aPCC doses used in early postsurgical prophylaxis [7,24,25]. In one report from Abildgaard *et al.*, AUTOPLEX® T was begun on Day 6 following total hip replacement, and a total of 12 infusions of 50–100 U kg^{-1} were given over 20 days; in another case, AUTOPLEX® T was begun on Day 6 following resection of the abdominal wall for a total of 14 infusions of 50–100 U kg^{-1} over 30 days, with control of bleeding noted in both cases [25]. Others have used similar dosages for late postsurgical prophylaxis. Such anecdotal experience would suggest that doses of AUTOPLEX® T of 50–100 U kg^{-1} given approximately every other day for 3–4-week periods were effective in bleeding prevention during the later stages of wound healing, which clearly requires less haemostatic capability than early operative prophylaxis and may be closer to doses required for primary prophylaxis.

Moreover, there are several published, though anecdotal, reports of efficacy of PCCs/aPCCs for routine prophylaxis of joint bleeds in inhibitor patients. In early investigations, it was noted that 30 U kg^{-1} of an early PCC product (PROPLEX® T) given every other day subjectively decreased the number of bleeds in several inhibitor patients for periods up to 8 months and that omission of the PCC was associated with recurrence of joint bleeding [3,23]. Using 40 U kg^{-1} of PCC (PROPLEX® T), another investigator used 'repeated infusions' to prevent bleeding in three inhibitor patients with chronic synovitis, frequent joint haemorrhages and severely limited mobility (two were wheelchair-bound and the other was unable to attend school) [18]. All three were reported to have diminished bleeding episodes with subsequent improvement in mobility and a return to normal activity levels. In another report, 50 U kg^{-1} of PCC (PROPLEX® T) was given every other day to an inhibitor patient for 6 months with an apparent decrease in bleeding episodes [22]. Although no published experience could be found on the use of aPCCs alone in the prevention of joint bleeding, it is interesting to note that investigators in Germany have been using twice-daily doses of an aPCC (FEIBA®) at 40–60 U kg^{-1} as adjunctive therapy for the prevention of bleeding in the Bonn immune tolerance protocol for over 25 years [8,26].

Thus, in attempting to define a minimum effective dose for the prevention of bleeding, reports suggest that PCC doses ranging from 30 to 50 U kg^{-1} given every other day for up to 8 months have resulted in subjective improvement both in the number of bleeds associated with target joints and in the management of chronic joint inflammation [3,18,22,23]. For aPCC use, doses as low as 50–100 U kg^{-1} every other day have been useful in late surgical prophylaxis for joint surgeries, and may be reasonable for a trial of primary prophylaxis.

Maximum safe dose and frequency of PCCs/aPCCs to avoid thrombogenic complications

It was recognized many years ago that life-threatening thromboembolic complications could be associated with

Table 1. Cases in which only PCCs/aPCCs were given for the prevention of surgical bleeding and postsurgical bleeding in haemophilia patients with inhibitors and administered ⩾2 days postoperatively

Reference	No. of patients	Type of surgery	Product	Dose (U kg^{-1} day^{-1})	Duration (days)	Concomitant EACA use	Bleeding during prophylaxis	Postprophylaxis bleeding (day following cessation of prophylaxis)	Thrombotic complications
Yolken [18]	1	Colostomy revision	PCC (PROPLEX® T)	40–140	9	No	No	No	None
Hutchinson [17]	2	Synovectomy	aPCC (AUTOPLEX® T)	75–120	5	No	Unknown	Yes (5)	None
		Synovectomy	aPCC (AUTOPLEX® T)	133–200	6	No	Unknown	Yes (2)	None
Heisel [19]	1	Drainage of subdural haematoma	aPCC (AUTOPLEX® T)	150	13	No	No	Yes (17)	None
		Multiple surgeries after recurrent haematoma	aPCC (AUTOPLEX® T)	180–300	18	No	Yes	No	None
Hann [20]	2	Dental extractions	aPCC (AUTOPLEX® T)	160	6	Yes	No	No	None
		Fasciotomy/ skin graft (multiple procedures)	PCC (KONYNE®) + aPCC (AUTOPLEX® T)	200–300	24	Yes	Yes	No	None
Penner [7]	1	Synovectomy	aPCC (AUTOPLEX® T)	150–400	11	Unknown	Yes	No	None
Negrier [21]	6	Dental extractions	aPCC (FEIBA®)	150	3	Yes	No	Unknown	None
		Arthroscopy	aPCC (FEIBA®)	200	6	No	No	Unknown	None
		TKA	aPCC (FEIBA®)	210	21	No	Yes	Unknown	None
		Synovectomy	aPCC (FEIBA®)	140–210	21	No	No	Unknown	None
		Prostate surgery	aPCC (FEIBA®)	210	32	No	No	Unknown	None
		Dental extractions	aPCC (FEIBA®)	210	21	Yes	No	Unknown	None

EACA = epsilon aminocaproic acid; TKA = total knee arthroplasty.

the use of PCCs, particularly when used in higher than recommended dosages in patients with haemophilia B [27]. Several early reports also linked their use and that of aPCCs, on rare occasions, to such complications in both haemophilia A and B inhibitor patients [21,28–37].

Table 2 summarizes the reports of these complications in 11 inhibitor patients, 10 of whom had factor VIII inhibitors and one of whom had a factor IX inhibitor. Of note is that in inhibitor patients, the major clinical complication of PCCs/aPCCs is myocardial infarction (MI), with a few patients showing laboratory evidence of disseminated intravascular coagulation (DIC) without clinical sequelae. In fact, in several of the patients reported to have DIC, PCCs were continued at lower doses without incident. Interestingly, there were no reported cases of venous thromboembolism in inhibitor patients receiving PCCs/aPCCs, in contrast to such complications reported frequently in haemophilia B patients receiving large or frequent doses of PCCs.

In addition to the 10 cases of MI in inhibitor patients noted in Table 2, several additional cases of MIs in inhibitor patients were reported to the Scientific and Standardization Committee of the International Society of Thrombosis and Haemostasis, but specific information regarding doses and duration of therapy are unavailable for these cases [27]. Autopsy findings from three of the MI cases and pathological examination of the heart from a patient receiving the heart transplant were remarkable for the presence of transmural haemorrhage in each case, without a significant degree of artherosclerosis [36]. Although the mechanism for such a complication is not entirely clear, at least one investigator has pointed to the great excess of factor VII (of the order of 200–300-fold) being administered to patients receiving either PCCs or aPCCs [38]. While factor VII may play a critical role in the haemostatic effectiveness of these products, it may also be linked to coronary thrombosis.

What is apparent from the reports listed in Table 2 is the relationship of complications with very large doses of PCC or aPCCs, which often exceeded 200 and even 300 U kg^{-1} day^{-1}. In the two reports of MIs occurring in

Table 2. Summary of reported cases of thromboses/DIC associated with the use of PCCs/aPCCs in haemophilia patients with inhibitors

Reference	Age (years)	Product	Dose (U kg^{-1} day^{-1})	Duration (days)	Concurrent EACA Use	Thrombotic complication	Outcome	Comment
Fuerth [34]	17	PCC (KONYNE®)	215–430*	6	No	MI	Unknown	
Agrawal [33]	15	PCC (KONYNE®)	225–400	7	Yes	MI	Recovered	
Gruppo [31]	17	PCC (KONYNE®)	300*	4	No	MI	Died	
Sullivan [32]	22	PCC (KONYNE®)	360	4	No	MI	Died	History of hypertension, obesity
Tabor [30]	29	PCC (unknown) + aPCC (AUTOPLEX® T)	450*	5	No	MI	Died	Three days of PCCs were followed by 1 day of AUTOPLEX® T, then another day of PCCs. On 5th day, an MI occurred
Fukui [28]	17	aPCC (FEIBA®)	225	6	No	DIC	Recovered	Laboratory evidence only, no clinical problems
Schimpf [35]	62	aPCC (FEIBA®)	120	7	No	MI	Recovered	Occurred 24 h post-last treatment; 1 year history of angina
Chavin [29]	15	aPCC (FEIBA®)	300	5	No	MI	Cardiac transplant	
Karayalcin [36]	8	aPCC (FEIBA®)	75–300	16	No	MI	Recovered	
Gruen [37]	10	aPCC (FEIBA®)	300	6	No	MI	Recovered	
Negrier [21]	61	aPCC (FEIBA®)	225–500	6	No	DIC	Recovered	Laboratory evidence only; no clinical problems
	45	VIIa + aPCC (FEIBA®)	108	1	No	DIC	Recovered	Laboratory evidence only, no clinical problems
	41	aPCC (FEIBA®)	160	1	No	MI	Unknown	Haemophilia B patient w/low-titre inhibitor; correction of FIX occurred

*Values calculated from total units given, based on assumption of 70 kg body weight. EACA = epsilon aminocaproic acid; FIX = factor IX.

patients receiving less than 200 U kg^{-1} day^{-1}, there were extenuating circumstances. In one exception noted by Negrier and colleagues, a factor IX inhibitor patient had an MI after large doses of FEIBA®, which were shown to have corrected his factor IX level [21]; in the other exception reported by Schimpf *et al.*, a 62-year-old man with a factor VIII inhibitor developed an MI after 7 days of FEIBA® at 120 U kg^{-1} day^{-1} but gave a history of exertional angina for 1 year prior to the MI. There were no reported instances of any thrombotic complications in any patient receiving aPCCs or PCCs in amounts less than 100 U kg^{-1} day^{-1}.

It is interesting to note that one experienced treater has used continuous infusions of aPCCs (both FEIBA® and AUTOPLEX® T), in total doses of 150 U kg^{-1} day^{-1} with or without concomitant epsilon aminocaproic acid (AMICAR®, Immunex, Seattle, WA, USA) every 6 h for periods up to 10 days for control of serious bleeding in 10 patients. No thrombotic complications or clinical evidence of DIC were noted in any of these patients (W. Bell, personal communication).

Also of note is that no cases of MI or any other thrombogenic events have apparently been reported with the use of AUTOPLEX® T alone [7,17,19,20], including with its longer-term use to control postsurgical bleeds (Table 1) and in patients who received doses as high as 180–300 U kg^{-1} daily for 13 days [24,25]. Possibly of benefit with regard to thrombogenicity is the addition of a small amount of heparin to AUTOPLEX® T in the manufacturing process, which may confer a degree of protection against thrombosis without inactivating the coagulant proteins [3,7].

Reviewing the data presented as well as general clinical experience, it seems reasonable to conclude that for most factor VIII inhibitor patients without underlying cardiovascular disease, the risk of developing an MI is clearly linked to total dosages of either PCCs or aPCCs greater than 200 U kg^{-1} day^{-1}. In addition, the likelihood of developing clinically relevant DIC with such doses appears to be quite low, or nonexistent.

Discussion

In patients with severe haemophilia without inhibitors, long-term studies of factor concentrates administered on a regular prophylaxis schedule have demonstrated marked reductions in clinically and radiologically significant joint disease [15,16]. Notwithstanding the high costs, complications and inconvenience of such therapy, many clinicians are now presenting prophylaxis as an important therapeutic option to parents of young children with severe haemophilia for the prevention of end-stage joint disease. Once a patient develops an inhibitor of greater than 5 Bethesda Units, replacement factor ceases to prevent or treat active bleeds, and that patient becomes extremely likely to develop permanent, severe and often crippling joint disease if the inhibitor cannot be eradicated. Since the early demonstrations more than 25 years ago that PCCs/aPCCs were effective in the treatment of active bleeding in inhibitor patients, clinicians have speculated on their ability to prevent joint bleeds, and a few have reported anecdotal success in a handful of patients. Hypothetically, use of both PCCs and aPCCs for prophylaxis appears reasonable and possibly of value in this patient population. Activated PCCs are of particular interest because of the more extensive published experience with their successful use in postsurgical prophylaxis. Having the potential to decrease joint bleeds and prevent joint disintegration, prophylaxis with aPCCs would be particularly beneficial to inhibitor patients who bleed frequently and have not yet developed severe or crippling joint dysfunction.

While there have been several reported cases in which prophylaxis with PCCs subjectively reduced bleeding and progressive joint dysfunction [3,18,22,23], data on the use of aPCCs for nonsurgical prophylaxis is anecdotal at this point. For over 25 years, investigators in Germany have had satisfactory experience using an aPCC (FEIBA®) as adjunctive prophylaxis to reduce significant or frequent bleeding episodes during immune tolerance therapy with daily high-dose factor VIII as part of the Bonn regimen [8,26]. It is also clear that individual treaters have positive unpublished experience in the use of episodic prophylaxis with aPCCs. One treatment centre in Germany has experience with several children in whom FEIBA® has been observed to reduce bleeds when given as either daily or every-other-day doses of 50–100 U kg^{-1}, for periods as long as 18 months (Wolfhart Kreuz, MD, Centre of Paediatric Haemophilia and Thrombosis, J.W. Goeth-University Hospital, Frankfurt-am-Main, Germany, personal communication). Another treater from the United States, administered an aPCC, AUTOPLEX® T, 60 U kg every 2–3 days in an adult patient and successfully prevented all bleeds for over 3 months. Prior to beginning this prophylaxis regimen, this patient averaged nearly 2 bleeds per week for several years (Anthony Cecalupo, MD, affiliated with Memorial Hospital, Colorado Springs, CO, personal communication). Other treaters have also successfully prevented bleeding using single doses of AUTOPLEX® T in allowing patients to pursue activities such as team sports, which would otherwise result in a high likelihood of bleeding (Naomi Luban, MD, Transfusion Medicine at Children's National Medical Center, and George Washington University School of Medicine, Washington, DC, personal communication; John Penner, MD, Michagan State University, personal communication). Such information, taken together with the many successful reports of aPCC use in postsurgical prophylaxis, would support the development of a clinical trial to study the efficacy of aPCCs in the prevention of joint bleeds.

Although there is a risk of MI or possibly DIC in inhibitor patients receiving PCCs/aPCCs, this risk is associated with large doses used in the treatment of serious bleeding. From available data, there does not appear to be a definite thrombogenic risk associated with doses less than 100 U kg^{-1} day^{-1} of either PCCs or aPCCs, which are the doses most likely to be used for prophylaxis.

Moreover, one aPCC product (AUTOPLEX® T) has been very rarely reported to be associated with thrombogenic complications despite numerous reports of surgeries in which high doses were given [25].

For clinical purposes, an important feature of any PCC or aPCC selected for study as a prophylaxis agent should be a low potential for provoking an anamnestic response in inhibitor titre in the majority of patients treated [39]. There are reports of anamnestic rises in inhibitors with all PCC and aPCC products [4,40,41]. In one large series of PCC products, early studies showed that 13% of treatment episodes were associated with a rise in inhibitor titre, but that 36% of individual patients demonstrated an anamnestic rise at least once. Although patients who had one anamnestic rise were more likely to experience subsequent anamnesis, these responses were generally unpredictable [42]. Among the aPCCs, AUTOPLEX® T reportedly causes anamnestic responses in less than 10% of patients in whom no other blood product could have been implicated [41,43], while FEIBA® has been reported to cause anamnestic responses in 15–20% of patients [44,45]. It is uncertain what anamnestic effect any of these products would have over a long period of time when given on a prophylaxis schedule of daily or every-other-day dosing, making factor VIII inhibitor monitoring an important aspect of such a trial.

Conclusion

There is anecdotal evidence to suggest that AUTOPLEX® T or FEIBA® may be useful for non-surgical prophylaxis in inhibitor patients in reducing the number of bleeding episodes and subsequent joint damage. Moreover, when used in doses less than 100 U kg^{-1} every other day, the risk of thrombotic complications would appear to be very low. Based on these encouraging findings, a clinical trial of these products used in doses of 50–100 U kg^{-1} every other day would appear to be warranted in patients who have permanent inhibitors and frequent joint bleeding.

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